3AN-06-05630CI Volume: 013
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State of Alaska vs. Eli Lilly & Co

VOL. 13

CIVIL

Begin: 3-10-08
End: 3-11-08

IN THE

PLAINTIFF'S ATTORNEY

TRIAL COURTS

OF THE

STATE OF ALASKA

DEFENDANT'S ATTORNEY

TYPE OF PROCEEDING

MASTER ASSIGNED	DATE ASSIGNED	DATE DISQUALIFIED	BY WHOM DISQUALIFIED

JUDGE ASSIGNED	DATE ASSIGNED	DATE DISQUALIFIED	BY WHOM DISQUALIFIED
Rindner	3-1-06		

FILING FEE RECEIPT# _____

INDEXED _____

OTHER _____

15764

CV-E-A

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

FILED IN OPEN COURT
Date: 3-11-08
Clerk: MZD

STATE OF ALASKA	)	
Plaintiff,	)	
	)	
v.	)	Case no. 3AN-06-5630CIV
	)	
ELI LILLY AND COMPANY	)	
Defendant	)	

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for **Alan Breier, M.D.** The highlighted excerpts are those that must be presented together with the State's affirmative designations to ensure proper context.

Start (Page:Line)	End (Page:Line)	
26:21	28:12	
95:6	95:23	✓
96:5	96:8	✓
96:11	97:11	✓
97:14	98:12	✓
98:15	98:16	✓
98:19	100:20	✓
112:3	112:10	✓
122:1	122:17	
137:18	139:5	

Start (Page:Line)	End (Page:Line)	
140:12	140:14	
140:17	140:24	
141:3	141:18	
160:6	160:15	
163:22	164:3	✓
164:6	164:10	✓
164:16	165:13	✓
185:24	186:19	✓
189:23	190:8	
201:10	202:2	✓
303:24	303:24	
304:1	304:7	
357:10	357:11	✓
357:14	357:24	✓
358:1	358:2	✓
358:5	358:10	✓
358:13	358:24	✓
433:2	433:21	
451:3	451:12	
451:15	451:16	
451:19	452:17	
457:8	457:9	✓
457:12	458:10	✓

Start (Page:Line)	End (Page:Line)
512:10 512:16	512:13 512:23
526:6 526:12	526:9 526:22

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Alan Breier:

Start (Page:Line)	End (Page:Line)	Objection
64:9	64:18	Vague; ambiguous; foundation; prejudicial (Alaska R. Evid. 401, 402, 403, 611)
125:23 126:13	126:4 126:15	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
167:15	168:2	Foundation; vague; misstates evidence (Alaska R. Evid. 401, 402, 403, 611)
192:10	192:19	Foundation; vague; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611)
199:18 200:4	200:1 200:11	Compound question; hearsay (admit for notice) (Alaska R. Evid. 401, 402, 611, 802)
201:3	201:10	Foundation; vague; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611)
219:20	221:24	Exhibit itself hearsay; misstates evidence (Alaska R. Evid. 802, 611)
281:24	282:23	Hearsay (Alaska R. Evid. 802)
287:12	287:23	Hearsay; compound question (Alaska R. Evid. 401,

Start (Page:Line)	End (Page:Line)	Objection
		402, 611, 802)
290:13	291:4	Hearsay (Alaska R. Evid. 802)
294:1	294:7	Hearsay (Alaska R. Evid. 802)
295:13	296:8	Hearsay (Alaska R. Evid. 802)
312:8	312:20	Hearsay (Alaska R. Evid. 802)
338:17	339:8	Vague; foundation; compound question; argumentative (Alaska R. Evid. 401, 402, 403, 611)
343:20	344:6	Foundation; personal knowledge (Alaska R. Evid. 401, 402, 602)
347:9	347:15	Vague; foundation; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611)
348:18	349:7	Misstates evidence (Alaska R. Evid. 611)
401:16	404:15	Relevance (Alaska R. Evid. 401, 402, 403;) Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
403:15	403:21	Personal knowledge; foundation (Alaska R. Evid. 401, 402, 602)
405:19	406:13	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
406:24	413:15	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
440:15	442:11	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action

Start (Page:Line)	End (Page:Line)	Objection
442:19	442:22	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
443:2	444:24	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
445:17	449:13	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
455:3	455:12	Vague; foundation (Alaska R. Evid. 401, 402, 403, 611)
511:8	512:2	Foundation; misstates evidence (Alaska R. Evid. 401, 402, 611); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude Evidence Relating to Defendant's Profits, Net Worth, and the Price of Zyprexa
515:24	516:6	Foundation; misstates evidence (Alaska R. Evid. 401, 402, 611); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude Evidence Relating to Defendant's Profits, Net Worth, and the Price of Zyprexa
518:16	519: 7	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
524:3	524:11	Asked and Answered (Alaska R. Evid. 611); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action
525:6	525: 13	Relevance (Alaska R. Evid. 401, 402, 403); Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign

Start (Page:Line)	End (Page:Line)	Objection
		Regulatory Action
525:14	526:5	Subject to Defendant Eli Lilly and Company's Motion in Limine to Exclude References to Foreign Regulatory Action

Lilly also objects to Plaintiff's exhibits for use during the testimony of Alan Breier:

Plaintiff's Exhibit	Objection(s)
Zyprexa Plaintiff's Exhibit No 320	M.I.L. regarding Foreign Regulatory Actions M.I.L. regarding adverse events Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Hearsay (Alaska R. Evid. 801, 802)
Zyprexa Plaintiff's Exhibit No 1110	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal planning document regarding internal market research, marketplace perceptions, and planning for proposed sales representative communications Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 1111	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal planning document regarding internal market research, marketplace perceptions, and planning for proposed sales representative communications Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 1440	Hearsay; Agree to admit for notice
Zyprexa Plaintiff's Exhibit No 1453	Hearsay; Agree to Admit for Notice

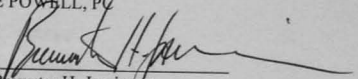
Plaintiff's Exhibit	Objection(s)
Zyprexa Plaintiff's Exhibit No 1605	Not Relevant (Alaska R. Evid. 401, 402) Hearsay (Alaska R. Evid. 801, 802) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Not a Complete Document Foundation (Alaska R. Evid. 901)
Zyprexa Plaintiff's Exhibit No 4051	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal briefing, labeling not discussed Foundation (Alaska R. Evid. 901)
Zyprexa Plaintiff's Exhibit No 4858	Agree to admit subject to M.I.L. regarding adverse events (hearsay - notice)
Zyprexa Plaintiff's Exhibit No 5565	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal communication regarding proposed responses to anticipated questions in Germany. MIL re: Foreign Regulatory Actions Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 7802	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Not a Complete Document Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Zyprexa Plaintiff's Exhibit No 9281	Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit No 10017	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal document discussing Lilly's foreign sales force M.I.L. regarding Foreign Regulatory Actions Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901)

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law,

based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

LANE POWELL, PC

By: 

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Dated: March 11, 2008

Confidential - Subject to Protective Order

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

IN RE: MDL-1596

ZYPREXA PRODUCTS

LIABILITY LITIGATION

THIS DOCUMENT RELATES TO:

ALL CASES

C O N F I D E N T I A L

- - -

January 11, 2007

- - -

Videotape deposition of

ALAN BREIER, M.D.

- - -

GOLKOW LITIGATION TECHNOLOGIES
1880 John F. Kennedy Boulevard
Suite 760
Philadelphia, Pennsylvania 19103
(877) 370-3377

CROSS-NOTICES SERVED FOR ALAN BREIER DEPOSITION
Patricia Tracy v. Eli Lilly, et al., CV-06-921, Jefferson County, Alabama
Eddie D. Cook v. Eli Lilly, et al., -CV-1004-ID, USDC Middle District Alabama
Betty Weathers v. Eli Lilly, et al., -cv-00666-WHA-DRB, USDC Middle District Alabama
Mary Mallard v. Eli Lilly, et al., 2:06-cv-481-VPM, USDC Middle District Alabama

Patricia Segrest v. Eli Lilly, et al., 2:06-cv-542-WHA, USDC Middle District Alabama

Charles O. Crowder v. Eli Lilly, et al., 2:06-cv-1321-WHA, USDC Northern District Alabama

Debra A. Betts v. Eli Lilly, et al., 1:06-CV-00742-CB-M, USDC Southern District Alabama

Sharlene Etheridge v. Eli Lilly, et al., 2:06-CV-774, USDC Southern District Alabama

Joel Algario v. Eli Lilly, et al., BC347855, Los Angeles County, California

Shafiqa Wardak v. Eli Lilly, et al., BC348211, Los Angeles County, California

Patricia Godley , et al. v. Eli Lilly, et al., BC347856, Los Angeles County, California

Los Angeles County, California
Karl Scoggins, et al. v. Eli Lilly, et al., BC347858, Los Angeles County, California
Michael Montana, et al. v. Eli Lilly, et al., BC360995, Los Angeles County, California
Erlinda Espeleta v. Eli Lilly, et al., RIC 456237, Riverside County, California
Alvin Young v. Eli Lilly, et al., 06 cv 2595 WQH (LSP), USDC Southern District California
Karl Kovacs v. Eli Lilly, 79D01-0601-CT-00001, Tippecanoe County, Indiana
Danny Tardy, et al. v. Eli Lilly, et al., CV-03-538, Cumberland County, Maine
In re: Risperdal/Seroquel/Zyprexa Litigation, #274, Middlesex County, New Jersey

Carol Lynn Jenkins, et al. v. Eli Lilly, 1:06-CV-2797, USDC Eastern District New York

Michael Richardson v. Eli Lilly, et al., 06-cv-00330, USDC Southern District Ohio

Victoria Smith v. Eli Lilly, 06-676-JPH, USDC Southern District of Illinois

Carl Bavone, et al. v. Eli Lilly, 05-L-770, St. Clair County, Illinois

Jeffrey Perkins, et al. v. Eli Lilly,

USDC Middle District Louisiana
Daisy M. Blackston v. Eli Lilly, -CV-2135, USDC Western District Louisiana
Gary Green v. Eli Lilly, et al., 3:06cv149-M-A, USDC Northern District Mississippi
Robert Sutherland v. Eli Lilly, 251-04-271, Hinds County, Mississippi
Anthony Ritter v. Eli Lilly, 3:06cv358HTW-JCS, USDC Southern District Mississippi
Sharon Osborne v. Eli Lilly, et al., 3:06CV706HTW-LRA, USDC Southern District Mississippi
Rick Galati v. Eli Lilly, et al., 05CW-CV00781, Callaway County, Missouri
Terrence L. Raine Sr. v. Eli Lilly, et al., 105CC4194, Greene County, Missouri
Don Stricklen v. Eli Lilly, et al., 0616-CV-12957, Jackson County, Missouri
Kyle Rolfingsmeyer v Eli Lilly, et al., 0611-CV03687, St. Charles County, Missouri
Lena Barnett, et al., v. Eli Lilly, et al., 06CC-00033, St. Louis County, Missouri
Aimee Daniels v. Eli Lilly, et al., 05CC-004759, St. Louis County, Missouri

S.M., et al. v. Eli Lilly, et al., 06CC-3930,

Frank and Jeanette Howard, et al.v. Eli Lilly, et al., 05-EV-000217B, Fulton County, Georgia
Wilbert Green v. Eli Lilly, -CV-2328-TCB, USDC Northern District Georgia
Kimberly J. Johnson, et al. v. Eli Lilly, et al., -cv-02994-TLW, USDC South Carolina
Christopher Daniel v. Eli Lilly, -3419, USDC South Carolina
Vickie Trapp v. Eli Lilly, -CV-02313-MDL, USDC South Carolina
Thompson Fry v. Eli Lilly, -CV-03076-MDL, USDC South Carolina
Samuel Davis v. Eli Lilly, 3:06-cv-2312-CMC-BHH, USDC South Carolina

Patsy Nissen v. Eli Lilly, 1:06-cv-02456-MDL, USDC South Carolina

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- - -

Videotape deposition of ALAN BREIER, M.D., held in the offices of Barnes & Thornburg, 11 South Meridian Street, Indianapolis, Indiana 46204-3535 Commencing at 9:37 a.m., on the above Date, before Rebecca J. Swinney, a Registered Merit Reporter and Federal Certified Realtime Reporter.

- - -

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INDEX OF PREVIOUSLY MARKED EXHIBITS

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THE VIDEOGRAPHER: We're on the record. Here begins the videotaped deposition of Dr. Alan Breier being taken by the plaintiff. Today's date is January 11th of 2007. We're going on the record at 9:37 a.m.

This deposition is being held at the law offices of Barnes and Thornburg located at 11 South Meridian Street, Indianapolis, Indiana. This case is pending in the United States District Court, Eastern District of New York, Cause No. MDL 1596. This is In Re the Zyprexa Products Liability Litigation.

My name is Pete Zinkan. I'm a legal video specialist in association with Golkow Litigation Technologies. The court reporter is Becky Swinney also in association with Golkow.

The attorneys may state their

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appearance for the record and the reporter will issue the oath.

MR. SUGGS: My name is David Suggs. I'm appearing on behalf of the plaintiffs. I'm with the firm of Richardson Patrick Westbrook and Brickman and I have agreed to be bound by the confidentiality order.

MR. FIBICH: My name is Tommy Fibich. I'm here on behalf of plaintiffs and I, too, am bound by the confidentiality order.

MR. ALLEN: Scott Allen for plaintiffs. I do agree to be bound by the confidentiality order.

MS. JOBES: Jana Jobes from Sidley Austin representing AstraZeneca and my understanding is AstraZeneca has entered into a confidentiality agreement with Eli Lilly.

MR. DINSMORE: Mark Dinsmore, Barnes & Thornburg, representing Eli Lilly and Company, and I agree to be

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bound by the protective order.

MS. RAY: Elizabeth Ray, Pepper Hamilton, representing Eli Lilly and Company. I'm bound by the protective order.

MR. KANTRA: Andy Kantra, representing Eli Lilly and Company and Dr. Breier. I'm also bound by CMO3.

MR. BOISE: Barry Boise, Pepper Hamilton, representing Dr. Breier and Eli Lilly and Company, and I'm bound by CMO3.

MR. FIBICH: Are you, too, with Pepper Hamilton?

MR. KANTRA: Yes. I'm sorry.

MR. O'HARA: Chris O'Hara with Hagans, Berman, Sobol, Shapiro on behalf of the third-party payor plaintiffs in the UFC Local Eli Lilly case and we are also bound by CMO3.

MR. ALLEN: This is Jennifer Martin, she's with me, my paralegal.

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She agrees to be bound.

MR. FARRELL: Tim Farrell with the Miller firm. We also agree to be bound by the terms of that endorsement.

MR. FIBICH: Who do you represent?

MR. FARRELL: I represent one of the plaintiffs.

MR. FIBICH: I'm sorry.

MR. BOISE: It's okay.

On the phone. Lydia?

MS. MAGEE: Lydia Magee with Richardson Plowden Carpenter and Robinson. I represent Dr. Helena Kirkpatrick and Magnolia OB-GYN and I agree to be bound by the confidentiality agreement.

MS. MOITRA: Alika Moitra from Sandberg Phoenix and Von Gontard. I represent Dr. Seagraves and Dr. Ilivicky, and I agree to be bound by the confidentiality agreement.

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MR. VINSON: Todd Vinson with Drinker Biddle and Reath. I represent Janssen Pharmaceuticae and I agree to be bound by the confidentiality agreement.

MR. SPERRY: This is Mark D. Sperry of Owen Gleaton Egan Jones & Sweeney. We represent Fulton Emergency Physicians. And I agree to be bound by the confidentiality agreement.

MR. BOISE: And that's in the Howard case, Mark?

MR. SPERRY: Yes, um-hum.

MR. BOISE: Anyone else on the line?

- - -

ALAN BREIER, M.D., after having been duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

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QUESTIONS BY MR. SUGGS:

Q. Good morning. Would you state you full name for the record, please.

A. Alan Breier.

Q. Okay. And what does that oath that you just took mean to you, sir?

A. To tell the truth.

Q. Does it mean no spinning of facts?

A. Absolutely.

MR. BOISE: Object to form.

Q. And do you know what spinning means?

MR. BOISE: Object to the form.

A. Yes.

Q. Okay. Do you realize that if you do tell the truth and nothing but the truth with no spinning that that may have negative consequences for Lilly in this litigation?

MR. BOISE: Object to the form. Lack of foundation.

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A. My responsibility is to tell the truth and I will.

Q. Who's John Lechleiter?

A. John Lechleiter is currently the chief operating officer of Eli Lilly and Company.

Q. And he's also the president of the company, is he not?

A. I don't believe he holds that title at this time.

Q. Do you report to him?

A. No.

Q. Okay. Do you recall promising Mr. Lechleiter and other executives back in 2001 that you would devote the rest of your career to the singular purpose of serving Lilly fully and without reservation?

A. I don't recall that --

Q. Okay.

A. -- those comments.

THE OPERATOR: James Cook has joined the conference.

MR. SUGGS: We'll mark this document as Breier Exhibit 1.

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(Whereupon, Deposition Exhibit(s) 1 duly received, marked and made a part of the record.)

MR. SUGGS: For the record this is an e-mail from Alan Breier dated October 16, 2001, to John C. Lechleiter, Greg B. Reynolds, Albertus van den Bergh and Augustus M. Watanabe.

MR. BOISE: Who joined us?

MR. COOK: This is James Cook with the Dutton law firm.

MR. BOISE: One more time?

MR. COOK: James Cook. C-O-O-K.

MR. BOISE: Law firm?

MR. COOK: Dutton, D-U-T-T-O-N, Braun, B-R-A-U-N, Staack, S-T-A-A-C-K and Helman.

MR. BOISE: And who do you represent?

MR. COOK: Various plaintiffs.

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MR. BOISE: Can you give me the name of some of these various plaintiffs?
MR. COOK: Mr. Bradley, Robert Griffith.
MR. BOISE: Have you signed the endorsement to the protective order?
MR. COOK: I have.
QUESTIONS BY MR. SUGGS:
Q. Dr. Breier, did you, in fact, write what we've marked as Breier Exhibit 1 on or about October 16, 2001?
A. I did.
Q. And who were the individuals to whom the e-mail's addressed?
A. John Lechleiter, Greg Reynolds, Albertus van den Bergh and August Watanabe.
Q. You previously said that Mr. Lechleiter is chief operating officer of Eli Lilly. What are the other individuals's positions?
THE WITNESS: At the time

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that this was authored?
MR. SUGGS: Yes.
A. Just to qualify, at the time this was authored, John Lechleiter was head of the Product Team organization; Greg Reynolds was an executive in Human Resources; Albert van den Bergh was President of Neuroscience, and August Watanabe was President of Lilly Research Laboratories.
Q. And you wrote this e-mail to them on the occasion of being promoted to G8, correct?
A. That's correct.
Q. And what does G8 mean?
A. G8 refers to a particular level in the company. I believe G stands for grade, so grade eight.
MR. ALLEN: Whoever's on the phone, you need to put your phones on mute because we can hear you. So put your phones on mute, please.
THE VIDEOGRAPHER: I'm also picking up somebody's device.
Q. You said that G8 refers to a

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grade level within Eli Lilly. How high up do the grades go?
A. I'm not 100 percent certain, but I believe it goes, perhaps, to G14, possibly G15.
Q. And in this e-mail, when you were promoted to level G8 you wrote to those executives on October 16, 2001, and said, quote, My commitment to you is I will devote the remainder of my career to a singular purpose, that of serving Lilly fully and without reservation; is that correct?
A. That's correct.
Q. And you are currently Vice-president and the Chief Medical Officer at Eli Lilly; is that correct?
A. That's correct.
Q. And you assumed that position in August of 2003?
A. Yes.
Q. And when you assumed that position in August of 2003, did your devotion to serving Lilly fully and without reservation stay the same or decrease from

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what it was back in 2001?
A. Stayed the same.
Q. Okay. By the way, when you wrote to these executives and said that you were going to devote the remainder of your career to serving Lilly fully and without reservation, was that a change in your attitude at that time or had that been your posture up to that point in time anyway?
MR. BOISE: Object to the form.
A. That was not a change.
Q. Okay. When you assumed the position of Vice-president and Chief Medical Officer in 2003, who did you replace?
A. I, essentially, replaced Mike McDonald. At that time, Gus Watanabe had held the title of Chief Medical Officer, Mike McDonald held the position of Vice-president of Medicine, and both of those titles were then consolidated into my new role.
Q. And who do you currently report to?
A. Steven Paul.

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Q. And what's his position?
A. He is president of Lilly Research Laboratories.
Q. And to whom does he report?
A. He reports to Sydney Taurel.
Q. And Sydney Taurel is the Chief Executive Officer and Chairman of the Board of the company; is that correct?
A. Yes.
Q. Could you briefly describe your duties and responsibilities in the positions of Vice-president and Chief Medical Officer?
A. My responsibilities are to lead the medical organization.
Q. How many people are in the medical organization?
A. We have, approximately, I'm going to say, 2,000 people in the medical organization.
Q. Okay. I'm going to be asking a lot of questions about your activities regarding Zyprexa, but before I do that, I'd like to find out more about your background.

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Am I correct that your received a Bachelor of Arts degree from the University of Toledo in Ohio in 1975?
A. That's correct.
Q. And you received a Doctor of Medicine degree in 1980 from the University of Cincinnati School of Medicine?
A. Correct.
Q. And then you were a resident in psychiatry from 1980 to 1984 at Yale University School of Medicine; is that correct?
A. Yes.
Q. And I know that you completed your residency in 1984, and that before you joined Lilly in 1997, you were at the University of Maryland and at the National Institute of Mental Health, sometimes referred to as NIMH, but I'm unclear as to what you were doing in that 13-year time period. Could you flesh it up?
A. Sure. When I left residency training at Yale, I joined the intramural program of NIMH. That was, primarily, for

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further research training. I focused at that time on primarily schizophrenia research. After completing a three-year research fellowship, I then assumed a position at the University of Maryland in the Department of Psychiatry and was an associate research professor there. After completing that position, I returned to the NIMH in a more senior position, and I was there for, I believe, about four years, and then joined Eli Lilly and Company in 1997.
Q. Okay. So you started off at NIMH to do a three-year fellowship after your residency, then you were at University of Maryland as an associate research professor for again how long was it?
A. I believe that was about six years.
Q. And were you tenured?
A. Yes.
Q. And then you went back to NIMH for, it would have been, what, four more years?

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A. Yes. And I just want to be absolutely precise. When I originally started at the University of Maryland, there were not tenure tracks, as I recall, for research professors, and I'm recalling that through that period of time that professors were then tenured.
Q. Okay. And were you tenured at the time you left University of Maryland to go to NIMH?
A. I believe so.
Q. Okay. And before joining Lilly, did you have any particular training or expertise in the diagnose and treatment of diabetes other than what is generally provided in medical school?
A. I did not.
Q. Okay. Am I correct that you had not conducted any research regarding diabetes before joining Lilly?
A. No, I did not.
Q. And you had not published any scientific articles regarding diabetes before joining Lilly; is that correct?

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A. That's correct.
Q. And would the same be true with respect to weight gain, that you'd had no prior professional involvement with issues relating to weight gain other than what would generally be provided to any practicing physician?
A. I would qualify my experience probably a bit more than that. When I was at the University of Maryland, I ran a research clinic for schizophrenic patients, and it was both a research and clinical care facility. So we were involved in both the clinical care as well as the research of schizophrenic patients over that six-year period. And health issues were not uncommon in that population including obesity, and to that matter diabetes as well.
Also -- and then returning to the NIMH, my position was also a clinical position. So we ran a clinical research unit and had predominantly schizophrenic patients but also patients with mood disorder, and we would then be responsible for the care of

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those patients, both the research and clinical. And so the problems that would come up on the medical side we would be involved with to some extent.
I also had a private practice during my period at NIMH and then was involved in issues that would come up with my patients that include weight gain.
Q. Had you ever conducted any research regarding weight gain before joining Lilly?
A. I'm recalling an analysis that we did that looked at the relationship between weight gain and clinical response. My recollection is that we were seeing a positive relationship between the two, and I believe we published those findings.
Q. Okay. Do you consider yourself as being an expert in the field of epidemiology?
A. I'm not an epidemiologist.
MR. FIBICH: Object to form or responsiveness of answer.
Q. Regardless of whether you had

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any formal training or hung out your shingle as an epidemiologist, do you consider yourself as an expert in that field?
A. I wouldn't qualify myself as an expert in epidemiology.
Q. Okay. What did you do to prepare for this deposition?
A. I met with my attorneys.
Q. Which attorneys?
A. Primarily the attorneys that we have here.
Q. Okay. Mr. Boise, Ms. Ray and Mr. Kantra?
A. Correct.
Q. And how many times did you meet with them?
A. We met for a few weeks in the spring because my deposition was originally scheduled for the summer of last year. That then was postponed. We suspended our meetings. It was then rescheduled for, I believe, it was either October/November of '06, and we began meeting a few weeks before that. That then was postponed. We suspended

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our meetings. And then began meeting about a week and-a-half ago to prepare for this deposition.
Q. And when you add all of those times together, how many hours would it be that you met with the attorneys to prepare for this deposition?
A. I don't know.
Q. Just a ballpark. Are we talking ten hours or 50?
MR. BOISE: Object to the form.
A. I don't really know.
Q. Well, just in the last week, how many time have you spent preparing for the deposition?
A. I would say approximately, I'm going to say somewhere in the neighborhood of maybe four to five hour days, typically, and we -- speculating -- somewhere in the neighborhood of maybe four to five days.
Q. Okay. So just in the last week or so about 25 hours?

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MR. BOISE: Object to the form.
A. Yes.
Q. Okay. And were you shown any documents?
MR. BOISE: You can answer that question "yes" or "no."
A. Yes.
Q. Were you shown any deposition transcripts?
MR. BOISE: Don't answer that question.
MR. SUGGS: Excuse me. You're instructing him not to answer whether he was shown?
MR. BOISE: You can answer that question "yes" or "no."
A. Yes.
Q. Okay. Do you recall which deposition transcripts you reviewed?
MR. BOISE: Don't answer that question.
MR. SUGGS: You're instructing him not to answer.

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QUESTIONS BY MR. SUGGS:
Q. And are you following his instruction?
A. Yes.
MR. SUGGS: Okay.
QUESTIONS BY MR. SUGGS:
Q. Did you bring any documents that were in your possession to these meetings?
A. No.
Q. Okay. Did any of the documents you were shown refresh your recollection as to events in the past?
A. Yes.
Q. Do you recall which documents refresh your recollection?
MR. BOISE: You can answer that question "yes" or "no."
A. Yes.
Q. Okay. How many documents refreshed your recollection?
A. I don't know.
Q. Was it one or two or ten or 20?

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A. I don't know.
Q. You can't give an approximation?
A. Not really.
Q. Okay. What was it that was refreshed?
MR. BOISE: Don't answer that question.
MR. SUGGS: And are you instructing him?
QUESTIONS BY MR. SUGGS:
Q. And are you going to follow his instruction not to answer that question?
A. Yes.
Q. Okay.
MR. SUGGS: I have to ask these questions for the record.
THE WITNESS: I understand.
QUESTIONS BY MR. SUGGS:
Q. Okay. Did you talk with anyone else about your deposition other than the attorneys you previously identified?
A. No. There occasionally would be an additional attorney from this firm that

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was involved, but outside of this legal team, no.
Q. Which other attorneys from the Pepper Hamilton firm were involved in the preparation?
A. I don't recall their names.
Q. Okay. I'd like to talk about your background at Lilly. Am I correct that you started at Lilly in 1997 as a clinical research fellow?
A. That's correct.
Q. And what were your duties and responsibilities then?
A. A clinical research fellow at Lilly is a senior technical position.
Q. And which products were you working on at that time?
A. Zyprexa.
Q. What did you do with respect to Zyprexa at that time in 1997?
A. My focus was predominantly on schizophrenia.
Q. Were you conducting clinical trials, doing -- what were you doing with

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respect to that?
A. My primary responsibilities were designing and conducting clinical trials.
Q. Okay. And what types of clinical trials were those?
A. We designed a registration strategy to develop a long acting depot, a long acting form of Zyprexa.
We developed a clinical plan to register the rapid acting intramuscular form of Zyprexa.
We conducted scientific investigations on areas that appear to be very important in understanding how Zyprexa worked in schizophrenia, for example, effects on cognition.
Q. Did you design and conduct any clinical studies with respect to using Zyprexa for indications other than schizophrenia or bipolar disorder? Again, I'm referring to you personally at that time.
MR. BOISE: In 1997?
THE WITNESS: In 1997?

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MR. SUGGS: Correct.
A. No.
Q. Who did you report to at that time?
A. Gary Tollefson.
Q. And who reported to you?
A. I had no direct reports.
Q. Am I correct that you became head of the Zyprexa Product Team in 1998?
A. Actually, I believe it was 1999.
Q. Okay. And do you recall what month that was?
A. I believe it was at the beginning of the year -- January.
Q. And did you still continue to report to Dr. Tollefson at that time?
A. Yes.
MR. SUGGS: Okay. I'm going to hand you what's been previously marked as Plaintiff's Exhibit 9070 and 9073.
(Whereupon, Plaintiff's Exhibit(s) 9070, 9073,

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previously marked, was presented to the witness.)
MR. SUGGS: If the you look in the lower left-hand corner of these you'll see that those exhibit numbers are there in pretty small print. And then at the bottom of each of the pages of the exhibits I'll be handing you there will also be a page number there.
First, Plaintiff's Exhibit 9070 and 9073.
MR. BOISE: Did you identify the first document by Bates or otherwise?
MR. SUGGS: You know what, I did not. Let me go back on the record and make sure we get that done.
For the record, what we previously marked as Breier Exhibit 1 is a one-page document that has the Bates No. ZY207409380.
For the record,

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Plaintiff's Exhibit 9070 is an article entitled Eli Lilly and Company Part A. It was apparently prepared by the Kellogg Graduate School of Management in November of 2002, and the Kellogg Graduate School of Management is part of Northwestern University.
QUESTIONS BY MR. SUGGS:
Q. Have you ever seen this document before, sir?
A. At first glance, no. I would need to read the document to determine if, in fact, I have or not.
Q. Let me direct your attention to Page 10 of this exhibit.
THE WITNESS: And we are on 09070; is that correct?
MR. SUGGS: Correct.
QUESTIONS BY MR. SUGGS:
Q. In the middle of Page 10 there is a bolded heading "Marketing At Lilly," do you see that?
A. Um-hum.
Q. I'd like to track through

some of the statements that are made in there, and I realize this article was written by someone at the Kellogg Graduate School of Management that was not with Lilly, but he describes the marketing structure at Lilly and the structure and functions of the product teams at Lilly.

And, basically, what I want to do is just track through this section of the document and find out from you if that's an accurate description of the way marketing and product trainings are structured at Lilly.

A. You know, I'm probably going to need to spend a little bit more time refreshing myself.

Q. I think we can speed things along here. Why don't I read you the language I'm concerned about and then you listen to my question, and if after my stating the question you need more time to read other parts of the document, we can do that. But I don't think it's going to be necessary. And would suggest that you hear what we're going

to be talking about first and then we can proceed from there. Is that fair enough?

MR. BOISE: Let's hear what the question is and we'll take it one at that time.

MR. SUGGS: Sure.

QUESTIONS BY MR. SUGGS:

Q. Let me direct your attention to the first paragraph in that section under Marketing At Lilly. It states: "Today" -- by the way, keep in mind this article was written in 2002 -- "marketing responsibilities fall into three axes at Lilly each with specific roles and responsibilities in the marketing function. The product team, the affiliates and the global marketing and sales organization or GMSO. Each different molecule or brand at Lilly is the responsibility of an individual product teams. These product teams are responsible for developing the overall global product strategy.

Each affiliate represents a specific geographic region in the world and

is responsible for tailoring and implementing the product strategy.

The GMSO is a corporate level function that is responsible for developing marketing capabilities and ensuring best practices within the organization."

Sir, my question to you is, is that an accurate description of the marketing structure at Lilly?

MR. BOISE: Object to the form of the question.

A. In, approximately, 2002, marketing no longer reported into the product teams and resided in a distinct marketing function. There was a transition at about that time.

Q. Okay.

A. I know this is a 2002 document. I am going to need a little more time to really, I think, read through this too.

Q. Okay. Then let me ask this question then: Is it fair to say that

between -- well, let me back up for a second.

In the following paragraph that starts off by saying "This structure was developed in the late 1990s." Do you see that?

A. I do.

Q. Was it fair to say that in the late -- do you recall when in the late 1990s that that structure that was described there, actually, came into being?

MR. BOISE: Object to the form. Foundation.

A. I joined the company in 1997 and probably don't have a good sense of the details prior to that. But again, I'm feeling like I would really like to read the document.

Q. Let me ask this question, sir: At the time you took over as head of the Zyprexa Product Team in 1999, was that structure that's described in that paragraph, was that an accurate description of the structure of marketing at that time in 1999?

A. Just take a moment.

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Q. Sure.
A. Okay. I've perused the --
Q. What material did you read, Doctor?
A. Well, I began at the beginning and certainly perused a variety of different paragraphs as I worked through. I think I may have read one or two paragraphs in more detail about Lilly and up to the paragraph you're asking me about.
Q. Okay. And my question to you was whether the marketing structure that's described in that first paragraph under the Marketing At Lilly section on Page 10 was an accurate description of the structure and function of marketing at Lilly when you assumed the head of the product team, Zyprexa Product Team in 1997?
A. Yeah, I think it's essentially accurate. It states here that -- see if I've still got it -- each different molecule or brand at Lilly is the responsibility of an individual product team. I would agree that the

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product team has defined responsibilities, but at least the way I'm reading that phrase, it may not portray the relationship quite as accurately. I would call the structure when I joined the team and became product team leader as quite cross-functional as opposed to a specific -- this strikes me as a little bit more of the tone of more of a silent organization as opposed to a more cross-functional one, but overall I think it's a fairly accurate representation.
MR. BOISE: In the following paragraph after first noting that this structure was developed in the late 1990s, it starts off in the third line by saying, "Like most companies in the pharmaceutical industry Lilly was a primarily science driven organization where the molecule was king and emphasis was placed on marketing or branding" -- pardon me -- "and little emphasis was placed on marketing or branding. Science came

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first and marketing consisted mainly of brochures about a product for the sales rep to give to physicians."
Do you see that language, sir.
A. I do.
Q. Is that your understanding, that that had been Lilly's posture up until that change was made in the late 1990s?
A. Let me just reread this paragraph quickly.
Q. Sure.
A. I would not agree with this. I would describe Lilly as a very strong, science-driven company first and foremost. I joined Eli Lilly for that very reason because of the step and strength of the science and felt that we maintained that strong science-driven focus throughout the time that I've been in the company.
MR. FIBICH: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. I'd like to direct your

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attention to the following page 11. There's a section there in the middle of the page that has a bold heading "Product Teams." Do you see that?
A. Yes.
Q. And you were, as you testified before, the head of the Zyprexa Product Team, correct?
A. Correct.
Q. Okay. In the second paragraph of that section it states, "Product teams consist of both medical and marketing personnel with each team having a clinical team and a global marketing team."
Do you see that language, sir?
A. Yes.
Q. And was that the case in 1999?
A. Well, again, there was a global marketing component to the team, there was an R & D component to the team. And again, we -- as I mentioned before, global marketing reported into the team until

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somewhere in the neighborhood of 2002 and then went out to a different organization.

Q. Do you remember when in 2002 the global marketing team stopped reporting in to the Zyprexa Product Team?

A. I don't recall the exact date.

Q. Okay. That paragraph goes on to say, "The clinical team is responsible for the scientific aspects of the molecule including research through post-marketing clinical trials, includes researchers, physicians, statisticians, and other clinical and operations personnel. The medical staff reports to both the product team as well as Lilly Research Labs, the research and development function at Lilly."

Was that an accurate statement in 1999?

A. Essentially that is correct. There was a substantial medical component on the team. The reporting lines vary a bit in that, for example, there would be regulatory scientists assigned to the team. They

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reported to the regulatory division. There's manufacturing people and product development people, but they reported back to their home function. And other people on the team actually reported into the product team organization.

Q. Okay. And that paragraph that I referred to before goes on to say, "The marketing team is responsible for the marketing activities that revolve around the product including developing the brand, brand positioning, and developing the core brand message."

Was that an accurate statement of the function of the marketing team within the Zyprexa Product Team at least as of when you took over in 1999?

A. I would describe the role of marketing on the team as having a global perspective, to working at a relatively high level on global marketing themes, both information coming in from the external environment. Then in terms of then science being conducted, scientists then working with

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marketing in terms of the communication of that science out but at a relatively high level related to core themes. And then the marketing output of the team would then go to the affiliate and the regions for refinement in their areas and implementation.

Q. Okay. The following paragraph on Page 11 of Exhibit 9070 starts off by saying, "The core product team leadership consists of a team leader who has overall responsibility for the product team, a medical director and a marketing director." Did I read that correctly?

A. You did.

Q. And that was the structure of the Zyprexa Product Team, at least when you took over in 1999, correct?

A. No. We -- I think each team had its own organizational structure. We clearly had a head of the team.

Q. That would be you, correct?

A. That was me in 1999.

Q. Okay.

A. We had a marketing director,

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but we did not have a medical director.

Q. Okay. So who functioned as a medical director? Would that have been you also?

A. No. We had a number of physicians on the team at different levels of seniority. And at least initially during my period as product team leader, those senior physicians took on specific lines of responsibilities.

Q. Okay. So this paragraph, which is describing the product team concept, generally in Lilly was not really accurate for Zyprexa because, at least as compared to this general statement, in the Zyprexa Product Team there was no one medical director; is that your testimony?

MR. BOISE: Objection to the form. Is the question 1999?

MR. SUGGS: Correct.

MR. BOISE: Okay.

A. I think that each product team had some variations on this theme. We did not have a single defined medical

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director as of 1999. We had a single defined medical director at some point later, I don't remember exactly what year, but we had very senior medical personnel on the team who were responsible for certain and specific components of the team.

Q. Okay. Who was the marketing director in 1999?

A. Roland Powell.

Q. Okay. And did he remain as marketing director until the time that -- well, let's leave it at that. How long did he remain Marketing Director?

A. I believe he was Marketing Director for two years.

Q. Okay. And then who succeeded him?

A. Denice Torres.

Q. And for how long was Denice Torres the marketing director of the Zyprexa Product Team?

A. Again, I would say that she was marketing director for, approximately, two years, and she was marketing director at

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the ball of this transition when marketing moved into a central marketing function.

Q. And you said it was your understanding that there was a marketing director at some point after 1999?

A. I know that's the case.

Q. And who was that?

A. Mauricio Tohen.

Q. And do you recall when it was he became medical director?

A. Approximately, I'm going to say in the '02 time frame.

Q. Okay. If I could direct your attention to the following paragraph. It states -- well, let me back up one second. I already handed you, I believe, Exhibit 9073. If you could turn to Page 8. That purports to be a diagram -- well, for the record, Exhibit 8 is another publication by Kellogg Graduate School of Management entitled Eli Lilly and Company Exhibits. And Page 8 is referred to as Exhibit 8, which is entitled "Individual Product Team Organization." And then it

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purports to set out a diagram, if you will, of the product team organization.

Do you see that, sir?

A. I do.

Q. And is that an accurate description of or characterization of the Zyprexa Product Team if we make a couple of changes: One is we don't have a medical -- in 1999 there was no medical director. No, let me back up.

MR. BOISE: Tommy is about to object to your question.

MR. SUGGS: Sorry.

QUESTIONS BY MR. SUGGS:

Q. Does Exhibit 8 accurately describe the Zyprexa Product Team organization, and if not, how not?

MR. BOISE: Is there a time frame? In 2002?

MR. SUGGS: Let's begin with 1999.

A. Okay. In 1999 we clearly had a team leader, a COO, a marketing director. And again, at that time, we had senior

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physicians who assumed responsibilities for medical director but did not have the specific title as a single medical director.

Q. And would they be part of that clinical team that's reflected there? Would those physicians have been part of that clinical team that's reflected there?

A. Yeah.

MR. BOISE: Let him finish his question and answer. It's natural to talk over each other. You're doing fine, but that makes the record more difficult to read.

QUESTIONS BY MR. SUGGS:

Q. Okay. And as of 2002, does this accurately characterize or describe the Zyprexa Product Team?

A. Well, again, at around that time, marketing moved into a separate marketing function. We did have a medical director, a single medical director at that time, Mauricio Tohen, and we had a chief operating officer.

Q. Who made the decision to move

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marketing over into a separate organization?
A. I don't know.
Q. As team leader of the Zyprexa Product Team between 1999 and 2002, were you responsible for both the medical and marketing aspects of the Zyprexa Product Team?
A. Yes, I was.
Q. Okay. And it's fair to say that there is at least a potential conflict of interest any time the medical and marketing functions are combined in the same team; is that correct?
A. I would not agree with that.
Q. Well, would you agree with me that the medical department's goal should only be to provide effective drugs that are safe for particular treatments and patients and to accurately and fairly inform doctors about both the risks and benefits of a drug?
THE WITNESS: Could you repeat your question?
MR. SUGGS: Could you read it back to him, please.

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(The Court Reporter read the requested material, as set forth herein:
"Q. Well, would you agree with me that the medical department's goal should only be to provide effective drugs that are safe for particular treatments and patients and to accurately and fairly inform doctors about both the risks and benefits of a drug?")
A. I would describe medical function as a scientific function. It was a function that was focused on answering important questions with high quality medical research, to analyze that information, to make it available. And so my description of medicine on the product team was both a medical, clinical, and scientific function.
Q. Okay. With the goal being to make sure that physicians had effective drugs that were safe, correct?
MR. BOISE: Object to the form.

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A. Would you repeat that?
Q. Sure. Wouldn't you agree that the goal of the medical department of a drug company should be to make sure that physicians -- well, to make sure that the products the company supplies to physicians are effective and that they're safe?
A. Yes, I would agree that that's an important responsibility of the medical function.
Q. And the medical department has the very important responsibility of making sure that the information which the drug company communicates to physicians is complete and accurate so that the doctors can weigh the risks and the benefits before they make the decision to prescribe a drug to one of their patients, correct?
A. I would agree with that.
Q. On the other hand, marketing people not being medically trained, are not qualified to assess either the efficacy or safety of a drug, correct?

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A. People in the marketing function have very different backgrounds, and there is a very distinct role and function between medical and marketing.
Q. And you would never have the marketing department determine whether a drug is effective or not, correct?
A. That's correct.
MR. BOISE: Let him finish his answer.
A. That's a medical responsibility.
Q. And you'd never have the marketing department determine whether a product is safe or not, correct?
A. That's correct.
Q. And you'd never have the marketing department determine what information should go to a physician to enable that physician to be fully and fairly informed so that he could make risk/benefit evaluations, correct?
A. The role of medical is to design --

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Q. Excuse me, you may have misunderstood me. I was talking about the marketing department.
A. I know.
Q. You would never want marketing to make the decision what information is marketed to physicians in order to provide them with sufficient information so that they could fairly and accurately assess the benefits and risks of a product and make the decision as to whether they were going to use that drug in their patients, correct?
A. The role of medical is to do high quality research and to make the scientific interpretation of what the data means. At that point, medical works with marketing to translate that science to the marketplace.
Q. Well, the marketplace for a prescription drug is to doctors, correct?
A. Doctors and patients.
Q. And doctors need scientific information, correct?

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A. When you complete a clinical trial, you may have volumes of data. Trying to hand over volumes of data is generally not very helpful to clinicians.
So the essence of the data is ascertained by medical, and it's at that point that medical will work with marketing in order to then translate or convey that information to the marketplace and, correct, the physicians and patients who use the medicines.
Q. Would you agree that marketing does not have the medical background to know what information is necessary and appropriate for prescribing physicians to have?
MR. BOISE: Object to the form.
A. Marketing has, as I think about it, two roles. The one hand, they are close to the marketplace, they're listening to physicians, they're doing research to determine what needs physicians and patients have. That's a very valuable and important

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service.
That then comes in to the medical component in terms of what are the critical questions that physicians and patients might have. So from that perspective they're an important conduit of information both into the company and out of the company.
Q. Sir, isn't it a concern that when you have medical and marketing people working closely together in a drug company, the medical people can get sucked into a spinning mentality to gain a competitive marketing advantage for the drug that their company is promoting?
MR. BOISE: Object to the form.
A. No.
MR. SUGGS: I'm going to hand you what's previously been marked as Plaintiff's Exhibit 9281.
(Whereupon, Plaintiff's Exhibit(s) 9281, previously marked, was presented to the

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witness.)
MR. SUGGS: For the record, Exhibit 9281 is an e-mail that Alan Breier wrote on February 6, 2004.
QUESTIONS BY MR. SUGGS:
Q. And do you recognize this e-mail, sir?
A. Just take a moment to refresh my recollection.
Q. Sure.
A. I see that, yes, I did write this. I'm familiar with it.
Q. I was confused when I saw this as to who this went to. It's addressed in the e-mail to U.S. underscore medical underscore medical U.S. Who was that or what group was that?
A. At a minimum, it would be medical personnel in the U.S. Quite frankly, I'm not sure if this would have gone outside of the U.S. or not based on just that header.
Q. And this would have been written by you some, what, 16 months or so after you'd taken over the position as chief

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medical officer?
A. That's correct.
Q. And how many people would have been in that U.S. medical group?
A. I'm not sure.
Q. Are we talking dozens or hundreds or thousands?
A. I would say hundreds.
Q. Okay. And I assume you gave careful thought to the language that's in this e-mail before you sent it out around to those hundreds of people; is that correct?
A. Yes.
Q. Okay. And in the middle of the first paragraph, pardon me, the middle of the first page, there's a paragraph that has a bolded title "Principles." Do you see that?
A. I do.
Q. And in that paragraph you stated, "Making medicine for people facing illness is a much different and higher calling than making consumer products for other markets. We do not sell soap. It therefore requires a different and higher

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code for conducting our business."
Do you see that language, sir?
A. I do.
Q. And I assume that no one ever came back and contradicted you about that; is that correct?
A. No.
Q. Okay. And if I could direct your attention to about the third line from the bottom, you state, "We are particularly challenged when it comes to presenting our data in a completely objective unbiased manner because of our passion for our molecules and the belief that spinning data is sometimes necessary to gain a competitive advantage. If we do not abandon the spinning mentality we will not restore confidence in our medical research and rebuild the public trust our industry has compromised."
Did I read that correctly?
A. You did.
Q. And the competitive advantage

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that you were referring to there would be a competitive advantage in the marketplace; is that correct?
A. Yes.
Q. Okay. And you clearly said that "If we do not abandon the spinning mentality we will not restore confidence on our medical research and rebuild the public trust our industry has compromised," correct?
MR. BOISE: Asked and answered.
A. That's correct.
Q. And "abandoned" refers to stopping something that was already being done, correct?
A. No.
Q. Would be what the word "abandon" means?
A. Leave behind.
Q. Okay. And when you talk about restoring confidence, you don't use that term "restore confidence" unless that confidence has already been compromised, correct?

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A. That's correct.
Q. And when you talk about rebuilding the public trust, you don't use that phrase "rebuilding" something unless that public trust has already been broken, correct?
MR. BOISE: Object to the form.
A. I would agree with that.
Q. Okay. I'd like you to refer back to Exhibit 9070.
THE WITNESS: Before we leave this particular item, could I provide a little more context for my remarks?
MR. SUGGS: No. Your attorney can ask you whatever questions I'm sure he has planned for this document. That will come at a later time. Right now I just need to ask my questions and you need to answer those questions, okay?
If I could direct your

attention back to Exhibit 9070.
That's the one, the Kellogg article.
And if I could direct your attention to Page 12.
QUESTIONS BY MR. SUGGS:
Q. In the first full paragraph on that page it's referring to product team responsibilities. And it states, third line from the bottom, "The team is also responsible for any new indications or any line extensions as well as the scientific content of the molecule."
By the way, when we use the term "molecule," that's synonymous with "drug," correct, or "drug product?"
A. Yes.
Q. Okay. So the language here says, "The team's also responsible for any new indications or any line extensions as well as the scientific content of the molecule. Said Baluch, quote, "You look at the label: How do you strengthen the label? How do you defend the label? That is the responsibility of the product team."

Do you see that language, sir?
A. I do.
Q. And was it fair to say that when you were head of the Zyprexa Product Team that you felt it was your -- that it was the responsibility of that team to defend the label?
A. If I could take a minute and read the context of these remarks.
Q. Well, regardless of the -- regardless of the document, sir, just put the document aside for a second. Let me ask you this question. When you were the head of the product team between 1999 and August of 2003, did you feel it was the responsibility of the product team under your leadership to defend the Zyprexa label?
A. No. Our responsibility was do the best science we could. Science that belonged in the label we would put in the label. And that was our responsibility in our labeling, was to get it right.
Q. Whose responsibility was it

to determine the content of the Zyprexa label? Was that the Zyprexa Product Team or was it some other entity?
MR. BOISE: Object to the form. You can answer.
A. The regulatory bodies determine the content of the label.
Q. Sir, who within Lilly determines the content of the label?
MR. BOISE: Object to the form.
A. Again, it's the regulatory bodies that determine that.
Q. Sir, Lilly drafts the labeling and then submits it to FDA for review, correct?
MR. BOISE: Object to the form.
A. That's one way that we work with the FDA on the label. We conduct science, science that we think might be important to the label to submit to FDA, but FDA ultimately determines what, for the U.S. label, what is in the label.

Q. And the law permits a drug company to include new language in the label without prior FDA approval as long as that language strengthens a safety information, correct?
MR. BOISE: Can you read that one back for me?
(The Court Reporter read the requested material, as set forth herein above.)
QUESTIONS BY MR. SUGGS:
Q. I should say, let me rephrase the question. The law permits a drug company to include new language in the label without prior FDA approval as long as that language strengthens safety information; is that correct, sir?
A. That's not correct as stated. A company can propose data, they can submit data for inclusion, but ultimately the FDA determines what stays and goes in the label.
Q. Ultimately, yes. But a drug company can change the label to strengthen safety information without prior FDA

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approval, submit that to the FDA, meanwhile, the label has been changed and can go out to physicians; isn't that correct?

MS. JOBES: Object to foundation.

MR. BOISE: Form and foundation.

A. Again, the FDA determines what's in the label. It's the pharmaceutical company's job to do the best science possible. Data that we think might be relevant to the label we submit to the label.

MR. FIBICH: Objection nonresponsive.

MR. BOISE: Let him finish his answer.

A. Ultimately, the FDA determines labeling.

Q. Are you familiar with the term "Changes Being Effected?"

A. Have to provide more context.

Q. Never heard of the Changes Being Effected label change?

THE WITNESS: Could you

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provide more context?

Q. That's something that's not familiar to you at all?

A. I hear those words, but if you could provide more context in terms of what your question is, I'd be pleased to answer it.

MR. SUGGS: Sir, I'm going to hand you what's been previously marked as Plaintiff's Exhibit 4858.

(Whereupon, Plaintiff's Exhibit(s) 4858, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a letter dated May 9, 2000, from Eli Lilly to FDA. And it states in the upper right-hand corner that it is a Special Supplement Changes Being Effected. Do you see that?

A. Yes.

Q. Do you recognize the term now?

A. In this context, yes.

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Q. And what this context is in May of 2000, Lilly on its own made a change to the Zyprexa label without prior FDA approval, submitted that label change to the FDA, correct?

MR. BOISE: Objection compound.

A. We submitted these changes to the FDA, correct.

Q. And in the meantime, the label was changed and distributed to practicing physicians, correct, in accordance with what you did on your own without prior FDA approval; isn't that correct?

A. Yes, but --

MR. BOISE: Objection to the form. Compound.

Q. I'm sorry, did you say "yes," sir?

A. This, I think, is a good example of the point that I was attempting to make. We submit things to the label. For example, diabetic coma is one of the items

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here that we submitted to the label that went into the label, was and is in the label today.

We submitted changes on neuroleptic malignant syndrome that was submitted, put into the label, and that's in the label today.

We also submitted laboratory values, Item No. 2, which is information on hyperglycemia that was put into the label but then it was taken out --

Q. We're going to go into that in great detail, sir, believe me.

MR. BOISE: Let him finish.

A. -- by the FDA. And the point I was attempting to make was that the FDA ultimately decides what goes in the label.

Q. And they did that five months later, right? Five months after you made that label change, the FDA came to you and said you have to take that out, right?

MR. BOISE: Object to form.

A. It was put in the label, the FDA reviewed the information, they asked us

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to remove it, we removed it.
Q. That was five months after you put it in the label, correct?
MR. BOISE: Object to the form.
A. I don't recall the exact time frame, but it was approximately in that time frame.
Q. In the meantime, the label had been changed and distributed to physicians including that information that was in that paragraph two there that you referred to, correct?
A. I believe that's the case.
MR. SUGGS: Okay. We've talked about the label or used the term "label." I'm going to show you one if I could find it here. Here we go. Have this document marked as Breier Exhibit 2.
(Whereupon, Deposition Exhibit(s) 2 duly received, marked and made a part of the record.)

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QUESTIONS BY MR. SUGGS:
Q. For the record, Breier Exhibit 2 is a copy of the Zyprexa label as it currently exists; is that correct?
A. I'm seeing a date on the back of 2006, so I would assume this is the case.
Q. I'll represent to you I downloaded this from the FDA web page a couple days ago. And this particular document is a 32-page document typed in normal size font, correct?
A. That's correct.
Q. This is sometimes also referred to as the package insert, correct?
A. Correct.
Q. Or the label, those terms are interchangeable, correct?
A. Yes.
Q. Okay. But when a physician gets a package insert, it doesn't look like this. It's not a 32-page document in normal size print, is it, sir?
A. They have access to this version. There's a package insert that also

Page 80

comes with the medicines itself.
Q. That's what I'm talking about. I'm talking about the package that Lilly distributes to physicians with the product. The actual package insert is not a 32 page 8 and-a-half by 11 document in full size normal font, is it, sir?
A. I don't understand your question.
Q. Does it look like this?
A. Information pertaining to the label is disseminated to physicians in many different formats.
Q. Sir, I'm asking about the package insert, the piece of paper that comes with the product, the package insert. Does the package insert look like this?
MR. BOISE: David, you just equated this as the package insert. There's some confusion. Which goes with the product I think is what you're asking.
QUESTIONS BY MR. SUGGS:
Q. The language which is in

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here, the language which is in Breier Exhibit 2 is the language that's in the package insert, correct?
A. Yes.
Q. Okay. The actual package insert doesn't look, it's not a 32-page, 8 and-a-half by 11 document in full size normal font, is it, sir?
A. No.
Q. It's several pages of very small print, correct?
A. Yes.
Q. Okay. And who is it that was -- who within Lilly was responsible for drafting this language contained in the package insert? Was that the responsibility of the Zyprexa Product Team or some other entity?
MR. BOISE: Object to the form.
A. Just to be clear, the ultimate responsibility of the label rests with the FDA.
MR. SUGGS: Move to strike as

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nonresponsive.
Q. Sir, please listen to my question. We've already agreed and you've already testified that Lilly first drafts labeling and submits it to FDA for review. That's a correct statement, isn't it, sir?
MR. BOISE: Object. Mischaracterizes what he did say.
A. We conduct research. Research that we believe belongs in the label we submit to the FDA. The FDA reviews that information and determines if it should be in the label. The FDA also has the ability and has access to other data that they could put into the label.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. Sir, Lilly, someone at Lilly, some group at Lilly or some individual at Lilly, physically drafts the language that is submitted to the FDA for review as the label for Zyprexa, correct?
MR. BOISE: Object to the

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form.
A. I can only repeat my answer. Data ultimately goes into the label that's determined by the FDA.
Q. Sir, please listen to my question. You're not being responsive at all, sir, that's very plain.
Somehow a piece of paper gets to the FDA that contains the language for the Zyprexa label that Eli Lilly has proposed. Would you agree with that concept?
A. I can't agree with that concept in total because it's not a complete appreciation of how the system works.
Q. Sir, let's just take this step-by-step, okay?
MR. BOISE: Let him finish.
Q. We'll talk about the various steps.
MR. BOISE: Not so argumentative, Dave.
MR. SUGGS: Well, he needs to respond to the questions, and we need to get straight about that.

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MR. BOISE: You don't need to raise your voice. You don't have to be disrespectful.
MR. SUGGS: Well, if he'd answer the question, we wouldn't be going that route. But let's just talk about the facts here, the physical facts.
MR. BOISE: I'd just ask you to be more respectful, Dave.
MR. SUGGS: Well, he needs to show respect for this process and answer the question.
MR. BOISE: I object to that.
MR. SUGGS: He's not showing respect for this process. He's not showing respect for the jury.
MR. BOISE: Let's take five minutes.
MR. SUGGS: No, let's not. I want an answer to this question.
MR. BOISE: No. Let's take five minutes.
MR. SUGGS: No, I'm not going

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to take five minutes now. I want an answer to this question.
MR. BOISE: After this question, we'll take five minutes.
QUESTIONS BY MR. SUGGS:
Q. Sir, does the FDA get a piece of paper from Lilly that contains Lilly's submission for proposed labeling? Yes or no?
A. I first need to indicate that I am respectful of this process, and you suggested that I was not, and that's not the case.
Point No. 2 is that to portray the labeling process as completely unilateral only coming from Lilly is not true because --
MR. SUGGS: Sir, you need to answer my question.
MR. BOISE: Let me finish.
MR. SUGGS: Counsel, would you please instruct him to answer the question.
MR. BOISE: We're going to take a five minute break.

MR. SUGGS: When you go on that break, would you please instruct him to answer the questions?

MR. BOISE: Let's take a five minute break, Dave.

THE VIDEOGRAPHER: This is the end of tape No. 1 of the deposition of Alan Breier.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: Back on the record, beginning of tape No. 2 of the deposition of Dr. Alan Breier; it's 11:06.

QUESTIONS BY MR. SUGGS:

Q. Dr. Breier, it is a correct statement that Lilly proposes labeling to the FDA which the FDA then reviews and either approves or rejects or sometimes there's a negotiation process going on between the FDA and Lilly as to the content of the label; is that a fair statement?

A. Yes.

Q. Okay. What person or group within Lilly is responsible for the content of the proposal that is made to FDA initially?

MR. BOISE: Object to the form. You can answer.

A. The draft language that we would submit for consideration at the FDA would be developed by medical and regulatory scientists primarily.

Q. And "medical," would those be the medical people within the Zyprexa Product Team or some other group of medical people?

A. They could include other medical people as well. It depends on exactly how the language works its way towards the draft. What I'm thinking about is we have a governance we call GPLC which will also review language prior to submission. Those would be individuals not on the Zyprexa Product Team, but scientists, physicians, statisticians.

Q. Who is initially responsible

for coming up with a draft of the -- by the way, let me back up for a second. The GPLC that you referred to is the Global Product Labeling Committee, correct?

A. That's correct.

Q. And that's composed of senior executives within the company?

A. It's composed of scientific experts, statisticians, epidemiologists, physicians.

Q. Well, the people actually on the committee are senior people, correct?

A. Not in every case. There are senior members on the committee. People are selected for that committee because of their scientific expertise.

Q. Okay. Would it be a fair description of the process as to how the labeling situation works within Lilly is that the medical group within the Zyprexa Product Team comes up with proposed labeling which is then submitted for review within the company by the Global Product Labeling Committee? Once that committee signs off on proposed

language, it then gets sent on to the regulatory people who then forward it on to FDA for review? Is that a fair description?

MR. BOISE: Object to the form.

A. That's one way that it can work.

Q. Was that generally the way it worked at Lilly?

MR. BOISE: Object to the form.

A. That's one way.

Q. Okay. What are the other ways?

A. The other way that language can appear in the label; is that your question?

Q. No. What's the other way that language for the label is generated within Lilly and submitted to FDA?

A. It may start with a regulatory scientist working with a statistician, it may start with an epidemiology group from pharmacovigilance

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looking at particular data, who then will engage perhaps physicians on the Zyprexa Product Team. It is a highly data driven process of assessment of data determining its veracity and validity and determining if it's the information that should reside in the label. And there are scientists on the Zyprexa Product Team that would be involved in that and there are also other scientists that would be involved as well.

Q. Is it fair to say the genesis of a product label change could occur from people in the Zyprexa Product Team or it could start with people in the regulatory side or perhaps even some other group within the company, but, ultimately, those changes or proposed changes get passed around within the Zyprexa Product Team and then get funneled up to the Global Product Labeling Committee for review?

MR. BOISE: Object to the form.

A. That's one way, yes.

Q. Okay. In instances where a

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label change is initiated by, let's say, pharmacovigilance or regulatory or someone else not in the Zyprexa Product Team, does the Zyprexa Product Team have a voice in what that content of that label change should be before it gets submitted to the Global Product Labeling Committee?

A. Typically, yes. The -- again, there are going to be multiple scientists involved, scientists from the Zyprexa Product Team. Depending on what data we're talking about, it might be pharmacovigilance or other scientific functions. Those scientists will work very closely together and through a process of sort of scientific assessment and inquiry a determination of the data that one's looking at is valid and clinically meaningful.

Q. Okay. And it would be fair to say that ultimately when labeling does go out with a product after it's been finally approved and it's out there in the marketplace, that doctors rely on the description of the drug in the package insert

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to make their decision about whether to prescribe the drug to their patients, correct?

MR. BOISE: Object to the form.

A. A doctor making a prescribing decision will look very carefully at the characteristics of his patient. He'll then determine the attributes, the safety and efficacy of the molecules that are available and then make a determination if that's the appropriate medicine for his or her patient.

Q. A doctor has to balance both the potential benefits of the drug and the potential risks of the drug, correct?

A. That's right. And then that gets married to the clinical profile of the patient.

Q. Okay. And one of the ways that the doctor obtains information about the potential benefits and the potential risks of the drug is with the package insert, the label that gets distributed by the drug company to physicians, correct?

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A. That's one way, correct.

Q. Okay. I've heard some people describe drug products by saying that the actual pill or the molecule is the hardware, but the labeling is the software for using the product. Have you ever used that phrase or description?

A. No.

Q. Okay. It would be fair to say, would it not, sir, that people on the Zyprexa Product Team were aware that if a warning was added to the label in the warning section that physicians in the marketplace would pick that up and may decide not to prescribe the drug because they would conclude that the risks outweigh the benefits. That was always a potential if something was added to the warnings, correct?

MR. BOISE: Object to the form.

A. I wouldn't think of that as data being added to the warnings or not. Ultimately it gets back to what you described before, which is the risk/benefit

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analysis and then the needs, the clinical needs of an individual patient. The data is accessed by physicians in multiple different ways.

Q. But one of the ways is from the label that they get from the drug company, correct?

A. That's one.

Q. Okay. And, sir, when you were head of the Zyprexa Product Team, were you aware that FDA regulations require that the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug and that a causal relationship need not have been proved? Were you aware of that, sir?

THE WITNESS: Could you repeat your question?

MR. SUGGS: Sure.

QUESTIONS BY MR. SUGGS:

Q. Were you aware, sir, back when you were the head of the Zyprexa Product Team that FDA regulations require that the

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labeling shall be revised to include a warning as soon as there's reasonable evidence of an association of a serious hazard with a drug and that a causal relationship need not have been proved?

THE WITNESS: Let me just understand. Are you describing criteria that would be used in order to determine where information would go in the label?

MR. SUGGS: No, sir. Well, in part. I'll represent to you, sir, that the FDA regulations do state that and require that the labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug, a causal relationship need not have been proved. I'll represent to you that's what the regulation states.

THE WITNESS: Um-hum.

QUESTIONS BY MR. SUGGS:

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Q. My question to you is, were you aware of that when you were head of the Zyprexa Product Team?

A. Yes.

Q. Okay. And in that context of that FDA regulation requirement, what did the term "association" mean to you when you were head of the Zyprexa Product Team?

MR. BOISE: Object to the form of the question.

A. Well, there's a number of different types of association. There's a temporal association, there's causal association. If we're talking about association that relates to labeling one must consider things like the consistency of the data, the strength of the data, the quality of the data.

So all of those factors are taken into account when determining information that should go into the label and then where in the label it belongs.

Q. Okay. You may have been responsive to this, but I'm not sure, so I want

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to probe this further.

A. Okay.

Q. In the context of that FDA regulation that I just talked about where the FDA does require the labeling shall be revised to include a warning as soon as there is, in the FDA regulations terms phrase, reasonable evidence of an association of a serious hazard, that's what the regulation says, what did "association" mean to you in that context?

MR. BOISE: Object to the form of the question.

THE WITNESS: And are we specifically talking about a warning? Is that what your question is?

MR. SUGGS: Yes.

A. Again, that would be -- a few of the things that would be very, very important would be the strength of the association, the quality of the data, the consistency of the data, if there is a causal relationship that would be important, the

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type of event we're talking about in terms of its gravity and seriousness.

So, again, multiple factors are considered when determining where one proposed to put something in the label.

Q. Okay. Would you agree, sir, that reasonable evidence of an association could include a statistically significant finding in a clinical study that an adverse reaction occurs more frequently with a particular drug as compared to placebo or some other control group?

MR. BOISE: Object to the form of the question.

Q. That that could constitute reasonable evidence of association?

MR. BOISE: Object to the form.

A. You, again, would kind of need to look at the exact phenomenon you're talking about, and one would look for quality, consistency, validity of the signal. It's a little difficult to talk about this in the abstract, but typically one study and one

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finding, if there's other data available that is perhaps contrary to that, one study would not suffice.

So one would need to look at the totality of the information in order to make their ultimate decisions.

Q. But you would agree that a finding of a statistically significant increased incidence of an adverse reaction in a clinical trial could constitute part of the evidence that would be assessed in making a determination as to whether there was reasonable evidence of an association, correct?

A. I can't agree with that statement as you just articulated because one would need to look at that particular clinical trial, the strength of the trial, the methodology, other data that might be available, mechanistic issues.

In other words, what I'm trying to indicate is that labeling is a very serious business. One needs to consider all of the relevant information, methodology,

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other data, et cetera, before one can make an informed labeling decision.

Q. Would you agree, sir, that results of a controlled clinical trial is often regarded as the gold standard of scientific evidence?

A. I would not agree with that statement as you articulated because each clinical trial is subject to its own strengths and weaknesses. And there are some clinical trials that provide certain sorts of proof or evidence, and other sort of clinical trials that don't.

So one would have to actually look at the clinical trial in question. We call it kind of looking under the hood, really understanding the methodology, the patient characteristics, all of those factors before one could make an informed decision on results from that trial.

MR. SUGGS: Okay. Let me show you what's been previously marked as Plaintiff's Exhibit 8562.

(Whereupon, Plaintiff's

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Exhibit(s) 8562, previously marked, was presented to the witness.)

MR. SUGGS: For the record this is a two-page -- take it back -- three-page document. It has a title at the top that says Zyprexa Business Processes.

QUESTIONS BY MR. SUGGS:

Q. Do you recognize this document, sir?

A. Let me take a moment to review it.

Q. Sure.

A. Okay.

Q. My question was, do you recognize the document?

A. I don't recognize this. Don't recall this specific document.

Q. Okay. I should note for the record also that when these documents are produced to us, Lilly also produces a computer database, and in some instances it shows a date, and in this particular instance, the

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Lilly-produced database shows that this document was dated August 27, 2001.
Sir, below that centered heading there's a side heading entitled "Zyprexa Key Decision Team." Do you see that?
A. Yes.
Q. Was there, in fact, a Zyprexa Key Decision Team in 2001 as noted in this document?
A. Yes.
Q. Okay. And does the document accurately describe the voting members of that key decision team?
A. I'm refreshing my memory from this document, but I must say that I don't recall specifically the voting members of this committee, but I accept what is on this piece of paper.
Q. Do you recall when the Zyprexa Key Decision Team was formed?
A. No.
Q. Do you know whether it was in place when you took over as head of the Zyprexa Product Team?

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A. I don't believe so.
Q. Okay. Did the Zyprexa product -- pardon me. Did the Zyprexa Key Decision Team exist within the Zyprexa Product Team during your tenure, pardon me, through August 2003 when you then moved on to be chief medical officer?
A. I don't recall.
Q. Okay. So the Zyprexa Key Decision Team did exist for some period of time within the Zyprexa Product Team, but you can't remember for sure exactly when it got started or how long it lasted; is that fair to say?
MR. BOISE: Object to the form.
A. That's correct.
Q. Okay. And the stated purpose, at least in this document, of the Zyprexa Key Decision Team is for efficient cross-representational critical decision making body for the Zyprexa Product Team. Did I read that correctly?
A. Yes.

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Q. And did that accurately state the purpose of the Zyprexa Key Decision Team?
A. My recall of this particular committee is not very sharp. I'm reading this and you're reading it appropriately, but I don't have a good firsthand recall of the intricacies of this particular team.
Q. Let me ask you with respect to the types of decisions. The document lists the types of decisions to be made by the Zyprexa Key Decision Team, and they included, again, according to the document, clinical study priorities, label changes/modifications, publication priorities, key issues management, key marketplace decisions, IPP final submission Zyprexa marketing plan. Did I read that correctly?
A. You did.
Q. And did that accurately describe the types of decisions that were made by the key decision team?
A. I'll have to answer it the same way as I did before: I'm not recalling

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this particular committee very sharply, but you're reading the document correctly.
Q. Okay. Do you have any reason to doubt that those were the types of decisions made by the Zyprexa Key Decision Team?
A. Well, I mean, I know how these kinds of decisions ultimately got made, and, I mean, I could speak to that.
Q. Okay. Well, the document indicates that down in the process section, the third paragraph within there, that "Decisions were made on the basis of a group vote. Alan Breier retains the right to make a final decision if he's opposed to the group vote."
Did that accurately reflect how decisions were made within that team?
A. I don't recall. It's very possible that this was a relatively short-lived committee and that could be why I'm not recalling it, but I don't have a recollection.

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Q. Independent of this team, and independent of this document, when you were head of the Zyprexa Product Team from 1999 through August of 2003, when key decisions needed to be made did you ask for people on your team to vote or did you make the decision and announce to the team what the decision was going to be?

MR. BOISE: Object to the form of the question.

A. There were certain areas that were my -- under my purview I would seek wide input on a variety of different issues depending on what the content was, and areas that I were responsible for I would make the ultimate decision.

Q. Okay. With respect to labeling changes -- before I get to that. One term I didn't understand in here back up in the types of decisions it says "IPP final submission"?

A. Um-hum.

Q. What does IPP stand for?

A. That is -- I believe that's the

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integrated product plan.

Q. Okay. Would that be like a marketing plan kind of thing?

A. I think, as I recall, it would be an annual plan that overviewed the activities of the team.

Q. Okay. With respect to label changes and modifications, how were decisions within the Zyprexa Product Team made about those? Were those by vote or was that something that you determined?

MR. BOISE: Object to the form of the question.

A. Those were not made by vote, let me assure you, those were made by very, very, careful analysis of data. That was a medical regulatory decision.

Q. Okay. Well, within the -- within the Zyprexa Product Team in conjunction with label changes, were you the one who made the decision to what the Zyprexa Product Team's decision was going to be with respect to a label change or modification?

MR. BOISE: Object to the

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form of the question.

A. Label changes were data driven. So the most accurate answer to your question is the data determined it.

Q. Well, would you agree with me, sir, that within a corporate organization, people are the ones that make decisions?

A. Yes.

Q. Okay. And you had a group of people that you were leading as the Zyprexa Product Team, correct?

A. That's correct.

Q. And when the Zyprexa Product Team came down with a position with respect to whether there should be a label change or whether there should not, what people or person within that Zyprexa Product Team made that decision that the position of the Zyprexa Product Team on this issue, on this labeling issue is X --

MR. BOISE: Object to the form.

Q. -- or Y?

MR. BOISE: I'm sorry, David.

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Object to the form of the question.

A. In analyzing data, a cross-functional approach would take place. A scientist, depending on what the data we would be considering, but scientists on the team, regulatory scientist, pharmacovigilance, it could be the job of those scientists to really ascertain the validity, the importance of data.

The actual decision to label or the process of labeling is dictated by federal rules of labeling. So there's not a decision process of saying that we label this or we label that, it's predicated on the data itself.

MR. SUGGS: Sir, move to strike your answer as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. I'm trying to understand how your team worked and who within your team made decisions and how such decisions were made within your team. And within your team with respect to labeling, who was it that made

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the determination as to whether or not a label change or modification would be proposed or recommended by the Zyprexa Product Team?

MR. BOISE: Object to the form.

A. Again, that would be a cross-functional group of scientists who were working with the data. If the analysis of the data indicated that this was something that warranted a label change and would change what we call our core label, we would then take that information to GPLC, the group we talked about earlier. GPLC would look at it, determine, yes, this should be added to core or no it shouldn't.

Q. Okay. Maybe I'm not being clear here or maybe I just need to explore this further.

Who within your Zyprexa Product Team made the decision as to whether or not a proposal would be made to the Global Product Labeling Committee to change or modify a label?

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MR. BOISE: Object to the form.

A. We generally made those decisions in a fairly cross-functional format. We had safety physicians on the team, we had other experts on the team who would be working with other scientists. They would then analyze data. If they felt this was something that should go to the team, I would be brought into the discussion. We would analyze and look at the data carefully, and then we would make a determination, yes, this is something that needs to go to GPLC, let's get on the GPLC agenda.

Q. Let me ask the question this way. You know how Harry Truman had a sign on his desk that said "The buck stops here?"

A. Yes.

Q. With respect to labeling decisions within the Zyprexa Product Team and whether a labeling change should be taken to the Global Product Labeling Committee for review, where did the buck stop in the Zyprexa Product Team for that type of decision?

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MR. BOISE: Object to the form.

A. On the Zyprexa Product Team, the buck would stop with me. That determination, again, would be predicated on a cross-functional group of scientists, content experts working on the data, and determining on the strength of the data we would then make a determination to go to GPLC.

Q. And would it be fair to say that while you were president -- pardon me -- while you were team leader of the Zyprexa Product Team, that you would have been aware of any proposal made by the product team to the Global Product Labeling Committee with respect to a label change?

A. Definitely.

Q. Okay. Would it also be fair to say that if a proposal was made by the product team to the Global Product Labeling Committee to change the Zyprexa label, not only would you have been aware of that proposal, but you would, in fact, have signed

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off on that proposal going to the Global Product Labeling Committee, correct?

A. I would be knowledgeable about it and I would endorse it going forward.

Q. Okay. And would it be fair to say that if something was taken to the Global Product Labeling Committee by your team, you would have wanted to make sure, in your own mind, that before that was done that the proposal was appropriate?

A. We would strive to get it right.

Q. Okay. And you would want to make sure that the basis for that proposal was well thought out and well analyzed before it was taken to the Global Product Labeling Committee, correct?

A. Ideally that is absolutely correct.

Q. Can you think of any -- As you sit here today, can you think of any instance where that did not occur?

MR. BOISE: What didn't

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occur?
Q. Okay. Well, I asked would you want to make sure that the basis for that proposal was well thought out and well analyzed before it was taken to the Global Product Labeling Committee, and you said "ideally that is absolutely correct."
My question to you is can you think of any instance where a proposal was made to the Global Product Labeling Committee about changing a label where you were not involved and where you had determined that this proposal was not well thought out and analyzed before it went to the Global Product Committee?
MR. BOISE: Object to the form. Compound.
THE WITNESS: Can you restate the question?
MR. SUGGS: I don't know if I can.
MR. BOISE: You want to restate it, rephrase it.
MR. SUGGS: Let me restate it.

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THE WITNESS: Yeah.
QUESTIONS BY MR. SUGGS:
Q. You said that before a proposal went from your product team to the global product committee, you would have determined that it was well-founded, correct?
MR. BOISE: Object to the form.
A. We would strive to do that, that's correct.
Q. Okay. Back to Exhibit 8562. It refers to, in the middle of the page --
THE WITNESS: I'm sorry, I'm not sure --
MR. SUGGS: That was this Zyprexa Key Decision Team.
THE WITNESS: Okay.
QUESTIONS BY MR. SUGGS:
Q. In about the middle of the page, it talks about other roles. And it refers to agenda development and outcome communication by Denice Torres and scheduling and minutes by Alice Finch. Do you see that?

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A. Yes.
Q. Was Denice Torres generally responsible for developing the agenda at those meetings?
A. Again, I don't have a sharp recollection of this particular committee.
Q. And who is Alice Finch? I don't know that I've heard her name before.
A. At this time, she was Denice Torres's administrative assistant.
Q. Okay. And it says here that Alice Finch was responsible for scheduling and minutes, correct?
A. Yes.
Q. And were there, in fact, minutes kept of meetings of the Zyprexa Key Decision Team?
A. I don't recall.
Q. Okay. If you wanted to find out whether minutes were kept, who would you go to to find that out?
A. Perhaps, Alice Finch.
Q. Okay. Sounds like a good start.

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MR. SUGGS: I'd like to go back in time, Dr. Breier, to November of 1999. And I want to hand you what's been previously marked as Plaintiff's Exhibit 8262.
(Whereupon, Plaintiff's Exhibit(s) 8262, previously marked, was presented to the witness.)
QUESTIONS BY MR. SUGGS:
Q. For the record, this is a string of e-mails. And the one I want to particularly focus your attention on is the one at the bottom of the first page which purports to be an e-mail from Alan Breier to a fairly lengthy list of people at Lilly, dated November 9, 1999, the subject being Executive steering committee for olanzapine-associated weight changes and hyperglycemia.
Do you see this document?
A. I do.
Q. And do you recall writing this on or about the date indicated?

A. Yes, I do.
Q. Okay. And did you also review this document recently?
A. Yes.
Q. How recently?
A. Within the last two weeks.
Q. Okay. Now, at this point in time in November of 1999, were you aware that the largest of Lilly's own clinical studies showed a statistically significant increased incidence of high blood glucose in Zyprexa users as compared to patients who received Haldol a conventional and much cheaper antipsychotic drug?
MR. BOISE: Object to the form of the question.
THE WITNESS: Would you indicate which study that you're referring to?
MR. SUGGS: HGAJ.
A. What HGAJ showed was an analysis of random glucoses. There was one data point in the acute trial that showed a difference. When that finding was followed

up with other time points in the acute trial and other time points in over a year period, it was found that elevations of glucose were not present and, therefore, the finding of an increase in glucose was not accepted as valid.
MR. SUGGS: Move to strike the nonresponsive portion.
Sir, I'm going to hand you what's been previously marked as Plaintiff's Exhibit 1605.
(Whereupon, Plaintiff's Exhibit(s) 1605, previously marked, was presented to the witness.)
MR. SUGGS: Which, for the record, is a computer printout from the HGAJ study dated June 19, 1995.
QUESTIONS BY MR. SUGGS:
Q. And if I could direct your attention in particular, sir, to Page 11. There is a reference on that page to glucose nonfasting?
A. Yes.

Q. And it indicates that -- by the way, in this HGAJ study, this was a study in which you had Zyprexa users and also patients who were using another drug called Haldol, correct?
A. That's correct.
Q. And Haldol was a first generation antipsychotic drug, correct?
A. Yes.
Q. Okay. And in this particular computer printout it shows that the Zyprexa users had a statistically significant increased incidence of high glucose, correct?
A. That's correct.
Q. And is it your testimony that you were, in fact, aware of this back in 1999?
A. I'm going to presume that I was.
Q. Okay.
A. Yes. So.
Q. This particular printout was generated in June of 1995, and you didn't come to the company until a couple of years later

and didn't assume the leadership of the Zyprexa Product Team until about four years later.
Do you recall how it was that you were familiar with this particular data?
MR. BOISE: Object to your math.
MR. SUGGS: Okay.
MR. BOISE: Or the form of the question as well.
A. I don't recall.
Q. Okay. But as you sit here today, you do, in fact, recall being aware that back in 1999 --
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. It's your testimony that you assume that you were aware back in 1999 of this data from the HGAJ study showing a statistically significant increased incidence of high glucose, correct?
A. As I stated before I'm presuming I did.

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Q. Okay. How -- and why is it that you were presuming that?
A. We're a very science-driven team. We looked at data a lot. We looked at signals. We had a process of continual iteration of data where a signal would pop up, we would reanalyze, we would look for better data. We would continually strive to understand what the studies were telling us. We did that with J, as well as other trials.
So I'm, again, I'm presuming that in the course of my activities, we probably reviewed this. And then as I was indicating before, went on to try to determine is this real or not, and through careful analysis determined that we did not feel this was a signal.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. When you referred in your answer to "J" did you mean that to be the HGAJ study?
A. Yes.

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Q. Do you also presume that the other members of the?
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. Do you also presume that the other medical members of the Zyprexa Product Team would have been familiar with the data from the HGAJ study, and in particular, this finding in June of 1995 that there was a statistically significant increased incidence of high glucose in the Zyprexa users?
MR. BOISE: 1999? The time period for that?
MR. SUGGS: Yes.
A. I can't speak for every physician or scientist on the team in terms of their knowledge of this particular finding because we had people working on, you know, vastly different themes. I would expect that scientists working, specifically, on this theme or on this particular trial would have been aware of it.
Q. Okay. Well, Dr. Beasley's already testified that he was aware of this

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information. Would you have expected other physicians, such as Dr. Baker and Dr. Kinon, to have been aware of it as well?
MR. BOISE: Object to the form of the question.
A. I can't speak for Kinon or Baker, they were not on the Zyprexa Product Team.
Q. Okay. Would you have expected Mauricio Tohen to have been aware of that?
MR. BOISE: In 1999?
MR. SUGGS: Well, whenever he came on the Zyprexa Product Team.
A. I, again, I can't speak for Mauricio Tohen. He was our bipolar expert. He tended to work and spend most of his focus on our bipolar program. I'm not sure.
Q. Okay. By November of 1999, were you also aware that there had been hundreds of adverse reaction reports relating to elevated blood glucose and diabetes-related events?
MR. BOISE: Object to the

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form of the question. Foundation.
A. I don't recall at that time the precise number, but I was aware that there were spontaneous adverse events of high glucose.
Q. And a large number of such reports?
MR. BOISE: Object to the form. Vague.
Q. Well, let me ask this. If, in fact, the evidence shows that as of September 1998 there were 200 adverse event reports tallied by Lilly relating to blood glucose elevations, would you have been aware of that?
A. Again, I'm not recalling the exact number. I was clearly aware that there were adverse events reported in the database. I just don't recall the number.
Q. And adverse events relating to blood glucose and diabetes?
A. Yes.
Q. Okay. And I'm assuming that you were aware in November of 1999 that Lilly

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was required to discuss hyperglycemia and diabetes in the special precautions and special warnings section of the European label for Zyprexa; is that correct?

THE WITNESS: I'm sorry, could you repeat the first part of your question, sir?

MR. SUGGS: Would you read it back to him, please.

(The Court Reporter read the requested material, as set forth herein above.)

A. Yes. We had a label change at that time on the topic that you're talking about in the European label.

Q. In fact, that had occurred in July of 1999; is that correct?

A. I believe it was July.

Q. Okay. And is it also fair to say that by November of 1999, Lilly's competitors were emphasizing the weight gain associated with Zyprexa and were at least claiming that that would put patients at greater risk for diabetes?

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MR. BOISE: Object to the form.

A. There was at that time what we refer to as counterdetailing where competitive companies will focus on potential side effects of competitor drugs.

Q. And do you recall that some of that counterdetailing, in fact, a large part of it by your competitors, was other drug companies pointing out to physicians the weight gain that was associated with Zyprexa and essentially telling doctors "if you use Zyprexa, your patients are going to be at risk for diabetes?"

MR. BOISE: Object to the form of the question.

A. I recall that there was counterdetailing on both weight gain and hyperglycemia.

Q. Okay. And, in fact, you do admit that Zyprexa can cause weight gain; is that correct?

A. It certainly can cause weight gain in some patients.

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Q. Okay. With that background in mind, let's go back to Exhibit 8262, which is your November 9, 1999, e-mail.

And can you describe, generally, the people to whom your e-mail is addressed?

A. Yes. They are all scientists at Eli Lilly and Company. Many of them are some of our top scientists across the organization. There are other scientists here who are what I would call specific content experts.

Q. Okay. And in your first paragraph, you state, you start off by saying, "Olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule." Correct?

A. That's correct.

Q. And Zyprexa was critically important to the financial success of Lilly, was it not?

A. It was an important molecule.

Q. And that was especially true

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in light of what the company referred to as Year X, correct?

MR. BOISE: Object to the form.

A. I don't think that it was predicated on Year X. It was -- it was an important molecule.

Q. Oh, it was important in its own right for sure, but the magnitude of its importance was going to become even more relevant in light of Year X that was coming along, correct?

MR. BOISE: Object to the form.

A. I didn't think about it that way.

Q. What was Year X, by the way?

A. Year X was a term that referred to the Prozac expiration.

Q. And it would be fair to say that at least in November of 1999, Lilly thought that the patent on Prozac was going to expire in a couple years in 2003, correct?

MR. BOISE: Object to the

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form. Foundation.
A. Sitting here today, I don't recall the exact expectation of the patent expiration at that time.
Q. Okay. Well, if I could direct your attention back to Exhibit 9070, in particular, page seven. At the bottom under the section "Shifting Priorities."
A. Yes.
Q. It states, "Although it was one of the most significant and profitable achievements in Lilly's history, the Prozac era came to an end when the company lost its patent for the drug in 2001. In August 2000 a U.S. court of appeals ruled that the company would have to cede its Prozac patent in 2001 rather than in late 2003, more than two years earlier than expected."
Do you see that language, sir?
A. I do.
Q. And does that refresh your recollection that Lilly had thought that the Prozac patent would go until late 2003?

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MR. BOISE: Object to the form.
A. No. Again, I recall and I'm aware that the Prozac patent expired in 2001, that we learned about it in 2000, but I don't recall what the previous expectation was.
Q. Okay. But even in 1999, the company knew that at some point the Prozac patent was going to expire in a relatively short period of time, but the company did not know when that was going to occur for sure, and that's why they referred to it as Year X; isn't that correct?
MR. BOISE: Object to the form.
A. Quite frankly, I don't know why it was referred to as Year X.
Q. Okay. If I could direct your attention back to Exhibit 8262, your November '99 e-mail.
A. Yes.
Q. After stating that Zyprexa-associated weight gain and hyperglycemia was a major threat, you went on

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to say, "In addition, it could be argued that Eli Lilly with its strengths in neuroscience, metabolism, endocrinology and diabetology is better positioned than any other institution to elucidate the mechanisms and develop treatments for this side effect."
Do you see that language, sir?
MR. BOISE: Object to the form. You misread it.
QUESTIONS BY MR. SUGGS:
Q. Do you see the language?
A. I see the sentence.
Q. Okay. And why was it that you thought that Eli Lilly could be better positioned than any other institution to elucidate the mechanisms and develop treatments for this side effect?
A. Well, again, I think here we're referring to weight gain, and our company has strengths in the areas that I articulate in that sentence, in endocrinology, metabolism, and neuroscience. So we had very deep expertise and, therefore,

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the potential to better understand this phenomenon, potentially, then to explore, examine, possible treatments.
Q. And, in fact, your company had for many decades had a large portion of its business the manufacture and sale of drugs designed to treat diabetes, correct?
A. We still do, yes.
Q. Still do. How many scientists would you say that the company has, just ballpark, who you would regard as experts in the field of diabetes?
A. I don't know.
Q. Are we talking, you know, a dozen or more like hundreds?
A. I don't know.
Q. Okay. When you have a question about the particulars of diabetes, is there someone that you go to on the diabetes side of the company as your source?
THE WITNESS: At what point in time?
MR. SUGGS: Let's say the 1999/2003 time period.

A. Again, one of the characteristics of Lilly and Lilly's scientific culture is that we're very cross-functional. So it was common for scientists from different disciplines to come together and discuss scientific issues.

Q. Well, was there any person or group of people in particular at Lilly that you would go to on questions relating to diabetes?

THE WITNESS: In '99?

MR. SUGGS: In that 1999 through 2003 period.

A. 2003. Well, I guess the best answer would be not a specific individual. Through the course of this actual steering committee activity, one of the results of that was to then have an endocrinologist assigned to the Zyprexa Product Team.

So, circa 2001, we had an endocrinologist who was assigned to the team. So that would be our first go-to person, who then was well connected to the other endocrinologists.

Prior to that person joining the team, there were other endocrinologists that we would consult with.

Q. Okay. The endocrinologist who joined your team, was that Dr. Margaret Sowell that you're referring to or someone else?

A. Margaret Sowell.

Q. And do you recall when she joined your team?

A. Again, I'm saying '01, around the '01 time frame.

Q. Do you remember beginning, middle, end?

A. No.

Q. But at least a year or more after your e-mail here, correct?

MR. BOISE: Object to the form.

A. I don't recall exactly when she joined. Again, it may well have been in 2000.

Q. Okay. On the second page of your e-mail you say, "We have formed a

cross-functional team" -- pardon me. "We have formed a cross-functional action team to meet these challenges." Who was the "we" who formed the team?

A. I'm not recalling precisely, but I'm going to venture that that was a cross-functional group of scientists that we, that the Zyprexa Product Team, probably brought together to work on this area.

Q. Was that at your instigation then?

A. I'm not recalling.

Q. Okay. And then you go on to say, "Success of this effort will contribute to securing the future of olanzapine and the financial health of our company and likely spur the development of next generation antipsychotic drugs, i.e., olanzapine without the weight gain and drugs for obesity."

Now when you said that "success of this effort will contribute to securing the future of olanzapine and the financial health of our company," do you recall what the sales of Zyprexa were at that

point in time in November of '99?

A. I don't recall.

Q. Were they in excess of 2 billion?

A. I don't recall.

Q. Do you recall what percentage of sales Zyprexa accounted for back at that time just roughly?

MR. BOISE: Object to the form.

A. I don't recall.

Q. Okay. It was a very large product, though, was it not, sir?

MR. BOISE: Object to the form.

A. It was a widely used medicine.

Q. Okay. And then later in your e-mail you refer to a meeting of this cross-functional team in a couple of weeks and state that "The purpose of the meeting was for the executive steering committee to review the ongoing work, future study plans, and resource needs, and to provide guidance

for the scope of future activities;" is that correct?

A. You read it correctly.

Q. And did the members of that executive steering committee that are listed there, which is composed of yourself and a number of others, did they stay involved in this process?

A. Yes. We had been working with a number of them before this and had a number of activities, scientific activities, going on.

The purpose of the steering committee was to update a broader group of what we were doing, get their input, and then suggestions for future directions. Because we had already had cross-functional interactions with some of the key people, we decided that we would continue on as we had before; in other words, I would take responsibility for bringing in key people at appropriate times as opposed to, say, having a biweekly meeting or something like that with these people on a formal basis.

So the spirit of that was continued on, but not as a regular meeting of those key individuals, although I took, again, responsibility to keep them informed and to continue to get their input.

Q. And when you described this situation at the beginning of your e-mail where "olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this greatly important molecule," for how long had that been regarded as a major threat within the company?

MR. BOISE: Object to the form of the question.

A. Well, the data on weight gain was in awareness from day one, so there was no question about that. As we went into the marketplace, it was very clear that this was a molecule that was having a very, very positive impact on this devastating illness, schizophrenia/bipolar.

There were at this time clinicians in the field asking more questions

about potential interventions for weight gain, et cetera. We reasoned if we were better able to understand it from a scientific perspective, offer more interventions, that would then allow more patients to take the medicine than were not being given the medicine because of the concerns around weight gain.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. For how long had weight gain and possible hyperglycemia been regarded by Lilly as a major threat to Zyprexa?

MR. BOISE: Object to the form of the question.

A. I'm going to have to answer it the same way I did before. We were very cognizant of weight gain from day one. It was very well described at that time, and those characteristics of weight gain did not change.

Q. Did you regard weight gain as a major threat to Zyprexa from day one?

MR. BOISE: Object to the form.

A. We acknowledged that weight gain was for some patients, particularly excessive weight gain, was an undesirable attribute of the drug.

Q. That's not my question. You used -- in your e-mail you describe olanzapine-associated weight gain and possible hyperglycemia as a major threat to the success of Zyprexa. My question is: For how long had you regarded that as a major threat?

A. And again, I'm putting the word "threat" into context, explaining it as those individuals who gained weight to an excessive amount, was a clear side effect of the drug.

MR. SUGGS: That's not my question, sir.

MR. BOISE: Just let him finish and then you can answer it.

QUESTIONS BY MR. SUGGS:

Q. You characterized that issue,

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the issue of weight gain and possible hyperglycemia, as a major threat to the success of Zyprexa. You're telling these people here you sent an e-mail out to "this is something you need to deal with."

My question is, for how long had you regarded this as a major threat? Was it just like the days before you wrote this e-mail or was it extending back from day one?

MR. BOISE: Object to the form of the question.

A. If I could answer in my entirety. From day one, it was clear that excessive weight gain could be experienced by some patients; that was undesirable. The reality is, as we talked about it earlier today, every prescription decision is a risk/benefit decision. The patient's illness, how severe it is, matching the attributes in the molecule.

For some patients, excessive weight gain was going to be a determinant that they not take the medicine. That then

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would impact on the overall use of the medicine, and that would end up impacting the overall profits for the company.

The mantra that we had on the Zyprexa Product Team regarding this was that if we serve patients better than anybody, we would have a very profitable business. If we could meet unmet medical need and have a very successful molecule, that also would translate into a profitable business. What was good for the patients was good for the company.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. When did Lilly regard olanzapine-associated weight gain and possible hyperglycemia as a major threat to the long-term success of Zyprexa? Did it start -- did that perception start with your writing of this memo in November of 1999 or did it begin at some earlier point?

MR. BOISE: Object to the form of the question, Dave, he's

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answered you.

MR. SUGGS: No, he's not.

A. If you would accept my characterization of excessive weight gain, my answer to your question would be day one.

Q. On the second page of your e-mail you refer to a meeting of the cross-functional team on November 23, 1999; is that correct?

THE WITNESS: I'm sorry, were you in the last paragraph?

MR. SUGGS: Yes.

A. Yes.

Q. And the very next day you wrote an e-mail to the top levels within the company about Zyprexa and its associated weight changes; do you recall that?

A. I don't recall that now.

MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 918.

(Whereupon, Plaintiff's Exhibit(s) 918, previously marked, was presented to the

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witness.)

MR. SUGGS: For the record, this is an e-mail from Alan Breier dated November 24, 1999, and addressed to Gerhard Mayr, Gino Santini Lorenzo Tallarigo, Albertus van den Bergh with copies to himself, John Lechleiter, Roland Powell and Gary Tollefson.

QUESTIONS BY MR. SUGGS:

Q. Do you recall writing this memo on or about November 24, 1999?

A. I do.

Q. And who were the recipients of your e-mail?

MR. BOISE: Just point of clarification, David. Did you intend for it to be a four-page document?

MR. SUGGS: I believe this is how it came to us.

MR. BOISE: I just asked you because there's another e-mail.

MR. SUGGS: I understand. Your database says this is the

document so --
MR. BOISE: I just asked you if that was your intent.
MR. SUGGS: It was yours.
MR. BOISE: I didn't ask you why it was or how it was, just whether it was.
MR. SUGGS: I figure it was better just to keep it together than ripping it apart.
QUESTIONS BY MR. SUGGS:
Q. Back to my question: Who were the recipients of this e-mail?
MR. BOISE: Yes, and just so the record's clear, Dave, I understand your point about how it was produced. Just so the record's clear, there are apparently two e-mails in these four pages. When you say "this e-mail" you're referring to the first e-mail in time.
MR. SUGGS: Correct.
QUESTIONS BY MR. SUGGS:

Q. Who were the recipients of your November 24, 1999, e-mail?
A. The addressees were leaders in sales marketing.
Q. Okay. You start off your e-mail by saying, "John asked me to overview the topic of olanzapine associated weight changes." You refer to that as OWC, correct?
A. Yes.
Q. Okay. And who was the John, was that John Lechleiter?
A. Yes.
Q. You go on to say, "I want to emphasize to you that OWC has been and continues to be a top priority for the Zyprexa Product Team. Although it is a significant issue for us, perhaps our only/major clinical Achilles heel, and our competitors have robustly focused on it reminiscent of anxiety" -- and something is blanked out -- "the fact is Zyprexa offers the best combination of efficacy and safety and ease of use of any available treatment for psychosis and acute mania."

Do you see that language,
sir?
A. Yes.
Q. And do you know what would have been X'd out there?
A. No.
Q. Okay. Would it be fair to say, sir, that Lilly always emphasized the efficacy of Zyprexa to outside physicians?
MR. BOISE: Object to the form of the question. Vague.
A. We emphasized the data. So that would be, that would include efficacy, safety, other important datasets associated with the molecule.
Q. Okay. When you say here in your e-mail that "the fact is Zyprexa offers the best combination of efficacy, safety, and ease of use of any available treatment for psychosis and acute mania," that was the position that Lilly was asserting in the marketplace, correct?
MR. BOISE: Object to the form of the question.

A. That was our interpretation of the data.
Q. So you were telling the marketplace Zyprexa is better than anything else in terms of efficacy, safety, and ease of use for the treatment of psychosis and acute mania, correct?
MR. BOISE: Object to the form of the question.
A. This isn't a message to the marketplace, this is an e-mail.
Q. I understand this is your e-mail to those people.
MR. BOISE: Just let him finish.
David, you're talking over each other so --
QUESTIONS BY MR. SUGGS:
Q. I understand this is your e-mail to those people and this isn't going out to the world. In fact, in your representations to the world about the qualities of Zyprexa, Lilly claimed that Zyprexa was the best combination of efficacy,

safety, and ease of use of any available treatment for psychosis and acute mania, correct?

MR. BOISE: Object to the form of the question.

A. That's not accurate.

Q. Is it your testimony that you did not say that?

MR. BOISE: Let him finish, Dave.

A. The communications to the external world were multiple datasets to a number of different communication channels, and I couldn't reduce it to a phrase that you articulated. The data were much varied, much more complex.

Q. Well, you state here, "the fact is Zyprexa offers the best combination of efficacy, safety, and ease of use of any available treatment for psychosis and acute mania." Are you telling us here that Lilly did not make that claim to physicians?

A. Our claims to physicians were data-driven claims. The data would require

kind of a multiple different kinds of presentation. This was a summation statement that I was making to these individuals on this particular e-mail.

Q. You go on to say, "The most critical immediate issue is to keep the focus where it belongs -- superior treatment and outcome -- an arena where we have no peer." Did I read that correctly?

A. You did.

Q. And, in fact, that was the position that Lilly was taking in the marketplace, was it not, that Zyprexa really had no peer in the treatment of schizophrenia?

MR. BOISE: Object to the form of the question.

A. At that particular point in time, the data was very, very, strong on efficacy. There were no other molecules that were demonstrating those very significant positive effects for acute mania and psychosis. I think that's a reasonable statement.

Q. And the company was claiming that Zyprexa was superior to anything else out there in the marketplace.

MR. BOISE: Object. Let me make my objection. Let him finish his question, he'll let you finish your answer, we'll all be happy.

A. I don't want to take words from here and suggest that those were the communications to the marketplace. These were my words to these individuals. Again, they were multiple different -- I'm sorry.

MR. BOISE: Were you finished?

A. No. There were multiple -- there was multiple datasets that were communicated to the external world, and those datasets tend to speak for themselves in terms of what they showed. Some of them were on efficacy, some of them were on safety, some of them were on how you use the molecule.

So I don't want to translate or make synonymous the words in this e-mail

to these individuals to the communications that went out on this molecule to the external world.

MR. FIBICH: Objection, nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. Are the words in this paragraph describing Zyprexa in the first paragraph, are they true and accurate?

MR. BOISE: Object to the form of the question.

A. Yes.

Q. Okay. Then I'd like to direct your attention to the next section of your e-mail. It's in the Market Research section. And you have a number of bulleted points below there, correct?

A. Um-hum.

Q. I'd like to direct your attention to the fifth one down refers to outliers.

A. Um-hum.

Q. And you have the word "outliers" in quotes. And what does the term

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"outlier" refer to?
A. I'll just read the full bullet.
What I'm assuming that refers to is that in most data distributions, there's a bell-shaped curve. The majority of patients are in the middle of the curve, and then there are two tails of a curve. And as you get further out, those people further away from the median or the mean are considered typically outliers.
Q. Okay. And you say in your e-mail here, "Outliers are the main concern for physicians; 20 pound increase is viewed as threshold for concern." And then you have in parentheses, "Fact: Two-thirds of olanzapine-treated patients gain less than 20 pounds."
Do I read that correctly?
A. You do.
Q. But it was also a fact that there were some patients who gained considerable amounts of weight from Zyprexa, correct?

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A. That's correct.
Q. In fact, some people gained as much as 80 pounds, correct?
A. Is that possible? Yes.
Q. Okay. Well, in fact, do you recall that Dr. Charles Beasley calculated that 1 to 2 percent of Zyprexa users would gain 90 or more pounds?
A. I'm not recalling that, that calculation.
Q. We'll go over that later. If I could direct your attention to the following bullet point that states: "Olanzapine is viewed to have more associated weight gain than risperidone, seroquel and traditional neuroleptics."
The term "neuroleptics" is another word for antipsychotic drug, correct?
A. It's generally reserved for the traditional or first-generation antipsychotic drugs.
Q. Okay. Such as Haldol and Thorazine and other drugs like that?
A. Yes.

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Q. And then in parenthesis state "Fact: The order of weight gain among antipsychotics is: Clozapine greater than olanzapine greater than seroquel greater than risperidone greater than traditional neuroleptics."
Did I read that correctly?
A. You did.
Q. Now clozapine is another second-generation antipsychotic, correct?
A. It is.
Q. In fact, it was the first second-generation antipsychotic, was it not?
A. You are correct.
Q. And the molecular structure of Zyprexa is similar to that of clozapine, correct?
MR. BOISE: Object to the form.
A. There are similarities and differences.
Q. Okay. By 1999, clozapine was often regarded as the gold standard for treatment of resistant schizophrenic

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patients; is that correct?
A. I think that's fair.
Q. However, clozapine had not much market share as compared to the other drugs because it also had some very serious side effects that were associated with it, correct?
A. It had significant side effects. It also had ease of use hurdles, if you will.
Q. And the ease of use hurdle, the main one was that doctors were advised in the labeling that they should be monitoring the blood of patients who were prescribed clozapine, correct?
MR. BOISE: Object to the form.
A. They were -- in my clinical view is there were two major hurdles: One was that clozapine required a very tedious and slow dose titration that sometimes would take weeks, maybe even months.
The other was a side effect called agranulocytosis, which means a drop in

white blood cells. And because of that drop in white blood cells, there was a requirement to blood monitor for the white blood cells.

Q. Okay. And, in fact, it was not just a recommendation, it was an actual requirement, was it not, that there be monitoring?

THE VIDEOGRAPHER: Excuse me.

MR. BOISE: There's a Blackberry renegade here.

A. You're correct.

Q. Okay. Directing your attention back to the e-mail. Olanzapine, that's referred to next in there in that chain or in that ordering of weight gain, olanzapine is just another name for Zyprexa, correct?

A. That's correct.

Q. And then Seroquel was another antipsychotic, second-generation, correct?

A. Yes.

Q. And risperidone was another one as well, correct?

A. Yes.

Q. And this ordering of weight gain where you say that the weight gain with clozapine is more than Zyprexa which is more than Seroquel which is more than risperidone which is more than traditional neuroleptics, was that based on research that Lilly had done?

MR. BOISE: Object to the form.

A. It was based on many different lines of evidence, some of what Lilly did, other investigators.

Q. Okay. But it's fair to say when you talk about -- when this is in the market research section of your e-mail, was that market research that was coming back and telling you that was the ordering of weight gain or was it actual clinical scientific research?

A. The first part of the bullet --

Q. No, the ordering --

A. I know.

MR. BOISE: I think he's trying to answer.

A. The first part of the bullet is the market research, the second part of the bullet that begins with "fact" is what we know about the data.

Q. Okay. And so the first part was the market research telling you that olanzapine was viewed by physicians to have more associated weight gain than risperidone, Seroquel and traditional neuroleptics and the fact was that that was true?

A. Correct. So those clinical observations that were captured in the market research was compatible or consistent with the known literature.

Q. If I could direct your attention to the third bullet point from the bottom in that market research section. You state, "Physicians view EPS as something they can address with dose adjustment but not OWC."

Need to get some translation here.

A. Okay.

Q. EPS stand for extrapyramidal symptoms?

A. Extrapyramidal, yes.

Q. Okay. Can you tell the jury what extrapyramidal symptoms are?

A. Yes. Extrapyramidal symptoms are involuntary movements that are produced by the traditional neuroleptic drugs, and it was considered one of the, let's call it the scourges of traditional neuroleptic drugs.

The atypical antipsychotic drugs tended not to be associated with extrapyramidal symptoms, and that was considered to be a very significant breakthrough.

Q. Okay. The OWC that's referenced in that bullet point is the olanzapine weight change, correct?

A. Yes.

Q. Okay. So what you were saying there, if I can do the translation, was the physicians were viewing extrapyramidal symptoms as something that they could address with dose adjustment by

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either decreasing it or increasing it or whatever, but that they couldn't adjust the dose to deal with olanzapine weight change? Is that a fair restatement?

A. Yes.

Q. Okay. And then in parentheses you say, "Fact: OWC is not dose dependent." Correct?

A. You've read that correctly.

Q. So the fact was the same as the perception, correct?

A. Yes.

Q. Okay. Then you also note that physicians, in the following bullet point that "Physicians want more data." I'm assuming that was based on market research, correct?

A. Yes. Each one of the bullets under this section of market research would have been data brought into the company through surveys of physicians from the market research department.

Q. Okay. And then in your next bullet point you say, "Blanket detailing will

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be damaging since many physicians do not see OWC as an issue."

Did I read that correctly?

A. You did.

Q. We need some more translation there. Blanket detailing refers to going out and having your sales reps -- well, let me back up for a second.

We need to talk about detailing. In the pharmaceutical business, the process of a sales representative calling on physicians and discussing the product with the physician is often referred to as detailing, correct?

A. That's correct.

Q. Okay. In fact, sales representatives used to be referred to as detailmen, correct?

A. I'm not familiar with that term, but that's consistent with what you said.

Q. Okay. So when you're talking about blanket detailing here, what you're talking about, that phrase would mean having

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sales representatives from Lilly go out and talk to all physicians about a particular issue, correct?

MR. BOISE: Object to the form.

A. No. What this phrase means is having a unidimensional message. In other words, as opposed to presenting all relevant data or important relevant data would be to have a single isolated message.

Q. And what you say here is blanket detailing will be damaging since many physicians do not see olanzapine weight change as an issue, correct?

A. That's what it says.

Q. Okay. And how was it determined that many physicians do not see olanzapine weight change as an issue, do you know?

A. Well, again, this is market research, this isn't Lilly's opinion. This is the information coming into the company from prescribing physicians. What I interpret this to mean is to say that

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physicians that were in the survey, some of them were saying I'm interested in different information in a detail call. I'm not seeing weight gain as a problem in my patients, but I've got questions about other things. So, don't give me a single message detail, but give me the information that's important to me.

I think each physician has, at various times, different questions and different needs for data, and that's what I interpret this bullet point to be referring to.

Q. Okay.

MR. SUGGS: I've been told that we have about five minutes left on this tape and it's now 12:30. You want to break for lunch?

MR. BOISE: Yeah.

THE VIDEOGRAPHER: Marks the end of tape two of the deposition of Alan Breier. We're off the record at 12:27.

(A lunch recess was taken by the

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parties at this time.)

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AFTERNOON SESSION

THE VIDEOGRAPHER: Back on the record. This is the beginning of tape No. 2 of the deposition of Dr. Alan Breier.

QUESTIONS BY MR. SUGGS:

Q. Dr. Breier, we're back from our lunch break, and just to refresh your recollection of where we were time wise, the last thing we were talking about, the last exhibit we were talking about was your November 24, 1999, e-mail to Gerhard Mayr and a number of other folks regarding olanzapine weight change.

Sir, do you recall that within a couple of months after that e-mail, the Zyprexa Product Team and Pharmacovigilance at Lilly recommended a label change that was triggered by an analysis showing that Zyprexa users had a three and-a-half times higher incidence of treatment-emergent hyperglycemia?

MR. BOISE: Object to the form.

A. I'm familiar with the analysis that you're speaking about.

Q. Okay. And we've talked before about the product team. Can you tell the jury with the Pharmacovigilance group is at Lilly?

A. Pharmacovigilance is our global product safety organization.

Q. And what is their purpose?

A. They have more than one, but a primary purpose is to survey the environment generally in the post-launch phase for adverse event.

Q. Okay.

A. They also do epidemiological studies and other kinds of data analysis and such.

Q. And would they also look at continuing data coming in to the company from its own clinical studies?

A. Yes.

Q. And, in fact, before Zyprexa went on the market, it conducted a number of clinical studies and submitted that data to

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the FDA in order to obtain approval to market the drug here in the U.S., correct?

A. That's correct.

Q. And am I correct that some of those studies were ongoing studies, in other words, that continued after the data was submitted to the FDA originally back in '95?

A. There were studies in the original clinical program that had a continuation phase, so that particularly for patients who were getting a good response could stay on the drug and more observational data could be gleaned. I don't recall if those studies continued on past the point you're talking about or not.

Q. Okay. But we also know from your prior testimony that even after 1996, when Zyprexa was approved for marketing in the U.S., that Lilly began, initiated clinical studies after that point in time?

A. Oh, most definitely.

Q. Okay. And all the data that came in from those studies -- well, let me ask you this: In each of the studies that

you did, were there measures of random blood glucose taken, to your recollection?
A. It was common to collect random glucoses in our clinical trials.
Q. Okay. Did you give any consideration to using fasting glucose in the clinical trials?
A. Yes.
Q. Okay. But ultimately, that was not done, was it?
MR. BOISE: Object to the form.
A. Yes.
Q. I'm not sure the record is clear. Was the fasting blood glucose done in any studies or was there just random blood glucose testing done?
MR. BOISE: Object to the form.
A. We -- just from a historical perspective, the majority of earlier trials used randoms. At a certain point in time we began to collect fastings and then exclusively fastings. And I don't recall

exactly when that time point was.
Q. Can you give me an approximation of when that transition took place?
A. It was the early 2000s, 2000/2001, somewhere in there.
Q. Okay. And I assume that your pharmacovigilance department that's responsible for monitoring the safety of drugs, they would have had access to the data from the clinical trials, correct?
A. Yes.
Q. Okay. And they would have also had access, obviously, to scientific information that was published in the medical literature, correct?
A. Yes.
Q. And it was their duty and responsibility to monitor that published scientific literature, correct?
MR. BOISE: Object to the form.
A. That was one of the things that they did.
Q. Okay. If, in fact, there were published scientific articles pointing to a possible association between the use of Zyprexa and the development of diabetes or hyperglycemia, you would have expected your pharmacovigilance people to have known about that published literature, correct?
A. The scientists at Eli Lilly, I would say pharmacovigilance scientist working on Zyprexa, as well as the Zyprexa scientists, would very much likely have been aware of published reports on a whole host of safety issues, potential safety issues.
Q. In fact, scientific reports like that are searchable by computer and were back in the '90s as well, correct?
MR. BOISE: Object to the form.
A. I think it would be fair to say that the majority of peer-reviewed publications would be available in certain search functions.
Q. Okay. And you would expect your pharmacovigilance people to make such

searches and to monitor the development of the scientific literature regarding the safety of Zyprexa; isn't that correct?
MR. BOISE: Object to the form.
A. Again, we as a scientific group followed the published literature of Zyprexa. So my expectation would be that important articles that were published about Zyprexa would be something that we would have most likely been aware of.
Q. And if there were important published medical articles regarding the safety of Zyprexa, Lilly is obligated to not only be aware of those, but also to disseminate that information to physicians, correct?
MR. BOISE: Object to the form of the question.
A. In terms of data that would be disseminated to physicians, it would be important that the data be solid, strong methodologically and convey clinically important information.

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And if we felt that there was important clinical information that could help physicians better understand the use of our drug, that would be the kind of information that we would be inclined to include in things like slide sets and things of that nature.

Q. And, in fact, it's not just a matter of whether you're inclined to provide that information, did you understand that Lilly had a duty to warn physicians of scientific information relevant to the safety of Zyprexa that was published in the scientific literature?

MR. BOISE: Object to the form of the question.

A. We had a duty to understand the safety profile of our molecule, to examine data, no matter what source it came from, our own trials or someone else's. And if we found important and scientifically meaningful safety information, we would include that in the communication of the profile of the drug.

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Q. Okay.

MR. FIBICH: Objection, nonresponsive.

MR. SUGGS: Let me hand you what's been previously marked as Plaintiff's Exhibit 990.

(Whereupon, Plaintiff's Exhibit(s) 990, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a multi-page document, the first page of which has a big bold heading at the top which says Attachment E and then attaches an Olanzapine Labeling Change and Hyperglycemia for the February 21, 2000, GPLC meeting.

QUESTIONS BY MR. SUGGS:

Q. Do you recognize this document, Dr. Breier?

A. I've seen it before.

Q. And when was the most recent time you saw it?

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A. I would say within the last month.

Q. In preparation for this deposition?

MR. BOISE: Don't answer that question.

Q. Did you go back to your files to see this within the last month?

A. No.

Q. Did someone else show it to you?

A. Yes.

Q. Okay. Do you know what this is an attachment to?

A. No.

Q. I'll represent, do you know who Michele Sharp is?

A. Yes.

Q. She's in the Regulatory Affairs department, correct?

MR. BOISE: Was. Object to form.

A. I believe she was at this time.

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Q. Okay. And she was part of your Zyprexa Product Team, was she not?

A. She had had in her regulatory role responsibilities for Zyprexa.

Q. Okay. I'll represent to you that she's testified in her deposition that this particular document, Exhibit 990, was an attachment to the agenda for the February 21, 2000 GPLC meeting. If, in fact, I'm correct as to her testimony, do you have any basis to dispute that?

MR. BOISE: Whether you're correct or not?

Q. Do you have any basis to dispute that this was an attachment to the agenda for the February 21, 2000 Global Products Labeling Committee meeting?

A. I don't know.

Q. Did you go to that meeting, by the way?

A. No.

Q. If you can turn to the second page -- every page of this document is stamped "confidential" at the top, correct?

A. Yes.
Q. And it says below the confidential stamp in big capitalized letters "Do Not Forward - To be distributed only by Global Operations Labeling Department, Indianapolis," correct?
A. Yes.
Q. Okay. And is this document from Page 2 on, is this a standard form for proposing a label change at Lilly?
A. Quite frankly, this does not look like the forms that I'm most familiar with. My experience with GPLC, particularly over the past three or so years, has been to have much more extensive information on submissions to GPLC, where the actual raw data is presented and much more depth than at least what I'm seeing here.
Q. Okay. But as you said, that has been your experience over the past three or so years, and this document actually dates back now, seven years, correct?
A. That's correct.
Q. Okay. If I could direct your

attention to the top of the page, there's a box that has the title "Proposal of the Product Team and PhV." Do you see that?
A. Yes.
Q. And the product team in this case would be Zyprexa, correct?
A. That's correct.
Q. And PhV stands for pharmacovigilance, correct?
A. I believe that's correct.
Q. And as we said before, you were the head of the product team, correct?
A. Yes.
Q. And your prior testimony was that you would have reviewed and approved any proposed label change that was submitted to the Global Product Labeling Committee; is that correct?
MR. BOISE: Object to the form of the question. Mischaracterizes prior testimony.
THE WITNESS: Would you repeat the question?
MR. SUGGS: Can you read it back, please?
Well, let me withdraw it.
QUESTIONS BY MR. SUGGS:
Q. Directing your attention within that box, it's the "Proposal of the Product Team and PhV,' do you see where there's a description of a new statement to be made?
A. Yes.
Q. Okay. We've had prior tes -- there's a little box that appears in that sentence that kind of makes it hard to understand what that sentence says, but we've had prior testimony that that sentence there should read random glucose greater than or equal to 160 milligrams per deciliter in patients with baseline random glucose less than or equal to 140 milligrams per deciliter has been occasionally seen in clinical trials.
Do you see that language, sir?
MR. BOISE: Object to what you said.

MR. SUGGS: Did I misstate the prior testimony?
MR. BOISE: Well, you confused two points. The record would seem as though you just read it literally. What you're saying is you plugged in those less than and greater thans to where the boxes are.
MR. SUGGS: Yeah, because we had prior testimony from Dr. Kinon and Dr. Kwong that that's --
MR. BOISE: I'm not quibbling with that. I'm just saying the way the question read is as you were reading it literally.
Q. Okay. Doctor, just so there's no confusion, we've had prior testimony that those boxes mean greater than or equal to or less than or equal to as I stated in the way I read the sentence. Will you accept that representation?
A. I prefer not to. I'll accept the sentence with the boxes, but I, quite

frankly --
Q. Okay, then what do the boxes mean?
A. I don't know.
Q. Okay. And you won't accept my representation as to what Michele Sharp said those boxes mean?
A. I guess I have to defer to my counsel. I don't know.
MR. BOISE: If you're going to represent that that's what they said and he should assume that as part of his answer without accepting the baseline assumption, accepting your representation, then you can answer the question.
A. Then I accept that.
Q. Okay. And were you aware that that proposal was being made back in February of 2000?
A. I don't recall this specific proposal back in 2000.
Q. Okay. Not at all. Okay. Would it be fair to say

that the way -- we talked earlier about the process by which proposals for labeling changes were made through the Zyprexa Product Team for submission to the Global Product Labeling Committee. Do you recall our earlier discussion this morning about that?
A. I do.
Q. Okay. And it's your testimony that you don't have any specific recollection of this proposal; is that correct?
A. That's correct. Proposal from the 2000 time frame.
Q. Okay. And would you agree that it would be fair to say that the procedures that you discussed this morning would apply to this particular submission?
MR. BOISE: Object to the form.
A. I don't recall this specific submission, so it's difficult for me to go beyond that in my answer.
Q. Nothing stands out in your mind that would say that the procedure that went through, this submission went through, was somehow out of the ordinary or treated differently than other situations from your team; is that correct?
A. Since I don't recall the submission, I can't attest to the process.
Q. Okay.
A. Excuse me. I can attest to an overall process by which we work with data like this, I just can't attest to this specific analysis.
Q. And we already talked about that general process earlier this morning, correct?
MR. BOISE: Object to the form.
A. And the general process that I was referring to was a iterative process, a series of analyses, sort of an evolution of looking at data, making sure it's correct, rechecking it, looking at it again, et cetera, until we're satisfied we have it right.
Q. If I could direct your

attention to the middle box on the first page, it says "How has that proposal arisen?" It states, "Recent review of random glucose levels of patients in olanzapine clinical trials revealed that the incidence of treatment emergent hyperglycemia in olanzapine group, 3.6 percent, was higher than that in the placebo group, 1.05 percent."
Do you see that language?
A. I do.
Q. And the phrase "treatment-emergent hyperglycemia" refers to hyperglycemia occurring during the context or after a person's been exposed to the drug in a clinical trial; is that correct?
A. I would characterize it as data coming from a clinical trial.
Q. And these would be in people who did not have hyperglycemia before they started taking the drug, correct?
A. I don't know that that's the case.
Q. Well, then, what does the

phrase "treatment emergent" mean?
A. "Treatment emergent" is a term that's used for an event that crosses a certain threshold. It doesn't refer to what the baseline was or the starting point.
Q. Well, doesn't the phrase "treatment emergent" indicate that the situation emerged during treatment?
A. Yes. But the reality of glucose, particularly random glucoses, is there's a lot of up and down. It's very possible that someone could have a high level at one point, say, a baseline, a low level later, a high level later on. So there's quite a bit of fluctuation with glucose.
So if you crossed a certain threshold at a certain point in time in a clinical trial, that would be considered a treatment-emergent event.
Q. Well, doesn't, in fact, the new statement that was proposed indicate that these were people whose random glucose was higher after they were treated than before they were treated?

A. Well, what this -- in this particular instance, what it indicates was that the random glucoses at baseline were, say, 140, and then the event was captured at some point around 160.
Q. So their baseline blood glucose level was lower at the beginning than it was after they took the drug, correct?
A. On this one measure. But what I was trying to convey with random glucose --
Q. I'm sorry, what one measure?
A. With this one blood measure at baseline that would indicate that they were below 140 but the day before they could have been at 160.
So what I'm saying and trying to indicate is that particularly with random glucoses, there's a tremendous amount of variability. And I don't think that the baseline starting point for a definition of a treatment-emergent event is necessarily the critical component.
Q. Well, apparently, though, your product team and pharmacovigilance group thought this finding of treatment-emergent hyperglycemia in the olanzapine group warranted a revision to the label, correct?
A. I don't know all or who was involved in this particular analysis because, as I noted before, I don't have recollection of it, but whoever put this table together suggested that it go into the label.
Q. Well, we know that at least according to the first page of the document this was the proposal of the product team, correct?
A. That's what it says, and Pharmacovigilance.
Q. And Pharmacovigilance.
Now, when they refer to the treatment-emergent hyperglycemia in the olanzapine group being 3.6 percent and that the incidence of a placebo group was 1.05 percent, the rate of treatment-emergent hyperglycemia in the Zyprexa group was three and-a-half times higher than in the placebo group, correct?

A. I would agree that 3.6 percent is three and-a-half times greater than 1.05 percent.
Q. And it's your testimony that you have no recollection of this submission being made to the Global Product Labeling Committee?
MR. BOISE: Objection. Asked and answered.
A. During the 2000 time frame, I do not have a recollection of this analysis or this document.
Q. Sir, in your November -- by the way, this label change was never made with this language, was it, sir?
A. I can attest that these data did not go into the label because we learned that these data were not reflective of the random glucose situation of this dataset.
MR. SUGGS: Objection, nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Your labeling never advised physicians of the proposal that was made

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here, correct? Yes or no?
A. We did not advise clinicians of this particular finding because additional analyses were conducted that were more valid and clinically meaningful than these analyses, and it was the correct analyses that we submitted to the FDA and shared with clinicians.
MR. SUGGS: Sir, you're giving me spin which I'm going to move to strike as nonresponsive. I need a yes or no answer.
MR. BOISE: I object to your characterization, sir.
MR. SUGGS: I need a yes or no answer.
QUESTIONS BY MR. SUGGS:
Q. Did your company advise prescribing physicians with the language that was proposed there, yes or no?
MR. BOISE: Object to the form of the question. Asked and answered.
THE WITNESS: I want to be

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very clear --
MR. SUGGS: Then say yes or no, sir.
THE WITNESS: I am not spinning any data during this proceedings nor have I at any other point.
QUESTIONS BY MR. SUGGS:
Q. Sir, can you give me a yes or no answer? Did the company tell doctors what was proposed in this label change or not? It's a simple yes or no question.
MR. BOISE: And he's answered your question.
MR. SUGGS: No, he has not. He has not.
I want a simple yes or no answer.
MR. BOISE: The record will reflect that he has answered it.
A. We don't share inaccurate data with clinicians.
Q. Sir, did you or did you not tell physicians of that label change that was proposed there by the product team and pharmacovigilance, yes or no?
MR. BOISE: Objection, asked and answered.
A. We do not share inaccurate data with clinicians.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. Sir, did you tell physicians at any time that analysis of clinical trial data from Lilly's own studies showed that the existence of treatment-emergent hyperglycemia was three and-a-half times higher than in the placebo group?
MR. BOISE: Object to the form of the question.
Q. Yes or no?
A. We did not.
Q. Thank you.
By the way, these clinical trials that are referred to there in that middle section where it says "a recent review of random glucose levels of patients in

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olanzapine clinical trials revealed that the incidence of treatment-emergent hyperglycemia was three and-a-half times higher than in the placebo group," what clinical trials were those, do you know?
MR. BOISE: Object to the form.
A. Again, I don't recall this specific analysis. My presumption would be that it would have well likely come from the integrated clinical trial dataset, which is a compilation of multiple trials.
Q. And do you know who did the analysis?
A. No.
Q. Do you know when they did the analysis?
A. This particular analysis?
Q. Yes.
A. Presumably the analysis were done prior to 2/21/2000.
Q. Do you know how they did the analysis?

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A. You mean in terms of what statistical tests were used?
Q. Yes.
A. No. In fact, I don't know if this was a statistically significant difference.
Q. But you're prepared to say under oath as you did previously that you think that this analysis is wrong and incorrect, even though you don't know who did it. When they did it, or how they did it, it's wrong?
MR. BOISE: Object to the form of the question.
A. Let me give you the answer how I know that. Because what I do know is that additional analyses were done on this very same dataset. That a more thorough analysis was done with more appropriate random glucose cutoffs. The analysis were looked at in several different ways, both continuous and temporary. Those analyses were done very, very, thoroughly. They were taken to GPLC. They were proved. And those

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were the data that we know are valid.
Q. Oh, we're going to talk some more about that data, sir. Let's get back to this proposal here.
You said you did not attend that meeting. Was it your custom not to attend Global Product Labeling Committee meetings?
MR. BOISE: In 2000?
MR. SUGGS: In 2000.
A. I, typically, did not intend.
Q. Were you informed that after that Global Product Labeling Committee meeting that someone on that committee let your -- by the way, Dr. Tollefson was your boss at that time, was he not?
A. 2000? I believe so.
Q. Okay. Were you informed that after that Global Product Labeling Committee meeting, someone on that committee let your boss, Dr. Tollefson, know that they were concerned about this analysis which found a three and-a-half times higher incidence of treatment-emergent hyperglycemia?

MR. BOISE: Object to the form. Foundation. Vague.
A. I'm not aware of that.
Q. Dr. Tollefson said that he couldn't recall who it was that complained about that analysis. Were you aware of anyone on the Global Product Labeling Committee complaining about the analysis?
A. No.
Q. If I could direct your attention to the third physical page or, actually, Page 4 numbered in the bottom right-hand corner. There's a reference to literature reports in the second box down from the top.
A. Yes.
Q. And in the second paragraph in that box there's a reference to a Dr. Daniel Casey that states, "Daniel Casey from Oregon presented in a seminar at Lilly at the end of 1999."
Did you know Dr. Casey?
A. Yes.
Q. Do you still interact with

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him?
A. I've not seen Dr. Casey for a few years.
Q. Okay. And was Dr. Casey a consultant to Lilly back in 1999 and 2000?
A. Yes.
Q. In fact, he'd been a consultant to Lilly going back at least as far as 1995; isn't that correct?
A. I'm not certain about that far back but it wouldn't surprise me if he was.
Q. He was a consultant to Lilly before you came to the company, correct?
A. Again, I don't know what his involvement with the company was prior to me coming to the company, but I do know that he was a consultant during the period that I was in the company.
Q. And is he still consulting for the company?
A. I don't believe so.
Q. Do you know when he stopped?
A. No.

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Q. Okay. That seminar that's referred to there at Lilly at the end of 1999, did you attend that seminar?
A. Yes.
Q. Okay. And I assume Dr. Casey was, must have been invited to come and give a presentation, correct?
A. I invited him.
Q. Okay. And at that seminar, according to this document, "He," referring to Dr. Casey, "performed chart review of 136 veteran patients who had been exposed to olanzapine therapy for at least four months, average of 1.4 year. Of the 39 patients who had normal fasting glucose levels before olanzapine therapy, seven, or 18 percent, had fasting glucose levels of 126 milligrams per deciliter or higher during olanzapine therapy." And then in parentheses it says, "threshold that met the 1998 ADA diagnostic criteria for diabetes."
Do you see that language?
A. I do.
Q. And the ADA that's referred

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to there is the American Diabetes Association, correct?
A. Yes.
Q. Okay. And so in this review of charts that Dr. Casey did of patients who had normal fasting glucose levels before they started using Zyprexa, 18 percent of them had fasting glucose levels that exceeded the criteria for diabetes after they had used it for at least four months; is that correct?
A. You are reading this correctly.
Q. Okay. Now, did Dr. Casey undertake that chart review on his own or was this part of a study that was being conducted by Lilly?
A. I don't know.
Q. Okay. When Dr. Casey came to Lilly and gave that presentation in which he said that 18 percent of people with normal blood levels had diabetic blood levels after using the drug for four months or more, did that come as a surprise to you at that point, or were you aware of his findings before he came to give the seminar?
MR. BOISE: Object to the form of the question.
A. I don't recall if he and I talked about the data before he came or not.
Q. Do you recall who else was at that seminar where Dr. Casey said that 18 percent of the people who use Zyprexa after four months had diabetic blood levels?
A. I don't recall, sitting here at this moment, who else was at the seminar.
Q. Okay. The very term "seminar" makes me think, and I could be wrong, that there was a group of people there. Is that a fair assessment?
A. I think that's a fair characterization.
Q. And would you have expected the majority of people from the Zyprexa Product Team to be there?
A. I, again, don't recall who was in attendance. Typically, when we have a seminar with an outside speaker, we advertise it fairly broadly within the company. It's

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an open-door policy, so those interested in this particular area were invited.
Q. Okay. And it's fair to say that, also, isn't it, sir, that Lilly never advised prescribing physicians in the labeling of Dr. Casey's findings, did it, sir?
MR. BOISE: Object to the form.
A. No, we didn't, because this gets to a very central point that we've been discussing today, and that gets to quality of data.
Q. Sir --
A. If I could just finish. These are 39 patients, a retrospective analysis in which there are no controls, no understanding of baseline factors, inadequate amount of data to really understand even a full temporal association. So these are the very kinds of data that, while it's important to look at all the data, and we were interested in looking at all the data, this is the type of

study alone that one cannot draw very many conclusions.

MR. SUGGS: Move to strike the nonresponsive portion of your answer after the word "no."

QUESTIONS BY MR. SUGGS:

Q. Sir, this proposal to change the label that was reviewed by the Global Products Labeling Committee did not go forward in February of 2000, correct?

MR. BOISE: Object to the form.

A. These data were not included in the label.

Q. Now, you did make a label change several months later in May of 2000, correct?

A. That's correct.

Q. And we've seen the document where that was done, Exhibit 4858. If you can find that in the pile. That was the May 9, 2000, letter?

A. Yes.

Q. And this May 9, 2000, letter

is from Gregory T. Brophy in the U.S. Regulatory Affairs Department in Eli Lilly to the FDA on May 9, 2000, correct?

A. Yes.

Q. And it informs the FDA that Lilly has already revised the package label for Zyprexa in three respects, correct?

A. Yes.

Q. And Dr. Brophy notes in his letter of May 9, "Effective immediately we will be implementing this change," correct? It's on the second page, second to the last paragraph, last sentence.

A. Yes.

Q. And so this label change was made without prior FDA approval, correct?

A. That's correct.

Q. Okay. Now, one of the things that this label change did had to do with the neuroleptic malignant syndrome. And that has really nothing to do with the issue of diabetes. Would that be a fair characterization?

A. It's an important safety phenomena. You're correct, it's not [illegible] to diabetes.

Q. Okay. And then another change that was made to the labeling was that there was an addition in the adverse reaction section of the labeling, in the post-introduction reports part of the label, inclusion of diabetic coma. So that that section then read, "Adverse events reported since market introduction which were temporally but not necessarily causally related to Zyprexa therapy include the following: Diabetic coma and priapism," correct?

A. Yes.

Q. And priapism is another condition that has nothing to do with diabetes, correct?

A. Correct.

Q. Okay. Priapism is involuntary sustained erection, correct?

A. Correct.

Q. Okay. And then the other change that was made was Item No. 2 in the

adverse reaction section, there was some additional language added regarding the laboratory changes section and findings of data from the olanzapine clinical trial database with respect to random plasma glucose levels, correct?

A. Yes.

Q. And could you read that into the record, please?

A. The --

MR. BOISE: What, the entire section?

MR. SUGGS: Sure.

MR. BOISE: You can read. I can read.

MR. SUGGS: Well, the jury might want to hear it.

MR. BOISE: Why don't you read it in?

MR. SUGGS: No, I'd rather he read it in. Would you please read it into the record, sir?

MR. BOISE: Is it a question?

MR. SUGGS: It's a request.

Would you please read that into the record, sir.

A. "In the olanzapine clinical trial database, as of September 30, 1999, 4,577 olanzapine-treated patients representing approximately 2255 patient-years exposures, and 445 placebo-treated patients who had no history of diabetes mellitus and whose baseline random glucose levels were 140 milligrams per deciliter or lower were identified. Persistent random glucose levels greater than or equal to 200 milligrams per deciliter, suggestive of possible diabetes, were observed in 0.8 percent of olanzapine-treated patients, placebo 0.7 percent. Transient, i.e., resolved while the patients remained on treatment, random glucose levels greater than or equal to 200 milligrams per deciliter were found in 0.3 percent of olanzapine-treated patients, placebo 0.2 percent. Persistent random glucose levels greater than or equal to 160 milligrams per deciliter but less than 200 milligrams per deciliter, possibly

hyperglycemia, not necessarily diabetes, were observed in 1.0 percent of olanzapine-treated patients, placebo 1.1 percent. Transient random glucose levels greater than or equal to 160 milligrams per deciliter but less than 200 milligrams per deciliter were found in 1.0 percent of olanzapine-treated patients, placebo 0.4 percent."

Q. Thank you. And would you agree with me, sir, that essentially that language is indicating that there was really not much, if any, difference in blood glucose levels between the patients who used Zyprexa and those who were on placebo?

MR. BOISE: Object to the form of the question. You took the time to have him read the whole thing verbatim into the record.

MR. SUGGS: Counsel, state objection to the form of the question.

MR. BOISE: I do object to the form.

MR. SUGGS: Fine.

Now you can answer.

A. The overall -- I mean, there's a number of different placebo/olanzapine comparisons described here. Overall, there is relatively little difference between the placebo-related values and the olanzapine-related values.

Q. Certainly no language in there would indicate to the physicians that the incidence of treatment-emergent hyperglycemia in Zyprexa users was three and-a-half times higher than placebo users, correct?

MR. BOISE: Object to the form of the question. Lack of foundation.

A. I'm going to have to go through again and look at these comparisons.

No, I guess the very last line shows a difference of 1 percent olanzapine versus .4 percent with placebo. So, technically, I guess that's a two and-a-half times difference, although very small.

Q. And that was referring to transient random glucose levels, correct?

MR. BOISE: Object to form.

A. Yeah.

Q. Okay. Who was it within Lilly that signed off on the final language of this label change?

MR. BOISE: Object to the form of the question.

A. GPLC.

Q. Okay. And do you know who it was that headed the -- who the members were of the GPLC was at that time?

A. I believe Mike Clayman, Dr. Clayman was the chair, but I'm not 100 percent positive.

Q. Okay. And would this language have been reviewed and approved by you first before it was submitted to the GPLC?

A. I was aware of the submission.

Q. Did you review and approve it before it went to the GPLC?

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A. Yes.
Q. Okay. I'll represent to you that we've had deposition testimony from Dr. Beasley and Dr. Kenneth Kwong that the analysis which formed the basis for this May 2000 label change was later expanded into a lengthy submission to FDA in July of 2000 and was also the basis for a paper for publication. Does that square with your recollection as well?
A. Yes.
Q. Okay. And you were one of the authors listed on the paper that was prepared; isn't that correct?
A. Yes.
Q. And, in fact, you were the most senior person at Lilly that was listed as an author; isn't that correct?
A. I don't recall the other authors in addition to Charles.
Q. Do you recall that the paper was never actually published?
A. I recall it being presented at scientific meetings, which would be

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considered technically a publication if there were publication of the proceedings, which is typically the case.
I recall it was also submitted to a peer-reviewed journal and not accepted for publication.
Q. It was submitted to the "Journal of Biological Psychiatry" and rejected due to methodological concerns; isn't that correct?
A. I recall it being submitted to "Biological Psychiatry" and rejected. I do not recall all of the reasons it was not accepted.
MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 1440.
(Whereupon, Plaintiff's Exhibit(s) 1440, previously marked, was presented to the witness.)
MR. SUGGS: For the record, this is a November 3, 2000, fax from "Biological Psychiatry" referring to

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Manuscript No. 5380 entitled Incidence and Rate of Treatment-emergent Potential Glucose Impaired Glucose Tolerance (Igt) and Potential Diabetes with Olanzapine Compared to Other Antipsychotic Agents and Placebo by Charles M. Beasley, Jr., Kenneth Kwong, Paul H. Berg, Cindy C. Taylor, Jamie Dananberg and Alan Breier.
QUESTIONS BY MR. SUGGS:
Q. Was that the title of the paper that was prepared and submitted?
MR. BOISE: Object to the form.
A. Yes.
Q. Okay. And do you recall getting this -- well, let me back up for a second. You used the term "peer-reviewed journal." A peer-reviewed journal is one in which articles are submitted for publication and the scholarly journal then has anonymous reviewers, who are considered peers of the authors who are engaged in that area of

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science, review the articles and make critiques or reviews of the article that's been submitted. Isn't that how the process works?
A. I think that's a reasonable description.
Q. Okay. And it would appear that this document that we have before us, Exhibit 1440, is a copy of the reviewer's comments from the biological psychiatry journal, correct?
A. Yes.
Q. Okay. And were you provided with these comments back in November of 2000?
A. Yes.
Q. Okay. And did you review this document recently?
THE WITNESS: This document?
MR. SUGGS: Yes.
A. No.
Q. Okay. If I could direct your attention to the first paragraph. By the way, there are several reviewers comments here, correct?

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A. There were three.
Q. And they're, actually, referred to as referees, correct?
A. That's correct.
Q. And the first referee starts off by saying, "The authors present the results of a comparison of nonfasting glucose measures among patients treated with olanzapine, placebo, and comparator antipsychotics from the Lilly clinical trial database. This is a welcome and important study since concerns have been raised regarding the propensity of olanzapine and other atypical antipsychotics, except ziprasidone, to cause glucose intolerance. The authors also examined risk factors for glucose intolerance including age, body weight, and increase in adiposity during treatment."

And glucose intolerance, is that a precursor of diabetes or is that the actual condition itself?
A. It is hypothesized to be in the mechanistic pathways.

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Q. And so if it's in the mechanistic pathway, that would indicate if somebody has glucose intolerance, that means they are on the road to diabetes?
MR. BOISE: Object to the form.
A. Again, my understanding is that this is a hypothesized mechanism.
Q. Okay. And apparently there had already been concerns raised by this point, November of 2000, regarding the propensity of Zyprexa to cause that glucose intolerance at least according to this referee, correct?
MR. BOISE: Object to the form.
A. It says since concerns have been raised.
Q. Okay. Concerns have been raised about the propensity of olanzapine and other atypical antipsychotics except ziprasidone to cause glucose intolerance, correct?
A. That's what it says.

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Q. And then in the second paragraph, the reviewer says, "The introduction is scholarly and complete." It goes on to say, "The importance of this study thus rests with its ability to compare the incidence and rate of treatment-emergent IGT or impaired glucose tolerance or diabetes during treatment with various atypical antipsychotics versus typicals and placebo."

That's what he saw as the importance of the study, correct?
MR. BOISE: Object to the form.
MR. SUGGS: I'm not sure if you answered.
THE WITNESS: I'm just rereading the sentence.
A. Yes.
Q. And then in his final paragraph of this, the first reviewer says, "My only concern regarding the methods of the study and thus what interpretation of their results, is whether the data were biased towards short-term studies of insufficient

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duration to detect the effect the authors were examining. This is especially relevant to the estimates obtained for patients receiving placebo. It would be very helpful to know how many of the 6,374 patients in the database were actually in treatment trials beyond eight weeks."

Do you see that language, sir?
A. I do.
Q. And, in fact, most of the patients from that database were not actually in treatment trial beyond eight weeks; isn't that correct?
MR. BOISE: Object to the form.
A. I don't recall the duration of the trials. This represents, what are we saying, over 6,000 patients. I know in the clinical trial dataset there was a wide range of trials that spanned weeks to months to years. So there was quite a lot of variability in the duration of the trials.
Q. If Dr. Kwong has testified

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that most of the patients were not actually in treatment trials beyond eight weeks, would you dispute his testimony?

MR. BOISE: Again, he's making the representation that that's what Dr. Kwong said.

A. Again, I'll stand by my answer. My recollection is that there was quite a diversity of duration of trials from weeks to months to years.

Q. Were you or Dr. Kwong more closely involved in the collection of the data that's referred to in this study?

A. When you talk about "collection of data," that implies designing clinical trials, running clinical trials, and assimilating the data.

MR. SUGGS: Let me restate the question.

MR. BOISE: Let him finish the answer.

A. Kenneth Kwong would not have been involved in any of those activities.

Q. Between you and Dr. Kwong as

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the authors of this study, which one of you was more involved in knowing the details of the patients who were included as, in this analysis?

MR. BOISE: Object to the form.

A. That would be me.

Q. Okay. But you don't have any recollection as to how many were actually in treatment trials beyond eight weeks, correct?

A. I don't recall now. I'm remembering that there could be as many as 70 to 80 different trials conducted all over the world --

Q. But you don't know the percentage?

A. But I couldn't tell you at this time sitting here today what percent were in eight weeks or less.

Q. Okay. Let me direct you to the comments on Page 2. He states, "The authors present a highly curious dataset. Since their own work has shown that olanzapine is associated with a clinically

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and statistically pertinent increase in weight compared to both haloperidol and placebo. They seem to be suggesting that olanzapine exerts a sizable antidiabetic power. It is estimated by the American Diabetic Association that a 1-pound increase in adipose tissue is associated with a 4 percent increase in the risk of diabetes. Given that olanzapine induces significant weight changes and the authors believe and report that it does not increase the risk of diabetes, olanzapine appears to be in the enviable position of eliminating the known risk of glucose" tolerance "associated with weight gain."

MR. BOISE: You misspoke.

MR. SUGGS: On what word?

MR. BOISE: Intolerance.

MR. SUGGS: What did I say, "glucose tolerance"?

MR. BOISE: I heard "tolerance" but the record will speak.

MR. SUGGS: You're right. I did misspeak.

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I don't want to read the whole thing again.

MR. BOISE: You did it so well almost.

QUESTIONS BY MR. SUGGS:

Q. Bottom line, this reviewer is saying that these findings that you had there, he regarded at least them as being very curious, correct?

A. "Highly curious" is the phraseology.

Q. Because you were finding, yes, Zyprexa causes weight gain but, no, it doesn't cause diabetes or increase the risk of diabetes, correct?

MR. BOISE: Object to the form.

A. That's the data.

Q. And this reviewer didn't believe that, did he?

MR. BOISE: Object to the form.

A. I wouldn't interpret curious as disbelief.

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Q. You had considerable skepticism expressed about the results of this analysis by other consultants to the company, did you not?

A. I would characterize that most people who saw the data found it very helpful. This was a unique dataset of over 6,000 patients in controlled trials. Just comparing it to the Casey report of a very small, retrospective, poorly-controlled dataset.

It were these kinds of studies, the Casey report, that were in the public domain that were not terribly informative. And we felt that we had a unique set of data, a one-of-a-kind in terms of quality and length, numbers of exposures.

And most of the input I received on this data was quite laudatory and positive. In fact, we not only submitted this data to the FDA, but we submitted it to regulatory bodies worldwide, and it's in the European label today. So those scientists looked at it and found it quite helpful and

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meaningful.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. Do you recall that outside consultants to the company in a meeting of October 2000 informed the company that they were highly skeptical of these findings?

A. Not quite sure what you're referring to.

Q. All right. We'll come back to that.

If I could direct your attention to the following page. This is comments from another reviewer. And the first numbered comment there the reviewer says, "The authors do not adequately emphasize how crude their method is for finding an effect. Random glucose values represent an insensitive method for assessing glucose tolerance."

Do you see that language, sir?

A. Um-hum.

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Q. And, in fact, at some point after this, Lilly switched from random glucose blood testing to fasting blood glucose testing, correct?

A. That's correct.

Q. And that's because, in fact, random glucose values are an insensitive method for assessing glucose tolerance, correct?

MR. BOISE: Object to the form of the question.

A. There are strengths and weaknesses to both approaches.

Q. If I could direct your attention to the second point there it states, "Most of the values were, probably, drawn during the first three months of each trial. It would be helpful to know the number of samples in each condition that were collected during the later stages of the trials."

And, sir, in fact, most of the values, the blood samples were drawn during the first three months of each trial;

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isn't that correct?

A. I don't know if that's the case.

Q. If Dr. Kwong has testified that that's correct, would you have any basis to dispute that?

A. I would prefer to rely on my own answer here.

Q. And your own answer is you don't know?

A. I don't recall.

Q. Okay. The third point raised there by this reviewer was, "Many of the early studies of olanzapine were biased toward low doses of the drug. Since there's a consensus that most patients require 10-milligram or more of olanzapine, it would be helpful to know if there is a dosage effect on glucose tolerance."

Do you see that language?

A. Yes.

Q. And, in fact, many of the early studies of olanzapine did use low doses of the drug; is that correct?

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MR. BOISE: Objection to the form.

A. 10 milligrams is the recommended starting dose and an adequate dose for the majority of patients.

Q. No. This reviewer is saying many of the earlier studies of olanzapine were biased towards low doses of the drug, in other words, doses lower than 10 milligrams. In fact, that is the case, isn't it, sir?

A. I don't know that I would agree with that.

Q. You just don't know one way or the other?

A. Again, sitting here today, I don't remember those aspects of the methodology of these particular analyses. I do know that our major Phase 3 trials span doses of 2.5 milligrams up to over 17 milligrams with the mean doses being in the 10-milligram range.

So my knowledge of the Phase 3 trials, the clinical trial sets for certain trials that occur since registration,

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10 milligrams would have been the dose most commonly used during those clinical trials.

Q. Sir, if I could direct your attention to the fourth item there, he states, "This study is important since there is relatively little controlled data in this area. At the same time it is a study with a good deal of commercial interest and a study that was designed and the data was analyzed by olanzapine's manufacturer. For this reason it would be important to have an independent analysis of the findings. If there is a Type II error in these findings this could lead clinicians to underestimate a serious drug risk."

Do you see that language, sir?

A. I do.

Q. And the Type II error that he's referring to is a type of scientific error in which no difference is found, or pardon me, no difference is detected even though there is, in fact, a real difference. Isn't that what type II error is?

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A. I don't know that I would agree with that, that definition. A Type II error is a statistical concern when there's multiple comparisons, and it could lead to an inaccurate understanding of the data.

Q. Okay. And this reviewer is saying this is critical information, and that if it's not done right, it could lead clinicians to underestimate a serious drug risk, correct?

A. You're reading the words on this page. I can tell you that the analysis were done properly.

Q. Okay. Well, and this reviewer is saying because the analyses were done by the drug's manufacturer, it would be a good idea, in fact, he says, "important to have an independent analysis of the findings." Do you see that language, sir?

A. I do.

Q. And do you recall that outside consultants in October of 2000, just a month before this, also recommended that there be an independent analysis of that

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data?

A. It was recommended that there be an independent analysis of these data. We obtained external experts to come in to do those independent analyses and those independent analyses confirm the findings.

Q. Those independent analyses that you're talking about referred to analyses of continuous data, correct?

A. Categorical.

Q. Well, when there was a later analysis of continuous data, it was found that the blood glucose was elevated in the Zyprexa users as compared to haloperidol and placebo subjects, correct?

A. Let's be clear about what was done and what was found. This paper was about categorical analysis. When you're using random glucoses, because they are so sensitive to food effects, categorical analysis could be argued as being the superior approach. They're clearly more clinically meaningful than continuous analysis. These analyses were done for that

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reason as categorical analyses. Those categorical analyses were reviewed by independent analysis, and the exact same categorical analyses that we're talking about here were confirmed.

In addition, we got in consultation that suggested we look at continuous analyses as well. We took that external advice. We did the continuous analyses. There were differences between Zyprexa and placebo and Haldol, not between risperidone, and significantly lower than clozapine. But those differences were very small. They were not clinically meaningful. And given the fact that these are nonrandoms, those analyses are not as informative.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. Sir, I've mentioned several times some meetings that you had with outside consultants in October of 2000, and I'm going to go into those in some detail, but before I do that, I want to talk about -- well, first

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of all, let me make absolutely sure. With respect to this article that was submitted to "Biological Psychiatry," it was, in fact, rejected and not published in that journal; is that correct?

A. That's correct.

Q. And it was not published in any other peer-reviewed journal, was it?

A. These analysis were presented at a number of scientific meetings and were published in the proceedings of those meetings.

The data then, again, were, external consultants were brought in. The data were reanalyzed with continuous and categoricals, and those data, as well, were presented at scientific meetings and published in those proceedings, but not in a peer-reviewed journal.

MR. BOISE: Take five, David, if you're done with the document?

MR. SUGGS: Sure.

THE VIDEOGRAPHER: This marks the end of tape three of the

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deposition of Dr. Breier. We're off the record at 2:36.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: Back on the record. It is 2:56, and this is the beginning of tape four of the deposition of Dr. Breier.

QUESTIONS BY MR. SUGGS:

Q. Dr. Breier, do you recall that earlier today we talked briefly about a federal court of appeals decision in August of 2000 that ruled that Lilly's patent on Prozac would expire in 2000 instead of 2003?

MR. BOISE: Object to the form.

THE WITNESS: Was it 2000 or 2001? The hearing came in 2000 but wasn't the expiration 2001?

MR. SUGGS: Let me restate the question.

QUESTIONS BY MR. SUGGS:

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Q. Do you recall that in that federal court of appeals decision, which was in August of 2000, that it held that Lilly's patent would expire in 2001 rather than 2003?

A. Yes.

Q. Okay. And that legal decision had a profound impact on Lilly's stock value; isn't that correct?

MR. BOISE: Object to the form.

A. I don't recall what happened to the stock at that time.

Q. Did you own stock in Lilly back in August of 2000?

A. Yes.

Q. Okay. Do you recall what the approximate value was at that time?

A. No.

Q. Okay. Let me hand you a document that I've printed out from the Wall Street Journal on line charting the Eli Lilly stock between August 1, 2000 and October 10, 2000. And it purports to show that beginning in as of August 1, the stock value for --

pardon me -- the value of Lilly stock was in excess of $105, and that it plunged, almost fell off the table, from that $105 value down to about $75.

Do you see that, sir?

A. I do.

Q. And does that refresh your recollection that Lilly's stock plunged by almost a third in one day?

MR. BOISE: Object to the form of the question.

A. I still don't have a recollection of the stock back at that time.

Q. Okay. If I could direct your attention back to Exhibit 9070.

MR. BOISE: Yeah, did you mark this?

MR. SUGGS: You know what, I didn't, and I meant to. Let's mark that Wall Street Journal stock chart as Breier Exhibit 3.

(Whereupon, Deposition Exhibit(s) 3 duly received, marked and made a part of the

record.)

THE WITNESS: Okay.

QUESTIONS BY MR. SUGGS:

Q. And if I could direct your attention back to Exhibit 9070, that was the Kellogg Graduate School of Management article.

THE WITNESS: I'm not sure I still have my copy.

MR. SUGGS: I hope so. Has Mr. Boise been pilfering your collection there?

MR. BOISE: I object.

MR. SUGGS: To the statement of the truth?

MR. BOISE: To your statement period. Although there is a copy in front of me.

MR. SUGGS: Actually, there's two copies in front of you, I'm assuming one was the witness's.

QUESTIONS BY MR. SUGGS:

Q. If I could direct your attention to Page 7, bottom paragraph, about

the middle of the paragraph, well, actually start at the second sentence. It says, "In August of 2000, a U.S. court of appeals ruled that the company would have to cede its Prozac patent in 2001 rather than in late 2003, more than two years earlier than expected. After news of the ruling, Lilly's stock plunged by almost one-third in a day to $75 wiping out $36.8 billion in equity."

Do you see that language, sir?

A. I do.

Q. Does that refresh your recollection that the Lilly stock plunged precipitously on that day following the ruling by the court of appeals that the Prozac patent would expire in 2001 rather than 2003?

A. I'm not disputing the drop in the stock that occurred. I'm just not having a recollection of the stock at that time, what it was, what happened to it during that day. I'm not quibbling with the data.

Q. If I could direct your

attention to Page 8 on that Exhibit 9070.

A. Um-hum.

Q. On the top paragraph in the first full sentence, it says, "When the Prozac patent expired a year later in August 2001, 80 percent of U.S. patients who used the drug switched to the cheaper generics making Prozac the biggest selling drug ever to come off patent. Sales of the molecule dropped faster than the company had expected and by the fourth quarter 2001 sales declined 66 percent. This brought the total sales for the year down 23 percent to $2 billion."

Do you see that language, sir?

A. Yes.

Q. And is that an accurate statement of what happened with Lilly sales after the Prozac patent -- pardon me -- when the Prozac patent expired?

A. I don't have a precise recollection of these figures. Again, I'm not quibbling, though, with the data.

Q. Okay. The following

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paragraph states, "Anticipating the challenges that the Prozac patent loss would undoubtedly bring, the company ensured that it had a comprehensive plan in place to create and capitalize on other opportunities. The company increased its support for five medications that became the primary sources of growth in recent years." It says, "See the Exhibit 5. Zyprexa, which is used to treat schizophrenia and bipolar disorder reached sales of 3.1 billion in 2001, making it both the first Lilly product and the first product for treating mental illness to achieve over $3 billion in sales."

Is that an accurate description, sir, of the sales of Zyprexa?

MR. BOISE: You were off three words there.

A. It rings true.

Q. It also goes on to point out that, "During the second quarter of 2002, Zyprexa worldwide sales increased 23 percent to $907 million for that quarter ahead of analyst estimates."

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Did I read that correctly?

A. Yes.

Q. And does that indicate that the marketing of Zyprexa was intense during that period?

A. I don't recall there being any change in how we approached Zyprexa from before the Prozac expiration to after the Prozac expiration.

Q. Sir, isn't it true that Lilly was betting the farm on Zyprexa?

A. I don't know what you mean by that.

MR. SUGGS: Well, let me show you what's been previously marked as Plaintiff's Exhibit 8584.

(Whereupon, Plaintiff's Exhibit(s) 8584, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a PowerPoint presentation entitled "Zyprexa Product Team Off-site July 25, 2001."

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QUESTIONS BY MR. SUGGS:

Q. Sir, was there more than one Zyprexa Product Team?

A. No.

Q. You were the head of the Zyprexa Product Team in July of 2001, were you not?

A. Yes.

Q. And do you recall that there was an off-site meeting on July 25, 2001 to discuss Zyprexa?

A. No.

Q. If I could direct your attention to Page 5. The title of this slide is "Straight Talk - What's at Stake. The company is betting the farm on Zyprexa. The ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa. If we succeed, Zyprexa will be the most successful pharmaceutical product ever. We will have made history."

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Do you recall attending that meeting, sir, where that slide was shown?

MR. BOISE: Object to the form.

THE WITNESS: Let me take a moment and review the document.

Thank you, what was your question?

QUESTIONS BY MR. SUGGS:

Q. My question was, do you recall attending a meeting where this slide was shown?

A. I don't have a recollection of this particular meeting.

Q. What does it mean when it says "the company is betting the farm on Zyprexa?"

A. I have no idea.

Q. What does it mean when it says "the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa"?

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A. Again, I'm not familiar with this slide.
MR. FIBICH: Objection, nonresponsive.
MR. BOISE: Let him finish his answer.
A. That sounds like a bit of an overstatement.
Q. What does "world class commercialization of Zyprexa" mean?
A. Again, I don't know who constructed these slides. I don't recall the meeting. I don't know what was in the mind of the person who constructed these slides.
MR. FIBICH: Objection, nonresponsive.
Q. I'll represent to you, sir, that the database that Lilly produced to us for this document shows that it came from the files of Denice Torres. She reported to you in the Zyprexa product team, did she not?
A. In '01, yes.
Q. Sir, am I correct that after Lilly suffered the shock of losing the patent

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on Prozac earlier than expected it decided to expand the marketing of Zyprexa to primary care physicians?
MR. BOISE: Object to the form of the question. Foundation.
A. I'm going to have to challenge it, the framing of your question. I don't recall the company experiencing a shock. My recollection is that the patent expiration, we knew the patent expiration was coming. It came earlier than expected and that there were plans in place to do that.
Again, I don't recall there being any change in the approach to Zyprexa from before the patent expiration to after the patent expiration.
Q. Sir, the sharp precipitous stock drop as reflected in Exhibit 3 was certainly a shock to the company, wasn't it?
A. Again, I wouldn't characterize it that way. I don't want to trivialize it, but I'm just not resonating with the way you're framing it.
Q. Sir, the decision by the

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Federal Court of Appeals regarding the Prozac patent was on August 9, 2000. I'll represent that fact to you, okay?
A. Um-hum.
Q. Sir, the next document I'm going to show you is dated not on the face of the document but on the database that Lilly produced to us of August 22, 2000, which would have been about two weeks after the Federal Court of Appeals' ruling on the Prozac patent.
MR. SUGGS: And this is Plaintiff's Exhibit 8479.
(Whereupon, Plaintiff's Exhibit(s) 8479, previously marked, was presented to the witness.)
MR. SUGGS: And for the record, the title of this document is 'Zyprexa - Primary Care Strategy and Implementation Overview."
MR. BOISE: Dave, what was the date you represented?
MR. SUGGS: The database

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shows it's August 22, 2000.
I'll also represent to you that the database shows that this document came from the files of Mike Bandick.
THE WITNESS: Okay, I've looked at the document.
QUESTIONS BY MR. SUGGS:
Q. Do you recognize the document, sir?
A. No.
Q. Okay. Do you know who Michael Bandick was?
A. Yes.
Q. Okay. And who was he?
A. Lilly employee. I believe his level was maybe director in marketing at the time of this e-mail or this message August 2000, was working in the U.S. Affiliate.
Q. Okay. And this document notes in the initial section there, "Background: Following several months of study by the U.S.A. Zyprexa Brand Team, the

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affiliate approved the recommendation that Lilly actively promote Zyprexa to selected current primary care prescriber targets."

Do you see that language, sir?

A. I do.

Q. And were you aware of that decision?

A. I know there was a launch into primary care.

Q. And, in fact, you supported that launch, approved it, did you not, sir?

A. I was not asked to weigh in or to approve. The decision to go into primary care would have been an affiliate-based decision.

Q. Okay. You certainly assisted in the launch of Zyprexa to primary care, did you not?

MR. BOISE: Object to form.

A. I attended the launch meeting.

Q. And you gave a presentation there, correct?

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A. Yes.

Q. Directing your attention to Exhibit 8479. In the middle of the page there's a section called "Challenges." And it refers to primary care physicians as PCPs on there; is that correct?

A. That's correct.

Q. And it says, "Most PCPs currently prescribe a low volume of antipsychotics and mood stabilizers."

And was that an accurate statement?

A. I don't know where that data came from. My clinical sense is that there would be a reasonable amount of antipsychotic and mood stabilizer use.

Q. Okay. In about the middle of the paragraph, it states, "Zyprexa's primary indications."

You see where I'm reading from there?

A. Um-hum.

Q. It says, "Zyprexa's primary indications, schizophrenia and bipolar, are

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not viewed as PCP-treated conditions. So there's not a specific indication for Lilly reps to promote in the PCP segment."

Do you see that language, sir?

A. I do.

Q. And, in fact, the only indications for Zyprexa back in 2000 were for schizophrenia and the acute manic phase of bipolar disorder; is that correct?

A. That's correct.

Q. There were no secondary indications?

THE WITNESS: Meaning?

MR. SUGGS: Well, the memo says Zyprexa's primary indications, schizophrenia and bipolar. I guess my point is there were no other indications.

MR. BOISE: In August of 2000.

MR. SUGGS: In August of 200.

A. That's correct.

Q. It says under Position:

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"Zyprexa: The safe, proven solution in mood, thought, and behavioral disorders. We will emphasize safety to address barriers to adoption, and merchandise the brand's 'Four years Four million patients' base of experience."

See that language, sir?

THE WITNESS: You are in what? I've lost the paragraph.

MR. SUGGS: This is in "Position," the next section.

A. I see that, yes.

Q. And there was no indication for Zyprexa for mood disorder or thought disorder or behavioral disorder, correct?

MR. BOISE: Object to the form of the question.

A. Not to those terms but --

Q. That's the terms I'm referring to.

MR. BOISE: Let him finish his answer.

A. But schizophrenia and bipolar mania are, in fact, comprised of those

symptoms.
Q. Sir, when we use the term "indication," that has a particular meaning in the context of drug products, does it not?
A. It does indeed.
Q. And what it refers to is the uses of the drug that are specified in the Indications section of the labeling, correct?
A. Absolutely.
Q. And if a drug is promoted for uses other than those in the Indications section, that's inappropriate, correct?
A. Yes.
Q. Okay. And there was no indication for Zyprexa for mood disorder, correct?
MR. BOISE: Object to the form of the question.
A. Bipolar mania is a mood disorder.
Q. Sir, I'm talking about the language, okay? Did the Indications section of the Zyprexa labeling state that mood disorder was an indication of Zyprexa?

MR. BOISE: Object to the form of the question.
A. No. It was bipolar mania and schizophrenia. But, again, I just want to just underline the fact that schizophrenia is a psychotic disorder and bipolar mania is a mood disorder, and the components of those disorders contain both mood and psychosis.
Q. And, sir, you're demonstrating exactly what Mr. Bandick was referring to in the latter part of this paragraph where he states, "Mental disorders, unquote, is intentionally broad and vague, providing latitude to frame the discussion around symptoms and behaviors rather than specific indications."
Did I read that language correctly?
MR. BOISE: Object to the form of the question.
A. You read the sentence correctly. What I was talking about is clinicians are taught to diagnose disorders like bipolar mania and schizophrenia by

recognizing symptoms. So you begin with symptoms. That then leads you through a diagnostic process to identify the disorder in question.
MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, in point of fact, the other indications that Zyprexa had in the label at this time in 2000 was for schizophrenia and for the acute manic phase of bipolar disorder, correct?
A. Yes.
Q. There were no indications in the label of Zyprexa back in 2000 for mood, thought, or behavioral disorders, correct?
MR. BOISE: Objection. Asked and answered. We've been through this three times now, David.
A. That's correct, I'm not.
Q. Thank you, sir.
MR. BOISE: Let him finish his answer.
A. I'm not reading these words

to indicate that the indication statement was mood and psychosis. What I'm reading these words to indicate is that the road or the pathway to schizophrenia and bipolar is through recognition of mood and psychosis.
MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Did you -- were you informed that the position of the Lilly marketing department was going to be as reflected in that position there: "Zyprexa, the safe, proven solution in mood, thought, and behavioral disorders"?
MR. BOISE: Object to the form of the question. Foundation.
A. I don't recall hearing that specific framing. The components -- safe, yes; proven solution for components of mood in both bipolar mania and schizophrenia, yes; thought disorders in bipolar mania and schizophrenia, yes.
MR. SUGGS: Time out for a second. I never mentioned

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schizophrenia and bipolar.
MR. BOISE: Let him finish.
MR. SUGGS: You're adding words there, sir.
A. And behavioral disorders associated with bipolar mania and schizophrenia. So these terms rooting back to bipolar and schizophrenia would be accurate terms.
MR. SUGGS: I move to strike the portion of your answer that's nonresponsive. Everything after "specific framing."
QUESTIONS BY MR. SUGGS:
Q. Is it your testimony that the Zyprexa Product Team had no involvement in approving this decision to market Zyprexa to primary care physicians?
A. That would not be the purview of the product team.
Q. Okay. And who did make that decision?
A. Decisions around sales force, the focus of sales force, all the

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implementation issues, are determined by the affiliates.
Q. And who would have been in charge of the U.S. Affiliate back at that time?
A. Gino Santini.
Q. Gino Santini, okay. What was his title at the time, do you recall?
A. I'm going to assume it was President of U.S. Operations, something of that nature.
Q. Is he still with the company?
A. Yes.
Q. And what's his title today?
A. I'm not certain.
Q. Sir, do you recall attending a, the launch of?
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. Do you recall attending the launch meeting of Zyprexa for primary care physicians?
A. Yes.
Q. And where and when was that?

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A. I believe it was Orlando, but I'm not 100 percent positive, and it would have been, I believe, in the 2000 time frame.
Q. Are you sure it was in Orlando or could it have been in Las Vegas?
A. I'm certain it was not in Las Vegas.
MR. SUGGS: Okay. Let me show you what's been previously marked as Plaintiff's Exhibit 4007.
(Whereupon, Plaintiff's Exhibit(s) 4007, previously marked, was presented to the witness.)
MR. SUGGS: For the record, this is a transcript entitled Viva Zyprexa, Audio Program No. 3, Post-meeting Communications Campaign, Cassette Version.
QUESTIONS BY MR. SUGGS:
Q. Are you familiar with the phrase "Viva Zyprexa?"
A. My only recollection of it is associated with this particular launch

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meeting.
Q. In fact, wasn't that the name that was given to the launch of Zyprexa for primary care physicians?
A. I don't know.
Q. Do you recall that they even came up with a Viva Zyprexa song that was using the tune from the Elvis Presley song called Viva Las Vegas?
A. I'm not familiar with that.
Q. Not familiar with Elvis or the song or with the --
MR. BOISE: I object to the form of the question. Compound.
A. I'm not familiar with the song. I am familiar with Elvis.
Q. If I could direct your attention to the fourth page. There appears to be there a transcript of some comments you made of that meeting, correct?
A. Yes.
Q. And do you recall how many people were in attendance at that meeting?
A. No.

Q. More than a hundred?
A. I don't know.
Q. The people who attended the meeting were who?
A. They would have been, primarily, the components of the sales force for primary care.
Q. Back in Exhibit 8479, the previous exhibit, the first paragraph it says, "Key decisions included: Launch will occur in October 2000, promotion will handle via the Primary Care-Neuroscience sales sleeve, 510 reps."
Do you see that?
THE WITNESS: I'm sorry, where were you? On the second page?
MR. SUGGS: No, the first page, first paragraph. Second half of that first paragraph.
THE WITNESS: Yes.
Q. Key decisions included: Launch will occur in October 2000, promotion will be handled via the Primary Care-Neuroscience sales sleeve, 510 reps?"

A. Yes.
Q. And does that refresh your recollection as to how many sales representatives were there at that meeting?
A. Frankly, it really doesn't. I don't really recall how many sales reps were there.
Q. Was it in the area of 500 people who were there?
A. That sounds like a very large number. I don't recall there being that many people. I don't really know.
Q. Directing your attention back to the transcript which is Exhibit 4007. In the last paragraph -- actually, let's talk about the second paragraph of your presentation. It says, "Now, why don't we go on and talk about some specifics around Zyprexa, and sort of what the future looks like. And I said that Zyprexa is a very, very special molecule."
You go on to say, "Let's go to the first one: Growing sales in the elderly. How many people, in their own lives

and their own families, have been touched by Alzheimer's disease."
Do you see that language, sir?
A. Yes.
Q. And did you make those statements to the crowd there?
MR. BOISE: Object to the form.
A. Yes.
Q. Pardon?
A. Yes.
Q. And in about the middle of that paragraph, well, actually, five lines down, you say, "And the need for better treatment in Alzheimer's and other elderly conditions is so paramount and so key, and what you're going to see, and you'll see it with your own eyes, is that Zyprexa is an optimally suited molecule for this disorder. Its attributes line up so beautifully in the elderly, our one clinical Achilles heel is weight gain. That's a plus in the elderly because of wasting of those individuals.

Controlling psychosis, controlling agitation. And there is a huge amount of business in the elderly."
Did you make those statements to the crowd there?
A. Yes.
Q. And there was no indication for Alzheimer's for Zyprexa in the label in 2000, was there, sir?
A. No. And we were very clear about that. The purpose of my presentation and why I was asked to present to this group was twofold: Firstly, was to overview the future developments for Zyprexa. We were in the midst of an Alzheimer's indication with data coming out and studies ongoing; and from a clinical perspective to talk with the sales force about the clinical realities that they would observe. Many of the people who were coming into the sales force, I was told, did not have a neuroscience background. And they would be in doctor's offices where Zyprexa was being used, because we know it's used, as other antipsychotic drugs, for a range of

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conditions.
So, my purpose had nothing to do with promotion. It had to do with overviewing the future of the molecule. The new indications we were pursuing. As well as to give them some clinical insights into the clinical realties that they would confront when they go into the primary sales area.
MR. SUGGS: Move to strike that portion of your answer that's nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, isn't it true that references to the elderly market are synonymous with using it in Alzheimer's patients?
A. No. Every schizophrenic patient and every bipolar patient grows old.
Q. Sir, if I could direct your attention to Page 6. The last paragraph on that page states, "One-third of all patients, all psychiatric patients, do not fit into a DSM category."
And am I correct that DSM

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stands for Diagnostic and Statistical Manual?
A. Correct.
Q. And that refers to a cat -- to a method of categorizing schizophrenic illnesses, correct?
A. To diagnostic categories.
Q. You go on to say, "They have symptoms, they just don't neatly fit into a category. But yet you got to treat anxiety, agitation, depression, where it exists. And we are learning that doctors are now adding Zyprexa, because of its stunning safety profile, more and more and more to states like that. We don't have an indication here. That would be challenging. But we know in reality that's what's happening. That's what doctors are doing. So this is kind of part of the future that has direct bearing on your business and your customer, and it's going to allow you to partner with them to go back to what I was talking in the beginning, and sort of tackle that awesome degree, that staggering degree of suffering that they have to face, and have in the past have faced with

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inferior molecules, and now they get the gold standard, Zyprexa."
Did you make those statements to the launch attendees?
A. Yes.
Q. Okay. Now when you talk about Zyprexa was going to allow the sales reps to partner with them, the "them" you were referring to there was prescribing, pardon me, was primary care physicians, correct?
A. In this instance, yes.
Q. And the gold standard you were referring to was Zyprexa, correct?
A. Yes.
Q. And you were saying that the gold standard, that Zyprexa was the gold standard for dealing with things such as anxiety, agitation, and depression, correct?
A. Only in the context of schizophrenia and bipolar mania.
Q. Can you point to me anywhere in this paragraph where it's talking about schizophrenia and bipolar?

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A. Again, I want to be very clear about this. This was not a promotional presentation. The attendees of this meeting, I understood, would have two to three days of direction, learning all of the necessary elements they need in order to work in that environment. Mine was talking about a clinical reality regarding these symptoms.
We had recently been to the FDA and talked to them about obtaining indications to treat depression and agitation, specifically, in schizophrenia because we had very good data on that point. They pointed out to us that that would be very challenging in order to obtain those indications, and I was relating that to this group.
I, then, at this point in the paragraph, circled back to my beginning comments to talk about the degree of suffering that patients with severe mental illnesses have.
MR. SUGGS: Move to strike as nonresponsive.

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QUESTIONS BY MR. SUGGS:
Q. Can you point to me anywhere in this paragraph where it mentions schizophrenia or bipolar disorder?
A. Not in that specific paragraph. In the paragraph up above I talked about bipolar.
And again, this is, this -- my purpose was not to direct the sales force or to teach the sales force how to do their job, it was to overview at a very high level the future developments for Zyprexa, what we were working on in terms of indications, what would be important to them, questions that they would get from their customers about our progress in Alzheimer's and our Alzheimer's registration and bipolar, and equipping them with that knowledge because I knew they would be getting questions in that environment.
MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. In fact, the whole thrust of your paragraph, at least the beginning part

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of it, is that one-third of all patients, all psychiatric patients, do not fit into a DSM category, they have symptoms, they just don't neatly fit into a category, yet you got to treat anxiety, agitation, depression where it exists.
That's how you lead off that paragraph, right?
A. I gave the remarks, and I can tell you what the intent of these remarks are. And --
Q. Sir, isn't that how you started off what you said right there?
MR. BOISE: Just let him finish then you can ask the next question.
A. And, yes, the fact is that once you get into a setting like primary care, the diversity of patients you see are a variety of different symptom types. What those clinicians will need to be able to do is to follow those symptoms back to the appropriate disorders, so that's a clinical reality.

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MR. SUGGS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, is age related -- pardon me. Is dementia-related psychosis related to Alzheimer's?
THE WITNESS: Repeat the question.
MR. SUGGS: Sure.
QUESTIONS BY MR. SUGGS:
Q. Is dementia-related psychosis part of Alzheimer's?
A. It can be. Alzheimer's is a dementia, and psychosis is common in Alzheimer's disease. There are other dementias that are not of the Alzheimer's type that also have psychosis.
MR. SUGGS: Can you pull out the labeling that we introduced earlier. I believe it's Breier Exhibit 2.
Mr. Boise stole your copy again.
MR. BOISE: Not pilfered,

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stored, maintained, held.
QUESTIONS BY MR. SUGGS:
Q. And we previously established that this was the current labeling for Zyprexa, correct?
A. Correct.
Q. And it now has a black box warning at the very beginning of "Increased Mortality in Elderly Patients with Dementia-Related Psychosis," correct?
A. That is correct.
Q. And do you know how many people, how many elderly people, used Zyprexa and died before this label change was made?
MR. BOISE: Object to the form of the question.
A. I don't know the exact number.
Q. Do you know an approximate number?
THE WITNESS: Would you repeat the question?
Q. Do you know an approximate number of elderly people who used Zyprexa and

died?
MR. BOISE: Object to the form of the question.
A. I don't know the number if you're referring to spontaneous adverse events. I just want to be certain in your question that you're not intimating a cause-and-effect relationship, because we do not have data on cause-and-effect nor does this label change suggest cause-and-effect.
Q. Sir, what I'm trying to get at here is we now have a black box warning for increased mortality in elderly patients with dementia-related psychosis, correct?
A. Yes.
Q. My question is, how many patients used Zyprexa for that purpose died?
MR. BOISE: Object to the form. Asked and answered.
A. Sitting here today, I cannot give you a precise number of --
Q. Which is why I asked if you could give me an approximation.
A. No, I can't.

Q. You have no idea whether we're talking about 2 people or 200?
A. Nope.
Q. When did this warning go on the label about increased mortality in elderly patients with dementia-related psychosis?
A. I believe it was 2005.
Q. Do you recall what month?
A. No.
Q. I believe you said that this launch meeting for primary care physicians where you were talking about the use of Zyprexa in Alzheimer's patients occurred in October of 2000; is that correct?
A. I believe that's correct. It was in 2000.
Q. Okay. And do you recall in that same month, October of 2000, that Lilly representatives met with a group of outside consultants in the field of diabetes to discuss the data that the company had put together?
A. We had a number of

consultations with external experts on diabetes. And I'm not clear which one you're referring to.
MR. SUGGS: Let me see if I can refresh your recollection. Let me show you what's been previously marked as Plaintiff's Exhibit 6998.
(Whereupon, Plaintiff's Exhibit(s) 6998, previously marked, was presented to the witness.)
MR. SUGGS: Which, for the record, is an October 9, 2000, e-mail from Robert Baker to Charles Beasley, Christopher Bomba, Alan Breier, Thomas Brodie, Patrizia Cavazzoni, James Gregory, John Holcombe, Jack Jordan, Suni Keeling, Bruce Kinon, Michael Murray, John Richards, Eugene Thiem, Mauricia Tohen and Paula Trzepacz.
QUESTIONS BY MR. SUGGS:
Q. If I could direct your attention, sir, to the first paragraph. It

states, "FYI: The Lilly diabetes/endocrine group held an academic advisory board meeting this weekend in Atlanta. They kindly allotted two hours for discussion of olanzapine's potential hyperglycemia risks, and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic."
Do you see that language, sir?
A. I do.
Q. And does that refresh your recollection that members of your Zyprexa Product Team had a meeting with outside consultants in October of 2000?
MR. BOISE: Object to the form.
A. I recall this message, and I recall that consultation. Just to be accurate, at this time I believe Charles

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Beasley was still on the product team. Patricia Cavazzoni clearly was on the product team. I'm not sure who Chris Bomba is. And I don't recall if Suni Keeling was on the product team or not.

Q. Was Jack Jordan on the product team?

A. No.

Q. Was Mauricio Tohen on the product team at that time?

A. Yes.

Q. So this e-mail's going to people who were on your product team and also other folks as well, correct?

A. Correct. You had just mentioned that members of my product team, and I just wanted to clarify that Chris Bomba and I'm not sure --

Q. My statement was correct, but there are other individuals besides people from your Zyprexa Product Team who this e-mail went to?

A. Oh, in terms of who it was sent to, yes, and also in terms of the

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attendees.

Q. Okay. Do you know how it was that this meeting came about?

A. The meeting that I understand this is referring to is a standing group of advisors that advised the company primarily on the endocrinology portfolio.

Q. Okay. So when it refers here to the Lilly diabetes/endocrine group, that refers to that group in the company that would be dealing on a regular basis with the company's drugs intended for the treatment of diabetes, correct?

A. Correct. So the endocrinology consultants would be members, would be experts in the area of diabetology endocrinology.

Q. Okay. So the diabetes side of the company which deals with diabetes all the time has this group of outside consultants, outside experts that they deal with. And some of your folks dealing with Zyprexa went down there to attend the meeting and presented the data to them, correct?

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A. That's correct.

Q. Okay. And the data they presented to them was essentially the same data that was reflected in your May 2000 label change and in the presentation to FDA in July of 2000 and in the paper that was submitted for publication to the "Journal of Biological Psychiatry." Isn't that correct, sir?

MR. BOISE: Object to the form of the question. Foundation. Compound.

A. What I recall is that the categorical glycemic data that we discussed earlier was presented. I believe also other data as well, including weight gain data and data of that nature.

Q. And, sir, have you reviewed this document since October of 2000?

A. Yes.

Q. When did you review it last?

A. Within the last month.

Q. Okay. In the second paragraph it states, "On the positive side,

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like other endocrinologists, they were not impressed with the Newcomer findings."

What were the Newcomer findings, if you recall?

A. I don't recall.

Q. It goes on to say, "They were however concerned by our spontaneous AE reports, and quite impressed by the magnitude of weight gain on olanzapine and indications for glucose."

And when they're referring there to "spontaneous AE reports," am I correct that that stands for adverse event reports?

A. Yes.

Q. Okay. And these would be reports made to the company or to the FDA by either treating doctors or patients, or, frankly, could be anybody recording an adverse event that occurred to a patient while they were using the drug, correct?

A. Typically, the treating physician.

Q. Okay. And continuing on in

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that paragraph dropping down a couple of lines, it says, "Citing methodological questions, at least the vocal members were not reassured adequately by our analyses, such as the finding that relative risk was not higher than comparative drugs. Disconcertingly, one member compared our approach to Warner Lambert's reported argument that Rezulin did not cause more hepatic problems than other drugs in its class."

Do you see that language, sir?

A. Um-hum.

Q. Are you familiar with the reference to Warner Lambert and Rezulin at that time?

MR. BOISE: Object to the form.

A. To the extent that my understanding is that there were similar comparative claims presented on Rezulin.

Q. Rezulin was a drug manufactured by Warner Lambert that was used

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for the treatment of diabetes, correct?

A. I am unclear what its indication was.

Q. Okay. But you are familiar with the fact that that drug was reported to have hepatic problems greater than other drugs, but Warner Lambert was essentially claiming that their rate of liver problems was no worse than other drugs in the class.

MR. BOISE: Objection --

Q. Is that your understanding?

MR. BOISE: Sorry. Objection. Foundation.

A. I don't have that depth of an understanding. My understanding was that Rezulin had hepatic problems.

Q. Okay. In any event, Dr. Baker -- by the way, it is Dr. Baker, correct?

A. Yes.

Q. Dr. Baker found that reference to Warner Lambert and the arguments that they had been making with respect to Rezulin, he found that disconcerting,

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correct?

A. Yes.

Q. Okay. If I could direct your attention next to Plaintiff's Exhibit 1453.

(Whereupon, Plaintiff's Exhibit(s) 1453, previously marked, was presented to the witness.)

MR. SUGGS: This is another string of e-mails. The very first one of which -- well, it's the first at the top of the first page of the document -- is from Robert Baker to Charles Beasley dated October 10, 2000.

As I said, sir, it's a string of e-mails. I think it probably makes more sense to track through this document from the back to the front because that reflects the time sequence of the e-mails. And so if I could direct your attention to the last page. It's an e-mail from Thomas Brodie to Robert Baker with a

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copy to Eugene Thiem.

QUESTIONS BY MR. SUGGS:

Q. Am I correct that Dr. Baker was in the medical marketing department?

MR. BOISE: Object to the form of the question.

A. No, he was a physician in the U.S. Affiliate.

Q. Okay. Did he work closely with the marketing department?

A. As a physician in the U.S. Affiliate, he had many responsibilities. Those would include designing and conducting clinical trials. He would have worked with marketing in terms of data interpretation, things of that nature.

Q. Okay. Now the author of this particular e-mail, Thomas Brodie, do you know who that was?

A. No.

Q. And the Eugene R. Thiem who's copied on this, do you know who he was?

A. No.

Q. The subject of this e-mail is

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the meeting with endocrinologic consultants. And it goes on to state, "Robert, clearly this group of endocrinologists who spoke up, and I would rate those who did speak up as the leaders of the pack, are very concerned with the approach Lilly is taking towards the issue that Zyprexa leads to diabetes. I can only hope that you and all of the team who attended the NADAB meeting are gaining the ear of senior leadership and articulating this finding. Although the board's recommendation is probably not the way Lilly typically does business, I do believe they made a very strong point that unless we come clean on this it could get much more serious than we might anticipate."

Do you see that language, sir?

A. I do.

Q. And you were informed of that language, were you not?

A. I was informed of the meeting.

Q. Well, and you were informed

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of this particular, these statements by Mr. Brodie, correct?

A. I have to trace the string of e-mails. I'm looking at this particular e-mail. I really have no idea what he was talking about. I mean, we --

Q. Well, if you can turn to the prior page, it would appear, and we've had prior testimony on this subject as well, that the e-mail just before that was from Robert Baker to Charles Beasley and you with copies to Christopher Bomba, Patrizia Cavazzoni, and Suni Keeling. And as you can see, at the top of the next page it says "forwarded by Robert Baker."

It appears that Robert Baker took that e-mail from Thomas Brodie and he forwarded it on to you and Charles Beasley with copies to those other folks; isn't that correct?

A. That appears to be the case.

Q. And, in fact, in his e-mail to you, Dr. Baker refers to what Mr. Brodie had been saying and tries to explain what he

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thinks Tom Brodie was referring to when he talked about not the way Lilly typically does business, correct?

MR. BOISE: Object to the form.

THE WITNESS: I'm reading that now.

MR. BOISE: When he's ready, you can read back the question.

THE WITNESS: Okay.

MR. BOISE: Read back the question.

(The Court Reporter read the requested material, as set forth herein:

"Q. And, in fact, in his e-mail to you, Dr. Baker refers to what Mr. Brodie had been saying and tries to explain what he thinks Tom Brodie was referring to when he talked about not the way Lilly typically does business, correct?").

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A. And again, I'm -- I don't know what was in Mr. Brodie's mind. What I can surmise from Dr. Baker's interpretation is that Lilly is a very careful company.

MR. SUGGS: Excuse me, sir, I'm not asking you to interpret what anybody said. My question has to do with what information was reported to you and what you did after that.

THE WITNESS: Okay.

QUESTIONS BY MR. SUGGS:

Q. And you would agree with me, would you not, sir, that you did, in fact, receive a copy of Mr. Brodie's e-mail to Dr. Baker and Mr. Thiem that's reflected on Page 4, correct?

MR. BOISE: Objection. Asked and answered.

A. That's correct.

Q. Okay. And when you saw the language in there that this group of endocrinologists "are very concerned with the approach Lilly is taking towards the issue that Zyprexa leads to diabetes" and "I can

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only hope that you and all of the team who attended the NADAB meeting are gaining the ear of senior leadership and articulating this finding," did you, in fact, communicate this to your superiors, this feedback that you'd received from endocrinology consultants?

MR. BOISE: Object to the form of the question.

THE WITNESS: So the question is what?

MR. SUGGS: Did you pass on, did you contact your superiors about this information you received from Dr. Baker?

A. Well, first of all, I think that I would be considered senior leadership. So, for the mere fact that it was being brought to me would be getting the ear of senior leadership.

Q. Sir, did you not hear my question? My question was, quote, Did you pass on, did you contact your superiors about this information you received from Dr. Baker?

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MR. BOISE: Object to the form. Are you withdrawing your prior question?

MR. SUGGS: No. My prior question stands. I want him to answer it.

MR. BOISE: You gave a prior speech which is very misleading to what the document says, he's trying to clarify that point.

QUESTIONS BY MR. SUGGS:

Q. Sir, when you received this information in this e-mail that this group of endocrinologists was telling you that Lilly needed to come clean on this and that he hoped that those who attended the meeting are gaining the ear of senior leadership and articulating this finding, did that cause you any concern?

MR. BOISE: Object to form.

A. The "come clean" comment to me -- I have no idea what that person was thinking about.

Q. So this didn't concern you

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one bit?

MR. BOISE: Let him answer.

A. Because we were doing the reverse. We were aptly disseminating this information. We were bringing it to external groups like this. We were taking it to the FDA. We were publishing it. We were putting it into medical letters.

So on this issue and many other important issues like this, we're a company that was very transparent about the data and we were transparent on this point.

When they refer to not the way Lilly typically does things, what I interpret that to mean is to rush out with something even if it isn't thoroughly understood, and that's something we, typically, do not do. We are very, very careful and we're very, very data driven.

Did I have contact about this with my supervisors? Absolutely.

Q. Okay. Fine. Thank you. I appreciate that answer.

Tell me, who did you

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contact to inform?

A. I was in contact with Gary Tollefson on a practically daily basis. These kinds of communications, we would have commonly had communications about these sort of thing.

Q. Anyone else?

MR. BOISE: Let him finish, Dave.

A. I don't recall, but I can tell you our normal way of working would be to have a lot of sharing of this kind of information. Consultants, bring them in, get input, bring the consultant feedback back into a group, talk about, analyze the input, and then on input that we thought would be helpful, we pursued.

And, in fact, the input we got from this particular consultation we did pursue. We brought in independent investigators to look at the datasets. They were proposing we do continuous analyses. We did continuous analyses. So we found this consultation to be very helpful.

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MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. You talked to Dr. Tollefson about this information you received, correct?

A. We talked nearly daily when we were both in the office. I can't recall sitting down with Dr. Tollefson and having an exact conversation about this topic. I assume we did because these are the kinds of things we talked about in our frequent communications.

Q. Okay. Directing your attention to the e-mail preceding the one from Mr. Baker, pardon me, the one from Mr. Brodie, the one at the bottom of Page 3 which starts off by saying, "FYI: My take was that this board of academic endocrinologists was impressed enough by the magnitude of weight gain and number of reports in the spontaneous adverse event database, that they were predisposed towards skepticism to any analysis that did not find higher hyperglycemia rates on olanzapine than

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comparators."

I read that correctly, right?

A. Yes.

Q. And that's, essentially, the same kind of concern or lack of belief that was expressed by one of the reviewers of your paper. Do you recall that?

A. I recall that. But I again want to reiterate that we follow the data. If the data were there and demonstrated important relationships then we would communicate that information, we would follow the data.

I, just on this point alone, I'm recalling a letter to the editor by the neuropharm division of the FDA who analyzed data, not only from us but other sponsors, and came to the exact same conclusion, that there is not support from clinical trials of the kinds of associations that we're talking about here. So although it might be surprising, at the end of the day the data has to speak for itself.

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MR. SUGGS: Move to strike everything in your answer after your first sentence "I recall that."

QUESTIONS BY MR. SUGGS:

Q. In fact, one of the reviewers said that the authors present a highly curious?

MR. SUGGS: Strike that.

QUESTIONS BY MR. SUGGS:

Q. One of the reviewers of your paper for publication that we looked at earlier, Exhibit 1440, said that "The authors present a highly curious dataset. Since their own work has shown that olanzapine is associated with a clinically and statistically pertinent increase in weight compared to both haloperidol and placebo, they seem to be suggesting that olanzapine exerts a sizable antidiabetic power."

That's what he said, correct?

A. That's what that one reviewer said.

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Q. And your consultants in the meeting in October of 2000 were skeptical of your results as well, correct?

MR. BOISE: Object to the form. Go ahead.

A. Again, what I got from the consultant was, okay, those categorical analyses are interesting, let's keep looking at the data, and they were suggesting additional analyses.

It's not unusual in science to have surprising findings, to have findings that maybe are not predicted, but the scientific process is to continue to do the experiments, look at the data, analyze the data, and let the science lead the way. And that's precisely what we did on this topic.

Q. Can I direct your attention to Page 2. This is an e-mail in the same chain from Dr. Beasley to you with copies to Robert Baker, Paul Berg, Scott Clark, John Holcombe, Roland Powell, Alvin Rampey and Roy Tamura, correct?

A. Yes.

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Q. And in his second paragraph he says, "These guys were really concerned about the weight gain. Not only because of a diabetes risk but all of the other potential health risks."

Do you see that language?

A. Yes.

Q. And what other potential health risks are there as a function of weight gain?

A. Well, one would first have to qualify weight gain as excessive weight or obesity as opposed to mere weight gain. If we're talking about obesity, then there are other health risks, cardiac, et cetera.

Q. Well, when you got this e-mail from Dr. Beasley where he said these guys are really concerned about the weight gain not only because of diabetes but all the other potential health risks, did you have anything in your mind as to what Dr. Beasley was referring to?

A. I'm not quite sure. I don't understand the question.

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Q. Or were you scratching your head when you got this e-mail from Dr. Beasley where he talked about all the other potential health risks or did you know what he was talking about?

MR. BOISE: Object to form.

A. Maybe I misunderstood your previous question. I thought you were asking me what are the other possible health risks of weight gain, and I qualified that to obesity, and I mentioned that there were other health concerns.

Q. Let's go on in Dr. Beasley's e-mail. He says, "They initially thought it might imply be a response to improvement in schizophrenia with a few outliers. A rather naive view but they ain't shrinks. When they understood that this is seen in nonpsychotic normals and animals on fixed diets, less concerned with animals, and that olanzapine is the worst offender other than clozapine, they advocated a different marketing strategy than we are taking."

Do you see that language?

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A. I do.

Q. And did you inform Dr. Tollefson of that?

A. Again, we had frequent and ongoing discussions about this topic.

Q. So you believe you would have told Dr. Tollefson about that?

A. Yes.

Q. And when you were getting input from outside consultants advocating a different marketing strategy for one of your top selling drugs that according to one of the other documents we saw you were betting the farm on, would you have expected Dr. Tollefson to bring that to the attention of the upper reaches of Lilly?

MR. BOISE: Object to the form of the question.

A. I'm going to -- again, I'm going to challenge the bet-the-farm comment. I don't exactly know what that means.

Q. Regardless of the bet-the-farm comment, when you get comments from outside experts that are experts in the

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field of diabetes and they're telling you that you ought to be using a different marketing strategy than what you're engaged in, and this is one of your top selling drugs, wouldn't you expect that Dr. Tollefson would have informed the top levels of the company about that?

MR. BOISE: Object to the form of the question. Calls for speculation.

A. There was broad knowledge across the company of the weight gain profile of Zyprexa.

Q. Sir, that's not my question. My question has to do with outside consultants telling Lilly they ought to be changing their marketing strategy. That's the thrust of my question.

Would you have expected Dr. Tollefson to tell his superiors that these outside experts in the field of diabetes are recommending that we change our marketing strategy for one of our top selling drugs?

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MR. BOISE: Object to the form of the question.

A. Again, the knowledge of the weight gain profile of Zyprexa was well understood across the company. It was extremely well-described in our label from day one. There was no question about weight gain.

We had medical letters out as early as 1996, we had posters, presentations, publications. So we were very active and forthright and earnest in communicating the weight gain profile of Zyprexa. So, quite frankly, I'm not quite sure what is meant by change your approach because our approach at that time was to be quite active in disclosing and transparent on weight gain.

Q. Sir, what they were telling you is not to be as aggressive in the marketing of this drug, isn't that correct? Isn't that what the outside consultants were saying?

MR. BOISE: Objection.

A. I don't read that anywhere

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here.

Q. Okay. Let's go on in the e-mail from Dr. Beasley. He says, "They believe we should aggressively face the issue and work with physicians to address methods of reducing weight gain."

Do you see that language, sir?

A. Yes.

Q. And, in fact, Lilly was telling physicians, outside physicians, that weight gain with Zyprexa was manageable; isn't that correct?

A. Again, we had many, many, different channels of communication on weight gain to the prescribing community.

Q. Sir, do you recall that Lilly told outside physicians, prescribing doctors, that weight gain with Zyprexa was manageable for most patients?

A. I recall --

MR. BOISE: Object to form.

A. I recall that we were, again, very forthcoming on this topic.

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Q. Sir, my question, please listen to my question, please listen to the words in my question and answer my question.

Do you recall that Lilly told outside physicians, prescribing doctors, that weight gain with Zyprexa was manageable for most patients? Are you denying that Lilly told that to doctors?

MR. BOISE: Objection. Compound. Which question?

Q. Sir, do you deny that Lilly told prescribing doctors that weight gain with Zyprexa was manageable for most patients?

MR. BOISE: Object to the form. Vague.

A. Again, I feel like we're kind of mixing themes.

MR. SUGGS: Sir, let's forget about the themes. Think about my words. Think about the words of my question and answer my question directly, please.

MR. BOISE: He's jumping

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topics. Don't be discouraged by it. Just answer his question.

QUESTIONS BY MR. SUGGS:

Q. Sir, do you deny that Lilly told prescribing doctors that weight gain with Zyprexa was manageable for most patients?

It's the third time I asked that question. Could you please answer it yes or no?

MR. BOISE: Object to the argumentative nature of your question.

A. I'm telling you what I know we did with weight gain and what we communicated on weight gain. And we communicated quite broadly and quite thoroughly about weight gain through numerous different channels that I talked about, starting with the label itself. We also took this advice in terms of pursuing research into interventions and different approaches to try to manage weight gain. So, I'm not seeing a disconnect.

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Q. Sir, let me try for the fourth time, and I'd appreciate just a simple yes or no answer to what I think is a simple question.

Did Lilly tell physicians that weight gain with Zyprexa was manageable for most patients?

MR. BOISE: Object to the form of the question.

A. I don't recall that exact phrase.

Q. Okay. In other words, you don't know?

A. I know what we did in terms of communicating weight gain.

Q. If I could direct your attention back to Dr. Beasley's e-mail. Three lines up from the bottom he says, "There does not seem much to say about scientific analyses of weight gain. We know it's a weighty problem. When you translate 1 to 2 percent gain of 40 plus kilos into the absolute number based on 5 million patients, the number is 50 to 100,000. 100,000 people

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putting on 90 pounds of weight is a lot."

Were you aware of that type of calculation before Dr. Beasley mentioned it in this e-mail to you?

A. I knew there was a distribution of weight gain. And knew, again, we talked about the tails of a bell-shaped curve.

Q. And you recall this morning I asked you whether you were aware that Dr. Beasley had done calculations indicating that there were some people who gained 80 to 90 pounds of weight and you said you didn't recall that?

MR. BOISE: Object to the form.

A. I'd need to refresh that transcript.

Q. Okay. Well, does this refresh your recollection that Dr. Beasley had, in fact, calculated on the order of 50 to 100,000 people gaining 90 pounds of weight while using Zyprexa?

A. I don't doubt the statistics.

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It's again a 1 to 2 percent. And those would be the tails of that bell-shaped distribution.

And the Kinon publication, I think we presented the data quite clearly on not only the more likely weight gain but also extremes at both ends.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. Sir, if I could direct your attention to the following page. At the top of Page 3, Dr. Beasley writes, "On the diabetes side, the concern was about the use of categorical analyses."

Do you see that language?

A. Yes.

Q. And who was it that decided to do categorical analyses?

MR. BOISE: Object to the form of the question.

A. I don't know that I know who decided initially. For approaches to data of this nature, we would typically do it in a

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cross-functional framework. We would consult endocrinologists in and outside the company, bring in our best people from stats and from neuroscience and create a delineated plan.

Q. Would that have originated within the Zyprexa Product Team, a decision to conduct categorical analyses of blood glucose?

A. I'm sure that Charles was involved in, Dr. Beasley were involved in those discussions.

Q. Okay. And back at this time in October of 2000 -- well, this analysis actually began in -- at least by February of 2000, as we saw earlier, correct?

MR. BOISE: Object to the form of the question.

A. Yes.

Q. Okay. And at that point in time there was nobody on the Zyprexa Product Team who was an expert in the field of diabetes, correct?

MR. BOISE: Object to the form.

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A. At that time I don't recall if we had a full-time endocrinologist. But again, it's the way we work at Lilly that we frequently have cross-functional meetings involving other people in the company.

So we would have to have the expertise of endocrinologists in the company on these types of issues.

Q. Is that a "no" or a "yes"?

MR. BOISE: Just read back the question.

QUESTIONS BY MR. SUGGS:

Q. At that point in time there was nobody on the Zyprexa Product Team who was an expert in the field of diabetes, correct?

A. Well, when you say "nobody on the team," does that mean --

Q. That means the team. Was there anybody, team member of the Zyprexa Product Team of which you were the head of, who was an expert in diabetes in the year 2000?

A. Missy Sowell began consulting with the team, then working part-time with

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the team, then working full time with the team. I quite frankly don't recall.

Q. You testified earlier that was in 2001.

MR. BOISE: You mischaracterized.

A. I said it could have been as early as 2000. And I'm not -- I don't recall precisely when her, again, consultation part-time/full-time began.

Again, I want to reiterate as I mentioned before, that Lilly is a company steeped in endocrinology expertise and we utilized that expertise throughout my time on the product team.

Q. Sir, my question has to do with the membership on your team. Can you name for me anybody who was, in fact, on your Zyprexa Product Team who was an expert in diabetes in the year 2000?

MR. BOISE: Other than what he's testified?

A. Again, I'm not recalling when Missy Sowell started, it could have been

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2000.

Q. Or it could have been, as you testified earlier, 2001, correct?

A. It's a possibility. I don't recall.

MR. SUGGS: Why don't we change the tape real quick.

THE VIDEOGRAPHER: Off the record. This concludes tape No. 4 of the deposition of Dr. Breier. It's 4:16.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: Back on the record, beginning of tape No. 5 of the deposition of Dr. Breier. It is 4:39.

QUESTIONS BY MR. SUGGS:

Q. When we took our break, Doctor, we were talking about Exhibit 1453, and I see that Mr. Boise has fumbled around with your exhibits and it's no longer in

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front of you?

MR. BOISE: Oh, for God's sake. They have been organized.

MR. SUGGS: You organized it right out of his sight.

Can I see your stack there and I can maybe help to find it.

MR. BOISE: With the help of the Court reporter, let the record reflect.

MR. SUGGS: What did you do, put them in no discernible order? Here we go. Here we go, 1453.

QUESTIONS BY MR. SUGGS:

Q. If I could direct your attention to Page 3. At the very top of the page it starts off by saying "On the diabetes side the concern was about the use of categorical analyses."

And I believe you told me that you weren't sure who had suggested the use of categorical analyses of your blood glucose data; is that correct?

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A. Again, my assumption would be that Charles Beasley working with endocrinology colleagues.
Q. Okay. And then if you could drop down about two-thirds of the way through that paragraph there's a sentence that says, "They specifically referred to the data as being 'tortured'." And the word tortured is in quotation marks. Do you see that? The word tortured is at the far left margin.
A. I see it, um-hum.
Q. And the "they" who are referring to the data being tortured were the outside consultants, correct? That was your understanding?
A. Um-hum.
Q. Did that surprise you when you learned from Dr. Beasley that the outside consultants felt that the data was being tortured?
MR. BOISE: Object to the form.
A. I don't recall having any particular reaction.

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Q. It's not a complimentary term, is it?
A. This makes it sound a bit paradoxical, but I believe that it is. Because what it describes as it's not giving up. It's really turning over every stone to determine what does the data really say.
And I agree with Charles's comment here that that's oftentimes in science considered a positive reference. So don't stop with the initial blush of data, but be certain it's real.
Q. But in this context, these outside experts in diabetes were skeptical of your conclusions and referred to the data as being tortured, correct?
A. I wouldn't put those two together. I think scientists --
Q. Well, let's break them apart. They were skeptical of your conclusions, correct?
A. You know, I'm going to have to take a minute more and read through the document. I don't recall them having

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problems with the categorical analysis. What I recall is that they were encouraging additional analyses and including continuous analysis. But I could read through the document to be certain about that impression.
Q. Well, let's move on to another area here within the document.
The last paragraph of Dr. Beasley's e-mail states, "With regard to the marketing side of this issue of impaired glucose tolerance/diabetes the message was clear, don't get too aggressive about denial. Blaming it on schizophrenia or claiming no worse than other agents, until we are sure of the facts and sure that we can convince regulators and academicians. WL with Rezulin was the example. Sounds exactly like what Dan Casey was saying."
Do you see that reference?
A. Yes.
Q. And the reference to "WL" is Warner Lambert; is that correct?
A. I assume so, yes.
Q. Okay. And this Dan Casey

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that's referred to there, is that the same Dr. Casey who back about a year earlier in November of 1999 presented data showing that 18 percent of people who used Zyprexa had diabetic levels of blood glucose that previously had been normal after using the drug for four months?
MR. BOISE: Object to the form.
Q. Is it the same doctor?
A. I believe it's the same doctor but I can't accept the statement that you made of the 18 percent.
We -- I already commented on that dataset and qualified it as not being a dataset that we could draw those kinds of conclusions.
Q. Okay. But that's what Dr. Casey was reported to have concluded but you did not agree, correct?
MR. BOISE: Object to the form.
A. As I recall, his dataset was a post hoc chart review of 38 cases with no

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comparator, no control for confound, not a clear understanding of all risk factors. And datasets of that nature, you can't make those kinds of conclusions.

Q. So you'd dismiss that report by Dr. Casey?

A. We don't dismiss it, but every -- and we look at all data, but all data are not created equal. And one has to look at each study based on its methodology in interpreting that data. And a post hoc case series of 38 individuals is not substantial enough data to make claims around 18 percent of patients. Just isn't.

Q. When Dr. Beasley here is saying "Sounds exactly like what Dan Casey was saying," was Dr. Casey also saying don't get too aggressive about denial?

A. What I recall Dan Casey saying, and what I agree with in this paragraph, is be sure, get it right, don't go out with data or messages that are not substantiated by the data, and be cautious. That to me is the Lilly way.

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Q. So, clearly you were under the impression these outside consultants were saying don't be too aggressive, correct?

MR. BOISE: Object to the form.

A. Don't get too aggressive about denial.

Q. "Blaming it on schizophrenia or claiming no worse than other agents until we are sure of the facts."

A. So the aggressive piece here, according to Charles, was don't get too aggressive about denial. I think that being energetic, he liked the word "aggressive." In terms of the science and the analyses is something I suspect they would support.

Q. In fact, sir, Lilly was very aggressive about marketing Zyprexa after October of 2000, correct?

MR. BOISE: Object to the form of the question.

A. Again, as I stated earlier, I didn't perceive any difference in our approach to Zyprexa before versus after that time period.

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Q. You were equally aggressive both before and after that meeting with the consultants, correct?

MR. BOISE: Object to the form.

A. I wouldn't characterize it as being aggressive.

MR. SUGGS: Let me hand you what's been previously marked as Plaintiff's Exhibit 4968.

(Whereupon, Plaintiff's Exhibit(s) 4968, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a multi-page document entitled "Zyprexa Diabetes Update." I'll also represent to you that the database produced to us by Eli Lilly dates this document as February 9, 2001.

QUESTIONS BY MR. SUGGS:

Q. And if I could direct your

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attention to Page 3, sir. The title at the top of that page is Hyperglycemia/diabetes U.S. Situation Analysis.

Do you see that page?

A. Yes.

Q. And in the middle of that page there's a heading with two bullet points under it that says "Lilly Actions in 2000."

Do you see that?

A. Yes.

Q. And it states, "DTP efforts across 4K consultants triple DTP spend."

I'm going to translate that from Lilly language to plain everyday English. DTP stands for direct-to-physician, correct?

A. I believe that's what it refers to.

Q. And 4K refers to 4,000, correct?

A. I would also agree with that.

Q. And the consultants that are referred to there are consultants that Lilly would hire to make presentations regarding

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Zyprexa, correct?
MR. BOISE: Object to the form.
A. I don't know that that's what it's referring to.
Q. Wasn't that what the direct-to-physician -- what was your understanding of what DTP or direct-to-physician marketing entailed?
A. Quite frankly, don't know what direct-to-physician means.
Q. Sir, isn't it a fact that that involved hiring outside physicians to speak to other physicians at presentations and seminars about Zyprexa?
A. I've heard the term, but I don't know what it is.
Q. In your Zyprexa Product Team, at least through 2002 or up to 2002, you had responsibility for supervising both the medical side and the marketing side, correct?
MR. BOISE: Object to the form.
A. We had on the Zyprexa Product

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Team a global marketing component and a R&D component.
Q. And you're telling us that you don't know what DTP meant?
A. That's correct.
Q. Okay. Were you aware that there was triple the direct-to-physician spending in 2000?
A. No.
Q. The next bullet point states, "Hyperglycemia Sell Sheet."
Do you know what sell sheet is?
A. What I'm assuming that means would be the materials that a sales representative would carry with them.
Q. Um-hum. And it refers to the "Hyperglycemia sell sheet Beasley PBO analysis in June," correct?
A. Yes.
Q. And that indicates that -- what, to you, sir?
A. PBO is not resonating.
Q. If I were to suggest placebo,

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would that ring any bells with you?
A. I don't know.
Q. Well, it was the Beasley analysis of the hyperglycemia data that went into the May 2000 label change, correct?
A. It was the categorical analysis that we talked about earlier.
Q. And that categorical analysis was presented to physicians in the hyperglycemia sell sheet, wasn't it, sir?
MR. BOISE: Object to the form.
A. I don't know.
Q. No one ever informed you of that?
A. Well, again, these are affiliate implementation activities. This was, this is really not at the level of the scope of the product team. So what was within a specific sell sheet or detail aid is something that would not have come under my examination.
Q. Sir, do you recall that it was in October of 2000 that the FDA made you

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take out that language that had been put in the labeling in May of 2000?
MR. BOISE: Object to the form.
A. Yes. They asked us to remove it. They felt that additional data would be helpful and we removed it.
Q. And, in fact, when they asked you to remove that language, they said that the information that you had put in the label on your own without prior FDA approval expressed a certain level of implied safety with respect to treatment-emergent hyperglycemia and was -- that this reassuring language was not appropriate for submission under a special supplement changes being effected; isn't that correct?
A. Let me look at that again.
MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 195.
MR. BOISE: I don't think he showed it to you yet.
(Whereupon, Plaintiff's

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Exhibit(s) 195, previously marked, was presented to the witness.)

MR. SUGGS: For the record this is an October 2000 letter from the FDA to Eli Lilly, specifically to the attention of Gregory T. Brophy.

QUESTIONS BY MR. SUGGS:

Q. And, sir, it was in this letter that the FDA directed Lilly to take out the language in the label that had been put in there in May of 2000 regarding hyperglycemia, correct?

THE WITNESS: I'm just completing the reading of the document.

A. Yes. They accepted diabetic coma and changes to neuroleptic malignant syndrome. They directed us to take the language on the categoricals out. And, you're right, they talked about the way you described, in addition indicated that a more complete submission of glucose data and

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additional discussions of pooling and analysis of the data was necessary.

Q. Specifically, the FDA said that the descriptive data expressed a certain level of implied safety and that that reassuring language was not appropriate, correct?

MR. BOISE: Objection. Asked and answered.

A. It was not appropriate for this, under this particular submission.

Q. Okay.

A. I don't ever recall them challenging the veracity of findings.

Q. Do you know how many physicians were presented with that presentation in which the FDA noted expressed a certain level of implied safety?

MR. BOISE: Objection to the form of the question.

MR. SUGGS: Let me restate the question.

QUESTIONS BY MR. SUGGS:

Q. Do you know how many

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physicians were told about that analysis by Lilly sales reps using a hyperglycemia sell sheet?

MR. BOISE: Object to the form.

A. I don't know the number.

Q. If I could direct your attention to at the bottom of the page --

MR. SUGGS: Strike that.

QUESTIONS BY MR. SUGGS:

Q. Let me direct your attention to the following page, Page 4.

MR. BOISE: Back to exhibit?

MR. SUGGS: 4968.

MR. BOISE: Okay.

QUESTIONS BY MR. SUGGS:

Q. The title on that page is Hyperglycemia/Diabetes U.S. Implementation Plan. Do you see that page?

A. I do.

Q. At the top of the page it says, "'Comparable rate,' slides in all DTP programs (SCC, CME advisory, et cetera) consistent with

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Accelerate Zyprexa/Blunt Pfizer strategy."

Do you see that language, sir?

A. I do.

Q. And "comparable rates" refers to the message that the rate of hyperglycemia with Zyprexa was comparable to the rates of hyperglycemia with other atypical drugs, correct?

A. That's correct.

Q. Okay. And that was the position that Lilly was taking in 2000 and 2001, correct?

A. Yes. And at that time, that was the best interpretation of the data.

Q. And Lilly was stating that position despite the fact that the outside consultants in October of 2000 were saying "don't get too aggressive about denial, blaming it on schizophrenia, or claiming no worse than other agents," correct?

A. Again, what I took from that consultation was to don't stop looking. Keep -- do the recommended additional

analyses. And we accepted their recommendations and conducted those.

So what I heard them say was, you know, there may be more to this story, continue to look, consider different analyses, et cetera, and that's what we did.

Q. Sir, when it say --

MR. SUGGS: Move to strike to nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. When it refers to "SCC," do you know what that stands for?

A. No.

Q. Does "CME" stand for continuing medical education?

A. Yes.

Q. And what does "advisory" refer to?

A. I'm not sure.

Q. When it talks about this comparable rate slide being consistent with the "Accelerate Zyprexa/Blunt Pfizer strategy," what does that refer to?

A. I'm not certain.

Q. Well, we know what "Accelerate Zyprexa" means, don't we?

MR. BOISE: Object to the form.

A. I don't know what's being referred to in this context.

Q. Okay. The next item on that page is, "'Comparable Rates,' end quote, Sell sheet in the hands of representatives beginning February 19." Correct?

A. Yes.

Q. So were you aware that there was a comparable rates sell sheet developed to give to sales reps?

A. It was my understanding that the sales force were equipped with the most recent data on metabolic issues. That would include data from PCS and other studies.

Q. Okay. With respect to this message of comparable rates, that was the message that Lilly was delivering in the market in, from at least 2000 continuing to the present day; is that correct?

MR. BOISE: Object to the form. Foundation.

A. I don't know what the message is today. I can tell you that the data is still consistent today.

Q. As far as you're aware the message is the same?

MR. BOISE: Object to the form. Asked and answered.

A. I don't know.

Q. Don't you still deal with Zyprexa anymore?

A. My responsibilities since I've been in my new role are quite a bit broader in terms of responsibility for aspects of other molecules. So -- and I, quite frankly, don't know what the marketing messages are on Zyprexa in the U.S. Affiliate. But I am familiar with scientific literature and can attest that the current data continues to show no significant differences among atypicals.

MR. SUGGS: Move to strike the nonresponsive portion of your

answer.

QUESTIONS BY MR. SUGGS:

Q. Sir, I'd like to explore some more with you about what the company was telling doctors about weight gain and diabetes.

MR. SUGGS: I'm going to hand you what has previously been marked as Plaintiff's Exhibit 1110, and also Plaintiff's Exhibit 1111.

(Whereupon, Deposition Exhibit(s) 1110, 1111, previously marked, was presented to the witness.)

MR. SUGGS: And I'll represent to you that these documents are dated in the database that was provided to us by Lilly as November 2001 -- actually, Exhibit 1110 is dated 11/29/01 and Exhibit 1111 is dated 11/28/01.

And I'll also represent that these documents came, again according to the database, from the

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files of Matthew Pike.
QUESTIONS BY MR. SUGGS:
Q. Do you know who Matthew Pike is, sir?
A. I don't recall Matthew Pike.
Q. Matthew Pike, I'll represent that he was in the Issues Management group that reported to Denice Torres. Does that ring any bells?
A. I'm not recalling that name.
Q. In November of 2001, Denice Torres reported to you in the Zyprexa Product Team; is that correct?
A. Yes.
Q. If I could direct your attention first to Exhibit 1110, the one on weight gain. In particular, the second page. There are several headings there. The first one is "Issue" and the second one is "Our Position." And under "Issue," the first bulleted point states, "Weight gain remains the No. 1 liability of Zyprexa and is leading to many of the new issues surrounding the drug -- diabetes, lipids, et cetera."

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Do you see that?
A. Yes.
Q. And were you aware in November of 2001 that weight gain remained the No. 1 liability of Zyprexa?
A. I wouldn't necessarily use those terms, but that was a significant side effect for some patients, and it was an area of substantial focus.
Q. And then below that issue is a heading titled "Our Position." And Our Position was, "Weight gain can occur with Zyprexa as with other antipsychotics and mood stabilizers. For most patients, this can be managed allowing him to receive the overwhelming benefits Zyprexa offers."
Do you see that language?
A. Yes.
Q. And were you aware that that was Lilly's position in 2001?
MR. BOISE: Object to the form of the question. Foundation.
A. You know, I'm reading the words on this page. I don't know precisely

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what was intended or meant here. We were heavily investing in management approaches to weight gain and getting data that some of them were successful for some patients, and this may well have been referring to that work.
Q. Sir, this statement in the physician section here that, "For most patients this," referring to weight gain, "can be managed allowing them to receive the overwhelming benefit Zyprexa offers."
That was just spinning the data, wasn't it?
MR. BOISE: Object to the form. Argumentative.
A. No.
Q. If I could direct your attention to the second page, pardon me, the following page on Page 3. There's a section in there about "Marketplace Feedback" and some bulleted items. And in the middle is a quote stating, "It is laughable when Lilly comes in and tries to talk about weight gain."

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Do you see that?
A. I do.
Q. Were you informed that the market research was that doctors were saying it was laughable when Lilly comes in and tries to talk about weight gain?
MR. BOISE: Object to form. Foundation.
A. This sounds like the quotation of one individual. It was not my impression that that was generally held. We, again, were quite active in our transmission of data on this particular topic. My general sense was that people were impressed with the work that we were doing.
Q. If I could get you to direct your attention to Page 4. There's a heading towards the bottom saying "What We Don't Know." The last bullet point in that section states, "Knowing that weight loss programs only work approximately 5 percent of the time in normal volunteers, does Lilly want to provide a program where if it doesn't work it may be looked at as another 'laughable

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attempt?"
Do you see that language, sir?
A. Um-hum.
Q. Were you informed that that was the kind of feedback that Lilly was getting about its position --
MR. BOISE: Object to the form.
Q. -- concerning weight gain?
MR. BOISE: I'm sorry, Dave. Object to the form of the question.
THE WITNESS: Could you restate your question?
MR. SUGGS: Can you read it back, please?
Let me strike the question.
MR. BOISE: The Court reporter's objected to your question.
Q. Sir, if, in fact, weight loss programs only work 20 percent of the time in normal volunteers, that means your position "for most patients weight gain can be

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managed" was just false; is that correct?
MR. BOISE: Object to the form of the question.
A. No. Again, I'll speak to the studies that we conducted which include pharmacological and nonpharmacological and were able to demonstrate in some patients interventions were quite helpful, other patients they weren't.
Q. Sir, if weight gain -- if weight loss programs only work approximately 5 percent of the normal time in volunteers, how could weight gain for most patients be managed?
MR. BOISE: Object to the form. Argumentative.
A. I'm not prepared to accept this 5 percent. I don't know who authored this document. I don't know what the resource was or their knowledge base. I'm familiar with the studies that we conducted on interventions. Again would state that for some patients the interventions were quite helpful and for other patients they were not.

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Q. Sir, for most patients they were not, correct?
MR. BOISE: Objection to form. Foundation.
A. We'd have to look at each study one at a time.
Q. If I could direct your attention to Exhibit 1111. This is the one that has the title "Diabetes." In particular, if I could direct your attention to Page 4. There's a heading at the bottom that says "What We Don't Know." And the second point there of "What We Don't Know" was "How to effectively deal with the weight gain associated with Zyprexa."
Do you see that?
A. I'm reading the page.
A. I see that.
Q. Sir, if you didn't know how to effectively deal with the weight gain associated with Zyprexa, then it would be a falsehood to tell doctors that for most patients weight gain's manageable; isn't that correct?

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MR. BOISE: Object to the form of the question. Foundation. Argumentative.
A. I'd have to raise the same concern with this document that I raised with the weight gain document. I don't know who authored this, I don't know what the source of the information was, I don't know -- for example, is this an early draft, is it one person's opinion, or what it was.
I will again indicate that we had a number of different interventions for weight gain. For some patients they were helpful, for other patients they were not.
Q. Sir, if, in fact -- I realize that you dispute what this says or the validity of what this says, but if, in fact, you didn't know how to effectively deal with the weight gain associated with Zyprexa, then it would not be right to tell doctors that weight gain can be managed with most patients, correct?
MR. BOISE: Object to the form of the question.

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Q. Those two statements are mutually incompatible, correct?
MR. BOISE: Object to the form of the question.
A. I mentioned earlier today that I did not know and cannot confirm that Lilly was telling doctors that weight gain could be managed for most patients.
Q. Isn't that what we saw in the weight gain document, Exhibit 1110?
MR. BOISE: Let him finish.
A. Because it appears in one document, again, that's not referenced, we don't know who wrote it, I can't -- I can't attest that that ends up becoming a Lilly policy or central statement.
Q. Sir, are you going to deny to the jury that Lilly told doctors that weight gain was manageable for most patients? Wasn't that, in fact, a central part of your marketing pitch in 2000, 2001, 2002, 2003?
MR. BOISE: Object to the form of the question. Foundation. Argumentative.

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A. Again, I'll say that I don't know that that was the case. I can speak, again, to the data. I've already reiterated that.
There were a number of different studies that were conducted to look at interventions, and some of them were effective and some of them weren't.
Q. So it's your testimony then that if, in fact, Lilly marketed Zyprexa by claiming that weight gain was manageable for most patients, that was something that was done without your knowledge; is that correct?
MR. BOISE: Object to the form. Mischaracterizes his testimony.
A. I'm just saying that I don't know the statement you just stated "weight gain is manageable for most patients" was a central tenet of the marketing message.
Q. Isn't that just another way of saying just what I said. If the marketing people were saying that to prescribing doctors, that was without your

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knowledge?
MR. BOISE: Object to the form.
A. Again I'll say -- I'll just have to keep repeating myself.
Q. If I could direct your attention to the second page of Exhibit 1111. And the first heading there, "Issue," the first bullet point states, "Latest U.S. market research shows that diabetes is the No. 1 reason physicians are concerned about potential weight gain with Zyprexa."
Do you see that?
A. Yes.
Q. And because you were the head of the Zyprexa Product Team, and at least throughout 2001 the Zyprexa Product Team included a marketing component, you would have been informed of that market research, would you not?
MR. BOISE: Object to the form of the question.
A. I was aware of market research that was coming into the team on

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Zyprexa. This particular statement in that time frame is not, not ringing true.
Q. Okay. So it's your testimony that this document is wrong and that at that time the market research was not showing that diabetes was the No. 1 reason physicians are concerned about potential weight gain? Is that correct?
A. I'm going to have to again indicate that I don't know the background of this document. I don't know who wrote it. I don't know what their sources were.
My understanding back at this time was that weight gain was a concern. But that it was, but that with diabetes connected was the No. 1 reason that doesn't -- I don't recall that.
Q. Okay. So it's your testimony this document is false?
MR. BOISE: Object. Mischaracterizes the document.
Q. Or the statement in the document's false?
MR. BOISE: Same objection.

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A. I'm just saying I don't know what the source is. I don't know who wrote it. I don't know where this came from.
Q. That's different from what you said earlier. Can you testify one way or the other as to whether this statement is true or not?
A. I'm not familiar with the statement so I don't think that I can.
Q. Okay. That's fair enough. Dropping down to the next heading there regarding Our Position. It states, quote, "Diabetes/hyperglycemia may occur in patients taking antipsychotics and/or mood stabilizers including Zyprexa at comparable rates with the possible exception of clozapine."
Do you see that, sir?
A. Yes.
Q. And you were aware and, in fact, endorsed that as Lilly's position, correct?
MR. BOISE: Object to the form. Mischaracterizes his

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testimony.
A. This is an accurate statement of the data.
Q. And you endorsed that position, correct?
MR. BOISE: Object to the form.
A. Yes.
Q. Okay. And then below that at the very bottom of the first page is the "Rationale For Position" and it states, "Showing that diabetes is a common occurrence for all antipsychotics and not just Zyprexa will help reduce the perception that diabetes is linked specifically to Zyprexa and, in turn, will help to eliminate this risk from the risk/benefit equation."
Do you see that, sir?
A. I do.
Q. And were you informed that at least the marketing department viewed that as a rationale for the position?
MR. BOISE: Object to form. Foundation.

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A. I am, again, going to say that this is an isolated point. I don't know where it came from. There's elements of this statement that are not something I would agree with and are not consistent with my view of the data.
Q. Sir, my question had to do with whether you were informed that the marketing department was stating that or not?
MR. BOISE: Object to the form. Foundation.
Q. Were you informed of that, that that was the rationale, the marketing rationale for the position?
MR. BOISE: Object to the form. Foundation.
A. I would challenge that that's not the marketing, that that's not the marketing position.
Q. Well, if this document came from the files of Matthew Pike who reports to Denice Torres, which department would that come from, sir?
A. I don't know. It could be

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one of many different things. It could be a preliminary document, it could be one person's thoughts, it could be a proposal from an intern. There's a lot of different possibilities. But I can tell you what the data said, and the marketing message reflects the data.
Q. Sir, the data doesn't address the rationale, correct?
A. It must be part of it.
Q. I'd direct your attention to Page 4 of this exhibit. There's a heading there entitled "What We Know." First bullet point says, "Olanzapine does cause modest elevations in mean random glucose."
Do you see that language?
A. Um-hum.
Q. And physicians were never told that, were they, sir?
MR. BOISE: Object to the form. Foundation.
A. Again, this is misleading, it's not accurate, and I can't -- I can't support it.

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Q. And you would agree with me, sir, that treating physicians were never warned by Lilly that "Olanzapine does cause modest elevations in mean random glucose," correct?

A. There is no data to support a cause-and-effect relationship.

Q. Sir, again, that's not responsive to my question. I need a direct answer to my question.

Lilly never told prescribing physicians that "Olanzapine does cause modest elevations of mean random glucose." Whether you think that's true or not, the fact of the matter is, Lilly never told doctors that, correct?

MR. BOISE: Object to the form of the question.

A. Our marketing message followed the scientific understanding of the data.

MR. SUGGS: Sir, can you please just listen to my question and answer it directly.

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MR. BOISE: Don't load it up. Just ask the direct question. There's a speech--

MR. SUGGS: I've asked it different ways. He never answered it.

MR. BOISE: -- around it. I know. There's a speech around it.

QUESTIONS BY MR. SUGGS:

Q. Sir, Lilly never told treating doctors that olanzapine does cause modest elevations of mean random glucose?

MR. BOISE: Object to the form of the question.

Q. True or not?

A. Correct.

Q. The next message, "Greater than placebo, greater that haldol, equal to risperidone, close to clozapine." Do you see that, sir?

A. Yes.

Q. And physicians were never told that olanzapine causes modest elevations of mean random glucose greater than placebo, greater than Haldol, correct?

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MR. BOISE: Let me have that read back.

MR. SUGGS: Let me strike that.

QUESTIONS BY MR. SUGGS:

Q. If you go to the third bullet point, it states, "Glucose elevation partially accounted for by weight gain."

Do you see that language?

A. I see it.

Q. Physicians were never advised of that, were they, sir, by Lilly?

A. It's not supported by the data. Again, we looked at that very carefully. So I -- we talked about this earlier today, and those data are not supported.

Q. Well, sir, isn't it true Dr. Beasley wrote you a memo in February of 2001 in which he specifically said these increases, pardon me, these changes are accounted for in part but not entirely by weight increase? Do you recall that?

MR. BOISE: Object to the

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form. Mischaracterizes the document.

A. I'd have to look at it.

Q. Well, independent of the document, before I hand it to you, do you recall that?

A. No.

MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 5565.

(Whereupon, Plaintiff's Exhibit(s) 5565, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a string of e-mails. The one I'm particularly concerned with, sir, is the one in the middle of the page, of the first page, from Charles Beasley to Ralf Dittmann with copies to you, Patrizia Cavazzoni, Mark Millikan, Anna Thornton and Gary Tollefson, Subject: Olanzapine and

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hyperglycemia, et cetera.
QUESTIONS BY MR. SUGGS:
Q. Do you recall receiving this e-mail from Dr. Beasley back in February of 2001?
A. I do.
Q. And when was the last time you reviewed this document?
A. Um, I believe within the last month.
Q. And in this e-mail Dr. Beasley wrote starting in the third sentence, "Our continuous analyses show that olanzapine does result in statistically significant mean increases in random glucoses relative to placebo and haloperidol. No significant difference relative to Risperidone but power is small. Clozapine is associated with a larger olanzapine versus haloperidol and a significant increase compared to haloperidol. These increases are occurring as early as week one. May not represent a true deterioration in glycemic metabolism but

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simply an increase in food intake since these are random and not fasting glucoses. These changes are accounted for in part but not entirely by weight increase."
Do you see that language, sir?
A. Yes.
Q. And, sir, does that refresh your recollection that Dr. Beasley told you that the glucose elevations that they were seeing were partially accounted for by weight gain?
A. Again, we've looked at this very carefully and --
Q. Sir, my question is whether that refreshes your recollection that that's what Dr. Beasley told you?
A. You've read this e-mail correctly. He and I have had multiple different conversations on this topic.
Q. And that's my question, is whether he told you about that, whether this refreshes your recollection that he told you? And does it now refresh your recollection?

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MR. BOISE: Objection. He never said he -- object to the form.
A. You've read the e-mail correctly. The key point I think in this e-mail is the problem with continuous measures of random samples.
Q. Sir, let's get back for a second. Remember before I showed you that document, I asked you do you recall Dr. Beasley telling you that increases in glucose with Zyprexa users were accounted for in part but not entirely by weight increase and you said no. So I showed you the document. And now I've shown you that language.
And my question is: Does this now refresh your recollection that Dr. Beasley told you that? That's my question.
A. And I would say yes at this one point in time, but in order to give you fuller context to the question --
Q. Sir, I'm just asking for a direct answer to my question, and you have

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answered it, yes, this does refresh your recollection that Dr. Beasley told you that, correct?
A. To that narrow question yes.
Q. That's my question.
A. I do think, though, it's important to appreciate that what he points out here is very, very important in interpreting the continuous data, and that is the food effect of random samples, and that alone makes it nearly impossible to draw the conclusions around weight.
THE WITNESS: Move to strike your answer as not responsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, can we get back to Exhibit 1111? That's the one in your left hand.
A. Yes.
Q. At the bottom of Page 4 is another heading that states "What We Don't Know." We already talked about part of that, the part that said you didn't know how to effectively deal with weight gain associated

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with Zyprexa.
I want to ask you about the first bullet point, though, that says, "Impact of olanzapine on patients already at risk of developing diabetes."
Do you see that language?
A. Yes.
Q. Lilly never advised physicians not to use Zyprexa in patients with diabetes, correct?
MR. BOISE: Object to the form of the question.
A. That's correct.
Q. Okay.
A. And perhaps just to further add that, our labeling is very clear on that point as well.
THE WITNESS: Move to strike as nonresponsive.
QUESTIONS BY MR. SUGGS:
Q. Sir, if I could direct your attention to Page 5 of Exhibit 1111. There's a reference to "Key Verbatims." And the term "verbatim" is a term of art in your company,

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is it not?
A. I'm not sure I know what you mean.
Q. Have you ever heard the term "verbatim" used before in connection with the marketing of Lilly drugs?
A. I'm familiar with the term "verbatim".
Q. And what does it mean?
A. It would be a verbalization.
Q. And it refers to instructions to sales reps as to what they are to say about a drug, correct?
A. I'd accept that. They're trained to interact with doctors and to provide information.
Q. Okay. And what this page reflects is the key verbatims that sales reps were to use in communicating with physicians about Zyprexa and diabetes, correct?
MR. BOISE: Objection. Foundation.
A. I'll have to take a read. Okay.

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Q. My question was, "And what this page reflects is the key verbatims that sales reps would use in communicating with physicians about Zyprexa and diabetes," correct?
MR. BOISE: Note my objection.
A. I can't tell from this document if, in fact, these were key verbatims for the sales force or if these were a summation of facts or exactly how these would be used.
Q. I'd like to direct your attention to Page 6. There's a table there entitled Desired Evolution. Are you familiar with that?
A. I've not seen this before, no.
Q. It lists as an action step: "Drive in the minds of our customers that risk of developing diabetes is no different on Zyprexa than other agents."
You were certainly aware of that, weren't you?

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A. Well, I was aware of the data that indicated that there were comparable rates among all atypical antipsychotic drugs.
Q. And the desired outcome for that action step was to "Lower the percentage of customers that directly linked Zyprexa with diabetes." Do you see that, sir?
A. Yes.
Q. And were you informed that that was the desired outcome?
MR. BOISE: Object to the form. Foundation.
A. Again, I'm, I don't know the origin of this document. I don't know who constructed it. That would not be consistent with our approach to doing the science that we could do, the best science we could do, and then creating the marketing messages from that science.
Q. Okay. So it's your testimony it would be inappropriate to have this as the desired outcome "to lower the percentage of customers that directly link Zyprexa with

diabetes"?
A. No.
MR. BOISE: Objection, mischaracterizes the testimony.
A. That's really not the point. It's what the data says.
Q. You said "that would not be consistent with our approach." If it's not consistent with your approach, then it would be inappropriate, correct?
MR. BOISE: Objection, mischaracterizes the testimony.
A. Let me tell you what I do mean. When it says "lower the percentage of customers that directly link Zyprexa with diabetes," if there was a misunderstanding or a misperception about the data, then correcting that misperception would be appropriate.
There's not a baseline here upon which to kind of further interpret that statement. The goal would be to help prescribers have a realistic understanding of what the data said.

Q. Sir, at least the language as stated in this document indicates that whoever wrote this, their desire was to get doctors so they didn't even think about diabetes with Zyprexa, and, in fact, took it out of the risk/benefit calculation; isn't that correct?
MR. BOISE: Object to the form. Compound.
A. No, that's completely inconsistent with our approach. We were very clear about the data. We were clear that there was a higher rate of diabetes in schizophrenic and bipolar patients. We had medical letters, slide sets, publications.
What I'm trying to address in this point is what is most critical is that prescribers have an accurate understanding of the information, and through multiple different approaches we strove to achieve that.
Q. Sir, you just denied that it was the approach of Lilly to have physicians take diabetes out of the risk/benefit

calculation. Can I direct your attention to Page 2 of this document? And you see at the bottom of that page there's a Rationale For Position?
A. Um-hum.
Q. Can you read that aloud for the jury, please?
MR. BOISE: You can read it. He's done reading for you before, David. You can read it aloud.
MR. SUGGS: Can you read it aloud, please?
MR. BOISE: Are you able to read it aloud?
THE WITNESS: I can do that.
MR. BOISE: Why don't you ask him a question?
MR. SUGGS: I've asked him to please read it aloud for the jury, what that says.
MR. BOISE: He's not going to read. He's not here to read. It's not his document, it's not his writing.

MR. SUGGS: I know you're embarrassed.
MR. BOISE: It's not embarrassed, Dave, it's not about embarrassed. It's not a question to ask a person. It's not his document.
QUESTIONS BY MR. SUGGS:
Q. Dr. Breier, are you refusing to read that language to the jury?
MR. BOISE: I'm telling you it's not an appropriate question and I'm objecting to it.
QUESTIONS BY MR. SUGGS:
Q. My question is, sir, would you please read that aloud for the jury, what this document says?
A. "Showing that diabetes is a common occurrence for all antipsychotics and not just Zyprexa will help reduce the perception that diabetes is linked specifically to Zyprexa, and in turn, will help to eliminate this risk from the risk/benefit equation."

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MR. SUGGS: Thank you, Dr. Breier. It's now about, it's past 5:30. Want to commence tomorrow at 9:30?

MR. BOISE: Fine. Are you done for today?

MR. SUGGS: Yes.

THE VIDEOGRAPHER: This marks the end of tape No. 5 of the deposition of Dr. Alan Breier. We're off the record at 5:33.

AND FURTHER THE DEPONENT SAITH NOT.

____

ALAN BREIER, M.D.

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STATE OF INDIANA)
) SS:
COUNTY OF MORGAN)

I, Rebecca J. Swinney, RMR-FCRR, a Notary Public in and for the County of Morgan, State of Indiana at large, do hereby certify that ALAN BREIER, M.D., the deponent herein, was by me first duly sworn to tell the truth, the whole truth, and nothing but the truth in the aforementioned matter;

That the foregoing deposition was taken on behalf of the Plaintiffs pursuant to the Indiana Rules of Trial Procedure;

That said deposition was taken down in stenograph notes and afterwards reduced to typewriting under my direction, and that the typewritten transcript is a true record of the testimony given by the said deponent; and that the signature of said deponent to his or her deposition was requested;

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That the parties were represented by their counsel as aforementioned.

I do further certify that I am a disinterested person in this cause of action; that I am not a relative or attorney of either party, or otherwise interested in the event of this action, and am not in the employ of the attorneys for either party.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 13th day of January, 2007.

____

Rebecca J. Swinney, RMR-FCRR
CSR No. 94-R-1047
Notary Public

My Commission Expires:
March 9, 2007

County of Residence:
Morgan

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ERRATA

PAGE	LINE	CHANGE

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK
IN RE: MDL-1596
ZYPREXA PRODUCTS
LIABILITY LITIGATION
THIS DOCUMENT RELATES TO:
ALL CASES

C O N F I D E N T I A L

- - -

January 12, 2007

- - -

Videotape deposition of

ALAN BREIER, M.D.

VOLUME 2

- - -

GOLKOW LITIGATION TECHNOLOGIES
1880 John F. Kennedy Boulevard
Suite 760
Philadelphia, Pennsylvania 19103
(877) 370-3377

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CROSS-NOTICES SERVED FOR ALAN BREIER DEPOSITION
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Eddie D. Cook v. Eli Lilly, et al., -CV-1004-ID, USDC Middle District Alabama
Betty Weathers v. Eli Lilly, et al., -cv-00666-WHA-DRB, USDC Middle District Alabama
Mary Mallard v. Eli Lilly, et al., 2:06-cv-481-VPM, USDC Middle District Alabama
Patricia Segrest v. Eli Lilly, et al., 2:06-cv-542-WHA, USDC Middle District Alabama
Charles O. Crowder v. Eli Lilly, et al., 2:06-cv-1321-WMA, USDC Northern District Alabama
Debra A. Betts v. Eli Lilly, et al., 1:06-CV-00742-CB-M, USDC Southern District Alabama
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Alvin Young v. Eli Lilly, et al., 06 cv 2595 WQH (LSP), USDC Southern District California
Karl Kovacs v. Eli Lilly, 79D01-0601-CT-00001, Tippecanoe County, Indiana
Danny Tardy, et al. v. Eli Lilly, et al., CV-03-538, Cumberland County, Maine
In re: Risperdal/Seroquel/Zyprexa Litigation, #274, Middlesex County, New Jersey
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USDC Middle District Louisiana
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Gary Green v. Eli Lilly, et al., 3:06cv149-M-A, USDC Northern District Mississippi
Robert Sutherland v. Eli Lilly, 251-04-271, Hinds County, Mississippi
Anthony Ritter v. Eli Lilly, 3:06cv358HTW-JCS, USDC Southern District Mississippi
Sharon Osborne v. Eli Lilly, et al., 3:06CV706HTW-LRA, USDC Southern District Mississippi
Rick Galati v. Eli Lilly, et al., 05CW-CV00781, Callaway County, Missouri
Terrence L. Raine Sr. v. Eli Lilly, et al., 105CC4194, Greene County, Missouri
Don Stricklen v. Eli Lilly, et al., 0616-CV-12957, Jackson County, Missouri
Kyle Rolfingsmeyer v Eli Lilly, et al., 0611-CV03687, St. Charles County, Missouri
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Frank and Jeanette Howard, et al.v. Eli Lilly, et al., 05-EV-000217B, Fulton County, Georgia
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Christopher Daniel v. Eli Lilly, -3419, USDC South Carolina
Vickie Trapp v. Eli Lilly, -CV-02313-MDL, USDC South Carolina
Thompson Fry v. Eli Lilly, -CV-03076-MDL, USDC South Carolina
Samuel Davis v. Eli Lilly, 3:06-cv-2312-CMC-BHH, USDC South Carolina
Patsy Nissen v. Eli Lilly, 1:06-cv-02456-MDL, USDC South Carolina

- - -

Volume 2 of the videotaped deposition of ALAN BREIER, M.D., held in the offices of Barnes & Thornburg, 11 South Meridian Street, Indianapolis, Indiana 46204-3535 Commencing at 9:41 a.m., on the above Date, before Rebecca J. Swinney, a Registered Merit Reporter and Federal Certified Realtime Reporter.

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THE VIDEOGRAPHER: We are on the record. Here begins Volume No. 2 of the deposition of Dr. Alan Breier duly taken by the plaintiff. We're going on the record at 9:41 a.m. Today's date is January the 12th of 2007.

MR. BOISE: Is there anyone on the phone that wasn't here yesterday?

Appearances are the same.

MR. SUGGS: Okay. Would you reswear the witness, please.

- - -

ALAN BREIER, M.D., after having been duly sworn, was examined and testified as follows:

- - -

EXAMINATION

- - -

QUESTIONS BY MR. SUGGS:

Q. Good morning, Dr. Breier.

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A. Morning.

Q. Yesterday we talked briefly about how you spoke to the sales force in October of 2000 about the use of Zyprexa for the treatment of patients with Alzheimer's. Do you recall that?

A. Could you restate the question?

Q. Sure.

Do you recall that yesterday we spoke about your presentation to the sales force in October of 2000 at the Viva Zyprexa launch meeting about the use of Zyprexa for the treatment of Alzheimer's?

A. I spoke about Alzheimer's in that one speech. Again, the purpose of that was because I knew that there were certain clinical realties that the sales force would encounter, and I wanted them to be aware of it, as well as to understand the future developments that were ongoing on Zyprexa, and Alzheimer's was one of those developments.

Q. Do you recall that by

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November of 2001, about a year later, sales of Zyprexa for use by the elderly was about $500 million --

MR. BOISE: Objection to form.

Q. -- per year?

MR. BOISE: I'm sorry. Foundation.

THE WITNESS: Could you repeat the question?

MR. SUGGS: Sure.

QUESTIONS BY MR. SUGGS:

Q. Do you recall that by November of 2001, approximately a year after you gave that presentation, Zyprexa sales for use in elderly people were on the order of $500 million a year?

A. I don't recall the specific dollar figure.

MR. SUGGS: Let me show you an e-mail that you wrote in November of 2001. We'll mark this as Breier Exhibit 4.

(Whereupon, Deposition

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Exhibit(s) 4 duly received, marked and made a part of the record.)

MR. SUGGS: For the record, this is an e-mail chain, it's a two-page document, starts off with the first page with an e-mail from John Lechleiter to a number of individuals. His e-mail is dated November 20, 2001, and this document bears the Bates No. ZY207409274.

QUESTIONS BY MR. SUGGS:

Q. Sir, if I could direct your attention to the second -- well, lower on the first page is an e-mail from yourself to John Lechleiter dated November 19, 2001; is that correct?

A. Yes.

Q. Okay. And on the second page of this document, towards the middle of the page is some language in bold font that says "Brand architecture suggests pursuing the Alzheimer's segment opportunistically with major focus placed on acutely and chronically

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ill nonelderly schizophrenic and bipolar patient, i.e., high dose segments. Lilly's current business in the elderly segment is about $500 million."

Do you see that language, sir?

A. I do.

Q. Does that refresh your recollection that as of November 2001, Lilly's current business at that point in the elderly segment was about $500 million?

A. I'd like to take a minute and just read the document, then I'd be very pleased to answer the question.

Q. Is it necessary to answer that particular question that I posed?

A. For that specific question, probably not but --

Q. Well, that's all that I'm concerned about right now. We'll deal with the other stuff later. To answer my standing question, does seeing that document that you, yourself, wrote in November of 2001 refresh your recollection that by November of 2001

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Lilly's business in the elderly segment was about $500 million?

A. I'm reading that here and that's a correct description.

Q. Okay. And that's $500 million per year, correct?

A. Presumably that's the case.

Q. Okay. Now do you recall that Lilly began promoting Zyprexa for the elderly in May of 1999?

A. We promoted Zyprexa for schizophrenia and bipolar mania exclusively. That would include all age segments over the age of 18 for those segments. There's a substantial number of bipolar patients and schizophrenic patients among the elderly, and we would be promoting for those segments.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. Do you recall that there was a launch into the long-term care market in July of 1999?

A. I recall that there was a

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long-term care sales force. I don't recall the launch date.

MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 1419.

(Whereupon, Plaintiff's Exhibit(s) 1419, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a document entitled "Zyprexa in the U.S. market Qualitative Update" and is dated May 5, 1999. And, sir, I would direct your attention to the second physical page.

QUESTIONS BY MR. SUGGS:

Q. Down towards the bottom there's an Issue No. 5 in bold. "Issue No. 5 - Getting killed in long-term care market. Risperdal share 2X Zyprexa."

Do you see that reference, sir?

A. I do.

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Q. And do you recall that there was a feeling at Lilly that the company was getting killed in the long-term care market?

A. No.

Q. Do you recall being aware at that time that the Risperdal share of the long-term care market was twice that of Zyprexa?

A. I don't recall that.

Q. If you can direct your attention to the language right below that it notes several actions. The first is "Launch into LTC market July 1999."

Do you see that reference?

A. Yes.

Q. "LTC" stands for long-term care, correct?

A. Yes.

Q. And does this refresh your recollection that Lilly launched Zyprexa in the language term care market in July 1999?

A. I'm reading the words on that page, and you've read it correctly.

Q. And does that refresh your

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recollection that, in fact, Lilly did launch into the long-term care market in July of 1999?

A. Again, I'm familiar that there was a long-term care sales force in the U.S. Affiliate. My recollection of when that sales force launched is being refreshed now by this document, and I'll accept that it was July of 1999.

Q. And who is in charge of that long-term care market in Lilly?

MR. BOISE: In 1999?

MR. SUGGS: In 1999.

A. I don't know.

Q. Do you know who was in charge of that market at any time?

A. No.

Q. What share of the market was Gino Santini involved with?

MR. BOISE: What share?

MR. SUGGS: What area of the market.

THE WITNESS: I don't understand the question.

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MR. SUGGS: I'll withdraw the question.

Q. You'll see the second numbered action number is "DTP PsychLink program on elderly patients in May."

We established yesterday that DTP stands for direct-to-physician; do you recall that?

A. Yes.

Q. And do you know what the PsychLink program was?

A. No.

Q. I'd like to direct your attention back to what we marked as Breier Exhibit 4, which was your November 2001 e-mail.

In November of 2001, well, prior to that time, Lilly had conducted a number of trials, clinical trials, to assess the efficacy of Zyprexa as treatment for Alzheimer's; is that correct?

A. Yes. We were at that time pursuing an indication for Alzheimer's psychosis. We had created a clinical plan to do that. That consisted of a variety of clinical trials, and those either had started or were about to start or were underway at that time.

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Q. And at the bottom of the first page of Exhibit 4, Breier Exhibit 4, you briefly summarized the results of four studies that were conducted regarding use of Zyprexa for Alzheimer's, correct?

A. Yes. These were components of a clinical program, four trials that were used to pursue an indication for Alzheimer's psychosis.

Q. I guess actually I misspoke. Although you list four clinical trials that are there, you only give the results on three, and you noted that the last one there, HGIV, was still ongoing; is that correct?

A. That's correct.

Q. Okay. And the three studies where you did report the results you note that for study HGOA the results were that Zyprexa was numerically but not statistically superior to placebo, correct?

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A. That is correct.

Q. With respect to study HGEU, you noted that the results were that 5 and 10-milligram doses of Zyprexa were significantly superior to placebo but there were some safety concerns, correct?

A. You've correctly read the line on the e-mail describing the EU trial.

Q. And with respect to study HGGU, you described the results as being that there was no separation between olanzapine versus placebo, olanzapine versus Risperdal or Risperdal versus placebo; is that correct?

A. You've read that correctly. It goes on to say a large placebo response may explain the negative findings, that's correct.

Q. Were you saying there that you were unable to detect any difference between olanzapine as compared to placebo?

A. The results of the HGGU trial failed to separate any of the treatment arms.

Q. So nothing was better than placebo, correct?

A. And what I was trying to describe is why we thought that might be the case.

Q. I understand that. But first I need to establish, I'm trying to find out what you meant by no separation. And basically what that meant was that nothing was better than placebo, correct, olanzapine wasn't, Risperdal wasn't. You just weren't seeing anything that would distinguish the drug treatments over and above placebo, correct?

A. That's correct. What we found was that there were there were three treatment arms, risperidone failed to separate from placebo, olanzapine failed to separate from placebo, and olanzapine and risperidone failed to separate from each other.

Q. Okay. And you also noted in your e-mail that the FDA has raised the threshold for acquiring an indication. That's on the second page. Is that correct?

A. That is correct.

Q. And the reason why the FDA raised the threshold for acquiring an indication for the treatment of Alzheimer's was because FDA viewed this patient group as being particularly vulnerable, correct?

A. That is partially correct.

Q. Isn't that what you wrote in your e-mail? You said, "This patient group is viewed as particularly vulnerable with a high sensitivity for an adverse events."

A. I think a little more context here would be --

Q. Excuse me, sir, can you first answer my question? Did you write that in your e-mail?

MR. BOISE: The question that's pending is are those words in your e-mail as opposed to what his understanding of what FDA was saying?

MR. SUGGS: Yes.

A. Those words are in my e-mail.

Q. Okay. And on the basis of

the fact that the FDA had raised the threshold for acquiring an indication, and the fact that your clinical studies weren't really showing terribly great results, you recommended that the company not pursue an indication for Alzheimer's; isn't that correct?

MR. BOISE: Object to the form.

A. That's correct with an important caveat, and that is as you noted, the HGIV trial was ongoing. If that trial showed very promising results, we, as a team agreed that we would consider revisiting this issue. But you are correct, at this point we were communicating to the organization that we were not optimistic and would be winding down the Alzheimer's program.

Q. And your bottom line as reflected on the second page of your e-mail was, "We recommend not pursuing a formal indication for Alzheimer's psychosis because of the mixed clinical results, the

need to initiate another global trial, the high FDA threshold, concerning safety risks, and strategic focus on high dose segments. The recommended approach is to support this segment with a publication strategy," correct?

A. You've read that correctly.

Q. And "publication strategy" refers to publishing articles, scientific articles about the use of a, use of Zyprexa for Alzheimer's, correct?

MR. BOISE: Object to the form.

A. We had trials that were winding down, as you noted. There was an ongoing trial. We have a policy of publications for our clinical trials. So we intended to publish the results of those trials.

Q. You knew that physicians were using Zyprexa for the treatment of Alzheimer's, correct?

A. We knew from market research and from clinical practice that antipsychotic

drugs, olanzapine as well as other antipsychotic drugs, were widely used by physicians who treat patients with Alzheimer's disease.

Q. To the tune of $500 million a year of Zyprexa in 2001, correct?

MR. BOISE: Object to the form of the question. Mischaracterizes his prior testimony.

A. That's not accurate. What I refer to there is the elderly segment, and noted that the elderly segment is comprised of substantial numbers of schizophrenic and bipolar patients.

Q. And also people with Alzheimer's, correct?

A. As noted, Zyprexa, as well as other antipsychotic drugs, were used by physicians treating Alzheimer's patients, that is correct.

Q. Did you ever inform physicians of the results of these studies that are referenced on the first page of

Breier Exhibit 4?

A. Yes.

Q. In the label?

A. The labeling of these trials were included for safety purposes. So there's an elderly section that includes safety information. Again, because of the awareness by the FDA that these drugs are commonly used, the efficacy sections were not included because we did not gain an indication.

Q. And, in fact --

MR. FIBICH: Excuse me, I want to object to the responsiveness of that answer.

Q. In fact, your studies showed either -- well, as you note here, your studies were mixed. In one you found that there was a numerical but not statistical support to placebo, and the other one you found superior efficacy but safety concerns, and the other one you couldn't find any difference at all between olanzapine and placebo.

Did you ever inform physicians in your labeling that the clinical studies that you'd done regarding the use of Zyprexa for Alzheimer's had those mixed results?

MR. BOISE: Objection. Asked and answered.

A. We were completely transparent with the results of these studies. We communicated all the results of all of these studies to the FDA. We labeled these studies appropriately in conjunction with FDA guidelines, i.e., we included the safety information but not the efficacy information because we did not have an indication, it would be inappropriate to do that. We published all of these papers.

Q. Sir, is the answer to my question no then, that you did not inform physicians in your labeling that the clinical studies that you'd done regarding the use of Zyprexa for Alzheimer's had those mixed results?

MR. BOISE: Objection, asked

and answered.

A. It would have been inappropriate to include efficacy information in the label on a disorder where one does not have an indication.

MR. SUGGS: Objection. Nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. You did not state in the label the findings of those results, correct?

MR. BOISE: Object to the form.

A. I can only keep repeating my answer. We labeled appropriately regarding these trials.

Q. Sir, I'm not asking your opinion, okay? You're not here as an expert witness, you're here to answer facts. I'm asking a factual question, not your opinion about what was appropriate or not appropriate.

And my question to you, sir, is, did your labeling ever state the findings of those results in the labeling?

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MR. BOISE: He's answered that question.
Q. Yes or no?
MR. BOISE: He's answered that question.
MR. SUGGS: No, he's not?
MR. BOISE: He's answered the question, Dave.
MR. SUGGS: No, he's not.
MR. BOISE: Objection. Asked and answered.
QUESTIONS BY MR. SUGGS:
Q. Did your labeling state that or not?
A. If you're asking me did we include the efficacy data of these four trials in the label, my answer is no.
Q. Thank you.
MR. FIBICH: Barry, can we get back to just "objection form?"
MR. BOISE: We can't have the same questions over and over again.
MR. SUGGS: He needs to answer the question.

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MR. BOISE: I'm allowed to say the basis for the objection.
MR. ALLEN: No, you're not.
MR. FIBICH: I thought Peter had ruled otherwise. It's objection form and not make talking. I thought we had this issue before.
MR. BOISE: I haven't made speaking objections.
MR. FIBICH: Sir?
MR. BOISE: I haven't made speaking objections. I think the record will be what it is. I'm entitled to state the basis for the objection. I'm not making speaking objections. I object to --
MR. SUGGS: If I ask you the basis you can tell me, otherwise just state "objection form," according to my understanding.
MR. FIBICH: Barry, you haven't been bad about it. When you tell him "asked and answered," when you tell him -- you had another one

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a minute ago -- I really do think it's suggestive. I'm just saying try not to do it.
MR. BOISE: I'm not suggesting anything. I'm trying to make sure we all comply with the notion we have the one question asked and not repeat it.
MR. FIBICH: We had this before. You might not have been on the call.
MR. BOISE: I was on the call I'm familiar with the order.
MR. FIBICH: Let's proceed.
QUESTIONS BY MR. SUGGS:
Q. Doctor, do you recall in 2002 the Japanese regulatory authority required Lilly to drastically change their warning and issue an emergency safety information letter to Japanese physicians warning of the risk of diabetes with Zyprexa?
A. In April of 2002, there were label changes to the Japanese label for Zyprexa that included a warning and a letter

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to doctors.
MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 320.
(Whereupon, Plaintiff's Exhibit(s) 320, previously marked, was presented to the witness.)
MR. SUGGS: For the record this document has a cover page which states Appendix Six, Japanese Dear Doctor Letter.
QUESTIONS BY MR. SUGGS:
Q. And, sir, do you recognize this as a translation of an emergency safety information letter that Lilly issued to Japanese physicians in April of 2002?
A. Yes.
Q. Okay. And in the actual letter, am I correct that the border that appears to be black on this black and white copy is, in fact, red?
THE WITNESS: In Japan?
MR. SUGGS: Yes. In the

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original letter that went to Japanese physicians.
A. Yes, that is their practice.
Q. Okay. And the heading at the top of the letter says "Important" in the upper left-hand corner and then in big bold letters right at the top says "Emergency Safety Information," correct?
A. Yes.
Q. This is definitely designed to get the attention of physicians in Japan, correct?
A. Yes. That's the purpose of a communication to prescribers.
Q. And in fact, it did definitely get the attention of physicians in Japan, correct?
MR. BOISE: Object to the form.
A. Physicians in Japan were aware of this warning and of the data.
Q. And Zyprexa sales went dramatically down after physicians in Japan received this label; isn't that correct?

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A. I don't recall the sales trends after this was issued.
Q. Sir, don't you recall writing a memo about those sales trends to Mr. Lechleiter?
A. Sitting here today, I don't recall that.
Q. Okay. We'll go into that in some more detail later.
Let's talk about this "Dear Doctor Letter" or this Emergency Safety Information Letter that went out. This was done at the order of the Japanese regulatory authorities by Lilly, correct?
A. Yes.
Q. Thank you. This was not something Lilly wanted to do. Lilly was ordered to do this by the Japanese regulatory authorities, right?
MR. BOISE: Object to the form of the question.
A. The issue of wanting or not wanting is not relevant. The Japanese regulatory authorities directed us to send

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this letter out, and we complied with that direction.
Q. After first opposing it. You told the Japanese regulatory authorities that you didn't think it was necessary, correct?
A. We engaged the scientists of the Japanese regulatory agency on the merits of the cases that they were basing this on. We pointed out to them that those cases are confounded. What that means is that they had multiple other factors that could have contributed to these events.
We also brought to their attention a worldwide database that would suggest that some of what they were recommending was not supported by that worldwide database. So we had scientific exchanges with the regulatory group.
Q. You objected to having to do this, and the regulatory authorities listened to what you had to say and then directed you to issue this letter to physicians in Japan, correct?
A. On the merits of the small

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number of cases that they were citing, the fact that those cases were confounded and an extensive worldwide literature, we felt that this action was not warranted. They disagreed, and we complied with their direction.
Q. And at this point in time in Japan there had been nine serious cases including two cases of death with hyperglycemia, diabetic ketoacidosis, and diabetic coma that had been reported in Japan. Correct?
A. That is correct.
Q. And by this point in time in June of 2000 -- well, it says since the marketing of this product in June 2001, there had been those nine serious cases, correct?
A. At the time of this action, June -- or I'm sorry -- it appears that what this is saying is that -- my understanding is that from the time that this issue was introduced there had been nine cases.
Q. And worldwide, Lilly was

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aware of hundreds of reports of hyperglycemia and diabetes by April of 2002; isn't that correct?
A. There were a number of spontaneous adverse event reports of a variety of different occurrences similar to the ones that we're talking about here that were, again, thoroughly reviewed, assessed for confounds, and presented to all the regulatory agencies around the world, including the Japanese regulatory agency.
Q. In the middle of the first page of this emergency safety information letter is a black box. Well, it appears to be black. Was it also bordered in red or was it actually in black, if you recall?
A. I don't recall.
Q. Okay. It has in some rather large font and bold print three principle points; is that correct?
A. There were three numbered points in the box.
Q. Okay. And the first one states "Do not administer to patients with

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diabetes mellitus and those who have a history of diabetes mellitus," correct?
A. That's correct.
Q. And in the United States, at least, Lilly was not taking the position that Zyprexa should not be used with patients having diabetes, correct?
A. Our view of the science was that the science did not support a contraindication for diabetes.
Q. You used the term there "contraindication." That's a term of art in the pharmaceutical industry, correct?
A. In the regulatory, in the regulatory world.
Q. Okay. And basically what it means is if there is a contraindication in the label, it means do not use this product for this particular type of patient or this particular type of illness or whatever, correct?
A. That's correct. Whatever is specified in that contraindication, you're correct.

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Q. So, the Japanese regulatory authority was making diabetes a contraindication for the use of Zyprexa, correct?
A. Correct.
Q. Okay. Diabetes was not a contraindication in the United States, correct?
A. It was not a contraindication at this time, nor is it a contraindication today, and, frankly, I'm not aware of there being a contraindication for diabetes any other place in the world.
Q. Okay. Point No. 2 in the Japanese Emergency Safety Information Letter was "During administration of this product" -- this is an English translation -- it says, "observe sufficiently with such as measurement of blood glucose." And I realize it's --
MR. BOISE: Those are your words, Mr. Suggs.
MR. SUGGS: Well, actually, it's whoever translated this for

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Lilly.
QUESTIONS BY MR. SUGGS:
Q. Was it your understanding that the Japanese regulatory authority was instructing physicians --
MR. SUGGS: Well, strike that.
QUESTIONS BY MR. SUGGS:
Q. Was it your understanding that the Japanese label --
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. Was it your understanding that the Zyprexa label in Japan instructed physicians to conduct glucose blood testing of patients who were using Zyprexa?
A. Yes. They were directing physicians to monitor for the occurrences of potential diabetes and to do so with blood monitoring.
Q. And did it specify a schedule for conducting such testing?
THE WITNESS: Let me take a look further into the document.

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A. I don't see an exact schedule here. I'll share with you my recollection, but I'm sure there would be a way to refresh this if I'm not completely accurate.

What I recall was that there was direction to monitor that would include but was not exclusive of blood monitoring.

I recall there being recommendations to take a blood glucose at the initiation of treatment, but I don't recall there was specificity around the frequency or the number of blood draws that would occur after treatment.

I also recall that Lilly partnered with the agency to assess this topic following these directions to try to refine guidance on blood monitoring. And that's my best recollection.

Q. Okay. It's fair to say that the situation with respect to the Zyprexa label in April of 2002 was as follows then: In the European labeling there was discussion of diabetes and hyperglycemia in the special precautions and special warnings section of

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the labeling and such discussion had been there since July of 1999; is that correct?

A. The European label does not have a separate warnings and a separate precautions, it's all inclusive so there's warnings and precautions. And you're correct that in 1999 there was information put into that section.

Q. And then we also had the warnings in Japan that we've just discussed, correct?

A. That's correct.

Q. But in the U.S. there was no language in either the warnings or the precautions section about diabetes or hyperglycemia, isn't that correct, in April of 2002?

A. At that time that is correct.

Q. Okay. Now as the head of the product team, did you have discussions within the company after the Japanese label change in April of 2002 as to whether or not Lilly should voluntarily change the U.S. label to include a warnings or precautions section

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about the risk of diabetes?

A. Because the approach to labeling varies from country to country, there's different practices and philosophies of labeling, we felt confident that we were accurately labeled in the U.S. at that time.

I will say that part of our practice was continual assessment of regulatory issues, labeling issues, multiple different issues. So that we would be having discussions about, and challenging ourselves was part of the practice on the team. But I can tell you as head of the team at that time we were confident that we were appropriately labeled in the U.S.

MR. ALLEN: Objection. Nonresponsive.

Q. You did have such discussions about whether the U.S. label was appropriate or whether it should be modified?

A. Again, we, throughout my tenure on the team, we continuously challenged ourselves on a range of important issues. We felt that it was through that

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sort of open back and forth that we would get it right. And that was our objective. And again, we felt that through analysis of new data, deliberations, consultation, we had it right.

Q. Okay. So you considered the issue of whether or not the U.S. label should be changed in April of 2002 after the Japanese label change but you came to the conclusion that that was not necessary, correct?

MR. BOISE: Object to the form.

A. Just to get full context here, we would have had discussions along those lines before the change, during and after, because that was our practice of working together, was continually looking at new data as it came in, continually asking the question are we labeled appropriately, and through those careful deliberations we came to the conclusion that we were.

Q. Let me show you -- Well, let me ask you a

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question first. What's the policy committee at Lilly?
A. There's a number of different governance committee and committees that work on policy.
THE WITNESS: I will assume that you're referring to the corporate policy committee; is that correct?
MR. SUGGS: Yes.
A. If that's the case, that would be the primary governance committee in the company.
Q. And who are the members of that policy committee?
A. The chair of the committee is Sydney Taurel, and depending on what time period we're talking about, there would be different representation.
Q. Say, April of 2002?
A. I will attempt to give you my recollection of the membership at that time, understanding that at certain points people retire and other people assume positions.

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At that time, I would -- my recollection is that John Lechleiter would have been a member, Gus Watanabe, perhaps Gerhard Mayr, Ms. Goss, Pedro Granidio, and there may have been a few more and I'm not recalling them at this moment.
Q. Okay. Are you presently on the policy committee today?
A. No.
MR. SUGGS: Let me hand you what's been previously marked as Plaintiff's Exhibit 4051.
(Whereupon, Plaintiff's Exhibit(s) 4051, previously marked, was presented to the witness.)
MR. SUGGS: For the record this is a four-page document. The cover page states Policy Committee Meeting April 12, 2002, Zyprexa Safety Overview. And it has some handwritten notes on the front page.
QUESTIONS BY MR. SUGGS:
Q. First of all, do you recall,

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sir, that there was a policy committee meeting which was given a Zyprexa safety overview in April of 2002?
A. Prior to looking at this document, I don't recall that specific date.
Q. Okay. Did you recall in general that there was a policy meeting in connection with the Zyprexa label at around that time period?
A. I can refresh my recollection with the document. It was not unusual to present reviews of Zyprexa to the policy committee, so it would be reasonable to assume that at some point in that period there would have been a presentation.
Q. Were there regular presentations to the policy committee regarding Zyprexa?
A. I wouldn't characterize them as regular. That would suggest a routine schedule or a quarterly update or something of that nature and they were not regular.
Q. Okay. How often were presentations made to the policy committee

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regarding Zyprexa?
A. I'm not completely sure. I will give a rough estimate.
Q. Sure.
A. I would say, perhaps, twice a year.
Q. Okay.
A. Something in that neighborhood.
Q. And was Sydney Taurel, the chief executive officer, was he usually present at these policy committee meetings?
A. Yes.
Q. And was John Lechleiter usually present at those policy committee meetings also?
A. Yes.
Q. Okay. And at these policy meetings, was it the usual practice to give a presentation regarding the safety of Zyprexa when Zyprexa was discussed?
MR. BOISE: Object to the form of the question.
A. The topics would vary. So it

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would depend on the particular theme that the policy committee was either interested in or we felt was important to present to them.

Q. Okay. And who would give the presentation to the policy committee regarding Zyprexa?

A. The format of that meeting was a relatively brief preread. And then --

Q. Can I interrupt you for a second? What do you mean by "preread"?

A. A short text of the topic at hand.

Q. So that would be given to the committee members before the meeting to review?

A. That's correct.

Q. Okay.

A. And then there would be a discussion as opposed to a presentation.

Q. Okay. And were you generally present at those meetings of the policy committee where Zyprexa was discussed?

A. I would say that I was frequently present. I would have been

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present for issues related to the product team.

Q. Okay. With that background in mind, if I could direct your attention to Exhibit 4051, and does this appear to be a preread that you referred to?

A. It appears to be.

Q. Okay. And who would have prepared the Zyprexa safety overview?

A. I don't have a recollection of who prepared this particular document. Given the nature of the document, I'm going to venture that it was likely physicians that worked on Zyprexa, scientists that worked on Zyprexa, members of the Zyprexa Product Team, perhaps other scientists as well.

Q. Okay. Who were the likely candidates for having a hand in that?

A. At this time myself, Patrizia Cavazzoni, Charles Beasley, are people who likely could have worked on this.

Q. Okay. I'm presuming that since this -- the members of the policy committee were all upper level executives,

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correct?

A. Yes.

Q. I'm assuming that in the preparation of these types of prereads that you would take care to make sure that things were stated accurately, correct?

A. Strive to do that.

Q. And I realize you're not a member of the policy committee but do you know whether minutes of such meetings are kept?

A. No.

Q. You just don't know one way or the other?

A. Correct.

Q. Okay. Do you recognize the handwriting on the first page?

A. No.

Q. I'll represent to you, sir, that the database that provided this document indicates that it came from the files of Mike Bandick. And was he part of the Zyprexa Product Team in April of 2002?

A. I don't recall precisely when

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Mr. Bandick joined the product team.

Q. Do you recall generally?

A. My recollection is it would have been in this time frame, but I don't have a precise recollection of when he joined.

Q. The handwritten note states "Mike, FYI, you may want to excerpt some of this material for JL discussion."

Do you see that?

A. I do.

Q. JL are the initials of John Lechleiter, correct?

A. They could be referring to John Lechleiter.

Q. Do you know if Mike Bandick had conversations with Mr. Lechleiter about the safety of Zyprexa?

A. I don't know.

Q. Okay. If I could direct your attention to the second page. In the introduction section, in the second to last sentence it states, "A side effect that is associated with Zyprexa is weight gain and the sequelae of weight gain."

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Do you see that?
MR. ALLEN: Right there in the first paragraph.
THE WITNESS: The first paragraph on the second page?
MR. ALLEN: First page.
MR. SUGGS: Well, it's in the introduction section, introduction paragraph, second to last sentence. "A side effect that is associated with Zyprexa is weight gain and the sequelae of weight gain."
MR. BOISE: One at a time.
MR. ALLEN: I'm just helping.
MR. BOISE: I know.
Is the question does it say that?
MR. SUGGS: Yes. He appears to be having a hard time finding it.
A. Yes.
Q. Okay. And what, the word sequelae is a medical term, is it not?
A. It is used in medicine.
Q. And when it's used in

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medicine it means the results of or the effects of something, correct?
A. I would say may be associated with.
Q. That's your understanding of the meaning of the word sequelae is may be associated with?
A. Yes.
Q. Doesn't mean to you the effects of?
MR. BOISE: Objection.
A. I would stick with my definition. To me it's a more nonspecific term.
Q. Okay. If I could direct your attention to the section on clinical data. There's a section there for weight gain that says, "Five atypical antipsychotic agents are associated with more weight gain than most traditional neuroleptic agents in the following order, most to least, Clozaril greater than Zyprexa greater than Seroquel greater than Risperdal." And then below that it says, "Zyprexa weight gain is roughly

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twice that of Risperdal;" is that correct?
A. You've read that correctly.
Q. And was that conclusion on the basis of studies that had been conducted by Lilly or was that an analysis of other data?
A. This would represent a combination of the available data at the time. So that would include Lilly data, but it would also include other sources of data.
Q. Okay. And it's also noted there that Pfizer's Geodon and BMS's Ara --
MR. ALLEN: Abilify.
MR. BOISE: Ari -- you need to look at the document, Scott.
MR. ALLEN: I'm just doing it out of memory.
MR. SUGGS: Let me start over.
QUESTIONS BY MR. SUGGS:
Q. "It also notes that Pfizer's Geodon and aripiprazole --
MR. SUGGS: Is that how you pronounce it? Probably, not. You

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can pronounce it.
THE WITNESS: Aripiprazole.
QUESTIONS BY MR. SUGGS:
Q. "Aripiprazole appear to have less metabolic issue than other atypicals." Have I stated that correctly?
A. You've read those words correctly.
Q. And that's a reference to other atypical antipsychotic drugs, correct?
A. The term "atypicals" is referring to other atypical antipsychotic drugs, that's correct.
Q. And Geodon and aripiprazole are two other atypical antipsychotic drugs, correct?
A. That's correct.
Q. And they had less weight gain than the four drugs that were listed above, and they had, appear to have, less metabolic issues than those drugs, correct?
MS. JOBES: Object to foundation.
A. My assumption, what's been

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Q. Sir, I need to have you answer my question as a matter of fact. I'm not asking for your opinion. I'm not asking for your spin. I just want you to confirm for the jury on this record that your labeling did not inform physicians that results of two Lilly epidemiological studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa. It's a simple yes or no question. Did Lilly tell that to doctors or did they not?

MR. BOISE: Object to the form of the question. Compound. You've asked about four questions there. What is the simple question?

Q. My simple question, sir, is: It is true, is it not, that Lilly's label did not inform physicians in the precautions or warnings section in 2002 that "Results of two Lilly epidemiological studies indicate that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa"?

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A. I first want to take umbrage with your comment about spinning. And I assure you that I'm not spinning any answers, I'm answering as forthrightly as I possibly can.

Q. Then can you please give me a yes or no answer to that question, sir?

A. Yes.

The approach to labeling requires that you take into account the totality of the data --

MR. SUGGS: Excuse me, sir. Can you please answer the question simply and directly yes or no, and then after answering directly, if you feel the need to expand on your answer then by all means you can say whatever you want. I'm not going to try to cut you off at all. But please, sir, would you answer the question directly and then give whatever other verbiage you feel is appropriate. Okay? Let me restate the question.

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QUESTIONS BY MR. SUGGS:

Q. It is true, is it not, that Lilly's label in 2002 did not inform physicians in the warnings or the precautions section that results of two Lilly epidemiological studies showed that the risk of diabetes is increased in patients treated with antipsychotics including Zyprexa? Yes or no?

A. The answer is no. And the reason for that is because it would have been inappropriate to include such language based on the data that was available in 2002. These studies did not change the appropriateness of the label as of 2002. They are used in labeling because we take a totality of all of the information when we examine our label. So these two studies did inform our thinking but reassured us that we were appropriately labeled in 2002.

MR. SUGGS: Move to strike the nonresponsive portion.

MR. BOISE: Okay, let's take

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five. Take a break.

MR. SUGGS: Okay.

THE VIDEOGRAPHER: Marks the end of tape No. 1 of the deposition of Dr. Breier. We're off the record at 10:45.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: We are back on the record. This is the beginning of tape No. 2 of the deposition of Dr. Breier; it's 11:03.

QUESTIONS BY MR. SUGGS:

Q. Dr. Breier, I'd like to direct your attention back to Exhibit 4051. In the bullet point just below the one we were talking about it states "FDA FOI Database of reports of DM cases: Clozaril 542, Zyprexa 434, Risperdal 244, Seroquel 57."

We need to do some

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translation of that into English.
MR. BOISE: It's in English.
MR. SUGGS: Well, kind of.
QUESTIONS BY MR. SUGGS:
Q. "FDA," obviously, is the FDA, but FOI stands for freedom of information; is that correct?
A. Yes.
Q. And the reports of DM cases refers to report of diabetes, correct?
A. Yes.
Q. And then the numbers behind the names of the various drugs there are the number of reports of diabetes adverse events that were contained in the FDA's freedom of information database.
Let me start over.
And then the number behind the names of the various drugs there are the number of diabetes adverse events that were contained in the FDA's freedom of information database; is that correct?
MS. JOBES: Object to foundation.

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A. I believe you've read that correctly.
Q. Okay. And did Lilly have someone who would periodically check the FDA database for adverse event reports of not only Zyprexa but also other drugs as well?
A. Yes. And additionally, we had our own before department that was serving the environment as well.
Q. And part of the pharmacovigilance department's function was to do that type of accessing of the FDA's database on adverse event reports?
MR. BOISE: Object to the form.
A. They would have been doing that as well.
Q. Okay. And this shows that for Clozaril there were 542 reports of diabetes, correct?
A. Yes.
Q. Okay. And Clozaril had been on the market for some years longer than Zyprexa, correct.

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A. Yes.
Q. Okay. Zyprexa had 434 reports of diabetes, and Risperdal had only 244, correct?
A. Correct.
Q. And Risperdal had also been on the market longer than Zyprexa, correct?
A. That's correct. They were registered at different times.
Q. By the way, am I correct that there is generally an understanding that the number of events that are actually --
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. Am I correct that it's generally assumed that the number of adverse events that are reported are only a fraction of what actually occurs because of underreporting?
MR. BOISE: Object to the form of the question.
A. You're correct in that all of the cases that occur are not always reported.
Q. And, obviously, no one, since

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there is underreporting, no one knows exactly the extent of underreporting but it's often assumed that only 1 to 10 percent of adverse, of actual adverse events in the real world get reported; is that correct?
MR. BOISE: Object to the form.
A. Those are rough estimates. And there's many assumptions underlying those estimates, including the types of events one would be considering, a variety of other factors that impact reporting patterns. So it's difficult to ascertain an exact ratio and these are rough estimates.
Q. It's often said the number of events that are actually reported are only the tip of the iceberg, one to ten percent, in that range, correct?
MR. BOISE: Object to the form of the question.
A. Again, it's quite variable depending upon the condition, the drug. They may change over time depending on the kinds of information, for example, that might be in

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the public domain. So there's a variety of different factors that would impact reporting trends.

Q. Okay. Do you recall attending -- now that we've talked about this preread for the April 12, 2002 policy committee meeting -- do you recall actually attending that meeting now?

A. I don't recall.

Q. Okay. There was no change in the Zyprexa label that came about in the U.S. in 2002 after the Japanese label change, correct?

MR. BOISE: Object to the form of the question. Vague.

A. As your question's worded, I'm thinking about any kind of label change.

Q. Let me be more specific. There was no change in the U.S. label to add any warnings or precautions regarding diabetes or hyperglycemia in the United States in 2002, correct?

A. Correct.

Q. Okay. Do you recall -- well,

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let me back up a second. Who is Bert van den Bergh?

A. Bert van den Bergh is an executive at Eli Lilly.

Q. And what's his position?

THE WITNESS: Currently?

MR. SUGGS: Well, what was his position back in April of 2000 -- strike that.

QUESTIONS BY MR. SUGGS:

Q. What was his position back in July of 2002?

A. He was President of Neuroscience and my boss.

Q. Okay. And do you recall traveling to Japan for four days in June of 2002 with Mr. van den Berg?

A. I do.

Q. And when you came back, you wrote a memo, you and Mr. van den Bergh wrote a memo to Dr. Lechleiter and Gerhardt Mayr and with a copy to Mr. Mascarenhas; is that correct?

A. I'm not recalling that

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specific, a specific message. When we returned from visiting Japan, we communicated notes about our trip. But I can't say I'm recalling a specific e-mail to the people that you mentioned.

MR. SUGGS: Okay. Let me show you a document that we'll have marked as Breier Exhibit 5.

(Whereupon, Deposition Exhibit(s) 5 duly received, marked and made a part of the record.)

MR. SUGGS: For the record, this is a three-page document dated July 1, 2002. It appears to be a memo from Bert van den Bergh and Alan Breier to Dr. Lechleiter, Mr. G. Mayr and Mr. A. Mascarenhas, and it has beginning Bates No. ZY203332491.

QUESTIONS BY MR. SUGGS:

Q. And did you, in fact, prepare this memorandum with Mr. van den Bergh on July 1, 2002?

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A. I'm not recalling the preparation of this specific message. I see both of our names at the bottom, so I'm assuming that we both worked together on this communication.

Q. Okay. And I'm assuming that you and your boss, when you prepared this memorandum for Dr. Lechleiter and Mr. Mayr, would have taken care to be accurate in your reporting on your trip to Japan, correct?

A. We'd strive to be accurate.

Q. Okay. By the way, who is Mr. Mascarenhas? Am I pronouncing his name correctly?

A. Mascarenhas. He was the country manager of Japan.

Q. And in the first paragraph of your -- let me back up a second. It appears that you went to Japan with Mr. van den Bergh from June 23 to June 27, 2002, correct?

A. That's correct.

Q. And this memorandum purports to be a summary of that trip, correct?

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A. Yes.
Q. And in the first paragraph of your memo you state in the second sentence, "It is clear that the impact of the label change in Japan has been very profound. We concluded that we have lost substantial ground and trust in our relationships with the MHLW."
And am I correct that MHLW are the initials for the Japanese regulatory authority?
A. You are correct.
Q. And your memo continues on to state, "Market research shows that we have also lost quite a bit of credibility with prescribers and opinion leaders. Basically they felt left in the dark with what they perceive as the late sharing of safety information. As a result, there has been a 75 percent drop in new patients who are being put on the drug and a continuing fairly high drop-out rate."
Did I read that correctly?
A. You've correctly read the

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words in the e-mail.
Q. And I'm assuming that that market research was conducted by Lilly, correct?
A. That would also be my assumption.
Q. Okay. And then if you could drop down to the third paragraph on the first page you state, "A further issue is team motivation and turnover in the sales organization and lack of trust, both from a sales force and a customer level. We have recommended, in line with the affiliate's proposal, to adjust promotional strategy to reflect the reality of the new label in Japan, enhance confidence by our message for the appropriate use of the product within the label, and point out how to specifically address concerns about hyperglycemia and the potential use of the product in patients with diabetes."
Do you see that language, sir?
A. I do.

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Q. And could you explain what you meant when you used the term or used the phrase "enhance confidence by our message for the appropriate use of the product within the label"? What did you mean by "within the label?"
THE WITNESS: I'm going to just take a moment and read the second paragraph, and I'd like to reread the beginning of the third paragraph.
MR. SUGGS: Sure.
THE WITNESS: I've read the second paragraph and the first part of the third paragraph.
QUESTIONS BY MR. SUGGS:
Q. And my question was, what did you mean by use of the phrase "use of the product within the label"?
A. The label had just been changed to include a warning on hyperglycemia and diabetes, as we had discussed. This then would require the company to approach customers in a different way, customers

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meaning, primarily, psychiatrists, in a different way. And therefore, it was essentially adapting the sales force approach to psychiatrists with the new information.
So, how were they going to present the new label change? What will that mean for using the product? We talked about blood monitoring, et cetera. So this essentially was referring to the implementation of the new label change.
Q. Well, when you use the expression there message -- "enhance confidence by our message for the appropriate use of the product within the label," did that mean that your sales force was going to go out to the doctors and point out the information that was in that letter that had sent around and say, "Hey, docs, we're saying here do not administer to patients with diabetes mellitus and those who have a history of diabetes mellitus, just as is in the black box in the letter. And also, during the administration of this product do blood glucose testing. And also, you know,

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explain sufficiently to the patient and the family members what the, about the possible occurrence of serious adverse reactions relating to diabetes."

Is that what you meant by the message for appropriate use of the product within the label?

MR. BOISE: Object to the form of the question.

A. Yes. The sales force got specific direction to carry the new label language into the doctor's office to make sure the doctors were aware and understood the new directions in the label, the new content of the label. And at the same time, what this phrase was referring to is that yes, this is new information in the label, it's important that doctors understand it and respond accordingly, but at the same time to still be able to express confidence in the molecule. It's still an efficacious drug and has an important place in the care of schizophrenic patients.

Q. Okay. Now if I could direct

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your attention to the last page. About four lines up from the bottom of that last paragraph there, there is language which states, "There appears to be a decrease of glycemic AEs since the label changes."

Am I correct that AEs refers to adverse events?

A. You are correct.

Q. Okay. So by -- if the label change went into effect at the beginning of April of 2002, only April, May, June, three months would have expired between the time of the label change and the time you wrote this memo, correct?

A. Two months, something like that.

Q. Okay. Well, all of April, all of May, and all of June, three months, correct? And already --

A. I'm going to have to refresh my memory on precisely when the label change, when in April was the label change made and when was the actual communication of the

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label change to physicians.

I know it was April, but I don't recall if it was the end of April or the beginning, the middle of April and when the sales force actually began to carry the document out. But in that time frame.

Q. Okay. In any event, whether it was the beginning of April or end of April, we're still talking about a fairly short time period from when the label change was made to the time of your memo, correct?

A. It was approximately two months, two and-a-half months.

Q. And yet even in that short span of time there appeared to be a decrease of glycemic adverse events since the label changes, correct?

MR. BOISE: Object to the form of the question.

Q. Isn't that what you said?

THE WITNESS: Let me take a moment and just read this paragraph.

MR. SUGGS: Sure.

THE WITNESS: I've read it.

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QUESTIONS BY MR. SUGGS:

Q. Okay. And my question was: Even in the short span of time between when the Japanese label change was made and the date of your writing of this memo it appeared that there was a decrease in the number of hyperglycemia adverse events, correct?

MR. BOISE: Object to the form.

A. You've reflected that sentence accurately.

Q. Okay. And you, after stating that to Mr. Lechleiter, you then went on to say, "Again, we will make every effort through promotional efforts and physician-to-physician and medical communications to ensure that we promote the use of the drug within the label, which would by design dramatically reduce the number of events."

Did I read that correctly?

A. You did.

Q. And the events that are being referred to there were also adverse events,

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correct?
A. Yes.
Q. Okay. So it was your expectation that if your sales force went out and promoted the use of Zyprexa within the new Japanese label and told physicians "don't give this to patients with diabetes, test people's blood glucose, and explain this issue sufficiently to the patient and family members," that that would, by design, dramatically reduce the number of adverse events, correct?
MR. BOISE: Object to the form.
A. That is correct. And the reason why is a very important point --
MR. SUGGS: Sir, I didn't ask for your opinion.
A. -- and that is because the data that we had at the time, including the TED analysis, indicated that the majority of cases or many of the cases that occur were, actually, latent diabetics at baseline prior to assignment or active diabetics

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undiagnosed, and they then were emerging on treatment.
So because of the high rate of diabetes in this population and the fact that patients were going on to treatment already with either prediabetes or diabetes, then for many of these cases it was a matter of time, irrespective of what drug they were on, that their diabetes then would be diagnosed.
So with the contraindication at baseline, those cases that were now going into the different treatment arms would now be going to other agents, and here again, irrespective of drug, would be emerging as cases of diabetes. So I think this puts things into an important context.
MR. ALLEN: I object to everything after "that is correct" as nonresponsive.
MR. SUGGS: I was going to make the same objection.
QUESTIONS BY MR. SUGGS:
Q. You recall being informed --

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MR. SUGGS: Well, let me back up for a second.
Let me show you what's been previously marked as Plaintiff's Exhibit 3211.
(Whereupon, Plaintiff's Exhibit(s) 3211, previously marked, was presented to the witness.)
MR. SUGGS: For the record, this is an e-mail from Vicki Poole Hoffmann to Kristine Healey with a copy to Robert Baker.
QUESTIONS BY MR. SUGGS:
Q. Do you know those individuals?
A. I have no recollection of Kristine Healey. I do know who Robert Baker is, and I'm not recalling who Vicki Poole Hoffmann is.
Q. Okay. In the first paragraph of Ms. Hoffman's e-mail, she states, "We are not sure that Zyprexa 'causes' hyperglycemia, because

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of the high background rate in schizophrenics, and we have not yet said, specifically, that Zyprexa is or is not associated with hyperglycemia. Our strategy has been to say that if these agents are associated with hyperglycemia then all agents are associated with it at comparable rates."
Do you see that language, sir?
A. Yes.
Q. And that was, indeed, the Lilly strategy, was it not?
MR. BOISE: Object to the form of the question. Foundation.
A. I would disagree with the statement as worded. Again, Vicki Poole Hoffmann, I don't know who that is. I don't believe this is a person with medical background, certainly is not a physician, and that would not be a precise articulation of our understanding of the data.
Q. Sir, was it your understanding that Vicki Poole Hoffmann was in the Issues Management Department?

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A. I'm just not recalling who that is.
Q. Do you recall being informed in June of 2002 that a clinical study by Lilly indicated that high nonfasting glucose in Zyprexa users was probably causally related?
MR. BOISE: Object to the form. Foundation.
THE WITNESS: I'm not understanding the question. Could you repeat it?
MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 7802.
(Whereupon, Plaintiff's Exhibit(s) 7802, previously marked, was presented to the witness.)
MR. SUGGS: Which, for the record, is a one-page document Listing of Treatment Emergent Abnormal Lab Findings in Olanzapine-Treated Patients. This

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is from study HGFU.
QUESTIONS BY MR. SUGGS:
Q. Are you familiar with study HGFU?
A. I'm recalling that to be a bipolar trial that looked at olanzapine plus mood stabilizers.
Q. And if you could direct your attention to the laboratory value for glucose nonfasting. It shows that 2.2 percent of the people who got olanzapine had high glucose and 0 percent had, of the placebo group, had high glucose; isn't that correct?
A. Yes. What I'm reading is 185 patients on olanzapine plus mood stabilizer, of the 185, four, or 2.2 percent, is on the glucose nonfasting high line. And that then looks like it's being contrasted with 92 patients with mood stabilizer plus placebo with zero cases or 0 percent.
Q. Um-hum. And to the right on that line there's some letters, A -- you see those letters A?
A. I do.

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Q. And if you could drop down to the bottom of the page there's a little legend describing what those letters mean. Could you read what it says for letter A aloud?
A. "Category: A equals event probably causally related."
Q. And did anyone inform you of that conclusion with respect to study HGFU?
MR. BOISE: Object to the form of the question. Foundation.
A. No. And I was, actually, quite aware of the data coming out of the FU trial, both efficacy and safety. I'm not familiar with categorizations of this nature. I don't know who produced this single page. It was not the position that the data would be reflected as described in this particular table. The data that I see on the page certainly would not support it if it were valid, and I don't know if it is or not. So I must say I'm -- I can't comment too strongly to this particular

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one-pager, given I don't know who authored it, I don't know where it came from, I don't know if it was, for example, a rough draft or an early draft or produced by someone who was not fully cognizant of the data. If we thought there was a new signal in FU, we all would have been working on it, we would have understood it, we would have communicated it to the FDA and we would have taken appropriate action.
MR. ALLEN: Object to everything after "no" as nonresponsive.
MR. SUGGS: Beat me to it.
QUESTIONS BY MR. SUGGS:
Q. Did you know a Dr. Simeon Taylor?
A. I have a recollection of that individual.
Q. And what's your recollection of that individual?
A. My recollection is that he was an endocrinologist who joined Lilly. Worked at Lilly, I'm recalling, for a

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relatively brief period of time and then left the company.

Q. And endocrinologists are types of doctors who specialize in the treatment of diabetes, correct?

A. They certainly can. Diabetes could be one of the conditions.

Q. An endocrinologist doesn't have to specialize in diabetes, but if somebody is specializing in diabetes, they're probably in the field of endocrinology, correct?

MR. BOISE: Object to the form.

A. I think that's a reasonably fair description.

MR. SUGGS: Let me show you what's been previously marked as Plaintiff's Exhibit 8666.

(Whereupon, Plaintiff's Exhibit(s) 8666, previously marked, was presented to the witness.)

MR. SUGGS: For the record

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this is a June 27, 2002, e-mail from Simeon Israel Taylor to a number of individuals.

QUESTIONS BY MR. SUGGS:

Q. And I would direct your attention in particular, sir, to the last two lines of -- well, actually, the last two sentences in the first paragraph of Dr. Taylor's e-mail in which he says, "However, I feel that we need to deal with the scientific facts, whatever they are. Ultimately, I expected a fair-minded, scholarly evaluation of the available data is likely to support several conclusions: 1, Zyprexa, like other members of the class, causes weight gain; 2, like other causes of weight gain, Zyprexa-induced weight gain probably increases the risk of diabetes."

Do you see that language, sir?

A. Yes.

Q. And were you ever informed that Dr. Taylor had expressed those views?

A. I'm not recalling this

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specific e-mail.

Q. Do you recall other instances in which Dr. Simeon Taylor expressed his view that Zyprexa-induced weight gain probably increases the risk of diabetes?

MR. BOISE: Object to the form of the question.

A. I'm not recalling that specific comment.

Q. Do you recall any general comments of Dr. Taylor regarding the issue of whether or not Zyprexa increased the risk of diabetes?

A. No.

Q. Okay.

MR. BOISE: Are you done with this document?

MR. SUGGS: Yes.

MR. BOISE: Just for the record, the document contains three separate e-mails. Appears to me, for what it's worth, is represented as one. Not that it was misrepresented, just for clarity

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purposes.

MR. SUGGS: Okay.

Dr. Breier, I'm going to hand you what's been previously marked as Plaintiff's Exhibit 7822.

(Whereupon, Plaintiff's Exhibit(s) 7822, previously marked, was presented to the witness.)

MR. SUGGS: For the record, this is a document which has a heading at the top "Zyprexa regulatory briefing."

I'll represent that it was -- the database that was produced to us indicates it was dated August 28, 2002.

I'll also represent that the blank spots where there's a word redacted were put in there by Lilly's counsel, not by plaintiff's counsel.

MR. BOISE: And upheld by the court.

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QUESTIONS BY MR. SUGGS:
Q. Do you recognize this document, sir?
A. I've seen it before.
Q. When was the last time you've seen this?
A. Within the last month.
Q. Okay. And the bottom of the page lists a number of contributors to this regulatory briefing. And you are listed there, are you not?
A. I am.
Q. And could you tell us what this document is, what it was used for?
THE WITNESS: Let me take a moment to read it.
I've had a chance to look at it.
QUESTIONS BY MR. SUGGS:
Q. Okay. And can you tell us what this document was used for?
A. I really can't. It's a one-page document. I don't know who authored it. I don't know if this was

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scenario planning for upcoming meetings creating a variety of different potential outcomes so we might better interact and prepare for interactions with the FDA. I, quite frankly, can't give you very much background on precisely what this document is, how it came about.
Q. When it says in the first paragraph, when it refers in the first paragraph to "differential labeling," what was your understanding of that?
MR. BOISE: Object to the form.
A. I don't know who wrote this. I can read the words on this page. Generally, when we talk about differential labeling, we mean differences in labels across a given class of agents.
Q. You mean Zyprexa would have a different label as opposed to the label for Risperdal versus Seroquel or some other drug?
A. It's difficult to ascertain precisely what is referred to here. I would be speculating.

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Q. Well, the first sentence says, "We anticipate differential labeling, (re: Risk for hyperglycemia, treatment-emergent diabetes and related metabolic issues) with our next submission."
Do you see that language, sir?
A. Yes.
Q. And did you anticipate differential labeling regarding the risk for hyperglycemia and treatment-emergent diabetes at that time?
MR. BOISE: Object to the form.
A. Again, I'm going with your assumption that this was 2002 time frame. I don't see any date on this particular document.
Q. Like I said, I represent to you the database that was produced to us by Lilly puts that date of August 28, 2002.
A. I don't have a recollection of this document from that time frame, so that's why I preface.

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So in 2002, I would say that, no, the data did not support differential labeling. So we would not be expecting differential labeling.
Q. So it's your testimony that you, personally, did not anticipate differential labeling even though this document says "we anticipate differential labeling;" is that correct?
A. The document says correctly as you just read "we anticipate differential labeling," and I am then speaking to my knowledge of the data and the team's position, and we did not feel that the data supported differential labeling and, therefore, would not have anticipated that we would have differential labeling.
Q. And below that first bulleted item states, "Expect label change in the precaution section at a minimum, more likely as a warning."
Did I read that correctly?
A. You read that correctly.
Q. But I'm assuming that your

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testimony is going to be that you, personally, did not expect a label change most likely as a warning at that time in August of 2002; is that correct?

MR. BOISE: Object to the form of the question.

A. You're correct. Again, I was quite knowledgeable of the data on this topic. The data did not support the change to a precaution or a warning. I am making the assumption that, again, this particular item sounds to me like someone doing some scenario planning, but I can't say for sure.

But I can say for sure that I am knowledgeable of the data and the data did not support a change to a precaution or warning.

MR. SUGGS: Move to strike the nonresponsive portion.

QUESTIONS BY MR. SUGGS:

Q. The last bulleted item in that first paragraph states, "Analyst community has indicated that this could be a trigger for Lilly disinvestment."

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Was it your understanding, sir, that business analysts had indicated that if there was differential labeling for Lilly regarding the risk of hyperglycemia and diabetes that that could result in a drop in investment in Lilly stock?

A. No.

Q. It refers to, by the way, in that first paragraph, the first line when it refers to "our next submission," do you know what submission that would be referring to?

A. In the 2002 time frame, accepting that that's accurate --

THE WITNESS: What was the month?

MR. SUGGS: August 28, 2002.

A. The next submission on board that I'm recalling would have been Symbyax.

Q. Okay. And Symbyax was a combination of Zyprexa and Prozac, is that correct, or am I misremembering?

A. You're remembering accurately. It is a combination of those two drugs.

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Q. Okay. And when was -- this was a submission for approval of that product?

MR. BOISE: Object to the form.

A. Yes.

Q. Okay. And when was -- what was the timing of that submission?

A. I don't remember precisely. I do recall that the submission was being prepared through the 2002 time frame, thus a submission would likely be end of 2002, early 2003.

Q. Okay.

And was that submission made?

A. Yes.

Q. Okay. And when was it actually made, do you recall?

A. I'm going to say end of 2002.

Q. Okay. In the second paragraph the first sentence starts off by saying, "There's a substantial risk in opening the Zyprexa label to a public advisory committee discussion. That risk is

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not new and has been previously communicated internally."

Do you see that?

A. Yes.

Q. And the advisory committee that's being referred to there is an FDA advisory committee, correct?

A. I presume that's true.

Q. Okay. And, typically, what happens when a new drug is submitted to FDA for review, the FDA will conduct its own review and then they will also have, convene an advisory committee of scientists who are regarded as experts in the field to review the data that has been submitted by the drug company to FDA in connection with the approval that's being sought, and the FDA committee will have a meeting, a public meeting, where they discuss the data and the issues relating to efficacy and safety, correct?

MR. BOISE: Object to the form of the question. Foundation. Compound.

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A. A long question, but there was one part of your question that I would say was not accurate and the rest of it I would say was accurate.

The part I think you said that I would not agree with is that it was common or usual or that -- I heard in your question that it implied that this was what generally took place. And most submissions do not have advisory committees.

MR. SUGGS: Okay. If I said that I misspoke.

MR. BOISE: Let him finish Dave.

Q. Because with Zyprexa there were --

MR. BOISE: Were you done with your answer? Dr. Breier, were you done?

THE WITNESS: Not quite.

A. They reserve the right to call an advisory committee when they feel they need additional expertise.

Q. And in fact, with the

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original Zyprexa submission, there was no advisory committee, correct, back in 1995?

A. That's correct.

Q. Okay. But in this instance when the Symbyax submission was made in 2002, this issue of whether or not there was an increased risk of diabetes or hyperglycemia with the use of atypical drugs was an issue that had fairly high priority, correct?

MR. BOISE: Object to the form of the question. Vague. Foundation.

THE WITNESS: Could you repeat the question?

MR. SUGGS: Sure.

QUESTIONS BY MR. SUGGS:

Q. At the time the Symbyax submission was made in 2002, the issue of whether or not there was an increased risk of diabetes or hyperglycemia with the use of atypical drugs was an issue that had fairly high profile in the medical field, correct?

MR. BOISE: Note my objection.

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A. There was a substantial scientific focus on that topic.

Q. And, in fact, there had been the previous label change in, in April of 2002 over in Japan, correct, that we previously discussed?

MR. BOISE: Object to the form.

Q. Correct?

A. Correct.

Q. Okay. And then in the bottom part of that paragraph it says, "Based on launch plans and sales forecasts in the U.S., as well as portfolio management decisions in other key affiliates, the blank may no longer justify the risk to the Zyprexa label."

Do you know what that's referring to?

THE WITNESS: I don't understand that sentence.

MR. SUGGS: Okay. Sorry for the blank, but I didn't put it there.

MR. BOISE: You don't have to apologize.

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MR. SUGGS: I guess it will just be a mystery.

MR. BOISE: You don't have to apologize.

MR. ALLEN: Symbyax NDA is my guess.

QUESTIONS BY MR. SUGGS:

Q. Is -- one of the attorneys in the room speculated that Symbyax NDA might fit in that blank. Would that be your best estimate?

MR. BOISE: Object to the form.

A. Well, again -- well, if, in fact, we are talking about Symbyax, I think this particular sentence speaks again to -- the nature of this document is sounding to me like a bit of a scenario planning because it was obvious that we moved forward, we submitted Symbyax, we got approval for Symbyax, and launched Symbyax. So I'm really kind of struggling with the context of this document.

MR. SUGGS: It is hard to

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figure out with all those redactions --
MR. BOISE: Oh, stop it.
MR. SUGGS: Perhaps we'll have to get another court to make a ruling on whether we get this document without the redactions.
MR. BOISE: Is that the last time you make the comment? Enough already on it.
MR. SUGGS: What, the redactions? You insist on them.
MR. BOISE: You challenge them and the Court rules. We don't need to deal with them here.
MR. SUGGS: And there are multiple courts.
MR. BOISE: You can forum shop.
MR. SUGGS: Okay, let's move on here.
Can I take a moment here. Somebody's been playing with my pile.

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MR. ALLEN: What are you looking for?
MR. SUGGS: We'll have to shoot Tommy.
MR. ALLEN: It was a short man from Texas.
MR. BOISE: I was getting ready for an accusation.
MR. ALLEN: Is that your pile?
THE REPORTER: Are we off the record?
MR. ALLEN: Let's go off the record.
(At this time, the parties went off the record, after which the following proceedings were had:)
THE VIDEOGRAPHER: We're back on the record.
MR. SUGGS: Dr. Breier, I'm going to hand you two exhibits. First is Exhibit 995 and the second is Exhibit 9201.

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(Whereupon, Plaintiff's Exhibit(s) 995, 9201, previously marked, was presented to the witness.)
MR. SUGGS: And for the record, Exhibit 995 is a memo to the policy committee from Alan Breier, Jack Jordan, Mike Bandick, dated July 7, 2003. And Exhibit 9201 appears to be a letter by Dr. Alan Breier, the addressee is not listed there but we'll go over that.
QUESTIONS BY MR. SUGGS:
Q. Turning your attention first to Plaintiff's Exhibit 995. Do you recall preparing this memorandum to the policy committee on or about July 7, 2003, as indicated?
THE WITNESS: I would need to review the document to refresh my memory on that.
MR. SUGGS: Okay.
THE WITNESS: I've read the -- this.

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QUESTIONS BY MR. SUGGS:
Q. Okay. And my question to you was: Do you recall preparing this memorandum to the policy committee on or about July 7, 2003, as indicated?
A. I don't recall the preparation of this document. The content, however, of the document is information that I do recall.
Q. And was this another preread to the policy committee in advance of an actual meeting or was this document just standing on its own as a report to the committee?
A. I don't recall.
Q. Okay. One of the things that the -- well, direct your attention to the bottom paragraph on the first page. It says, "Our goal is to influence key stakeholders, (clinicians, Lilly sales representatives, patients, Wall Street, the media, Lilly senior management, caregivers and thought leaders) with the facts about diabetes relative to the seriously mentally ill,

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Zyprexa, and other typical agents. Our message." And then there are seven items listed there, correct?
A. Yes.
Q. And at the core of your message was the position that the "Data do not support a causal link between Zyprexa and diabetes, and while the scientific literature is mixed there does not appear to be consistent differences among atypicals."
That would be item No. 4, correct?
MR. BOISE: Object to the form of the question.
A. You read item No. 4 correctly. That is reflective of the scientific information. You used the word "core." I don't know precisely what you meant by that. But this statement is here --
Q. Well, let me restate it. If you have a problem with that, let me state it this way: Included in your message was the Point No. 4 that "Data do not support a causal link between Zyprexa and diabetes;

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while the scientific literature is mixed there does not a appear to be significant differences among atypicals." Correct?
A. You read that correctly, and that is the best reflection of the totality of scientific information.
MR. SUGGS: Move to strike the nonresponsive portion.
QUESTIONS BY MR. SUGGS:
Q. When you stated there that there does not appear to be consistent differences among atypicals, that was referring to differences in rates of hyperglycemia and diabetes, correct?
MR. BOISE: Object to the form of the question.
A. That's my reading of that item.
Q. And on the second page under the heading Corporate Response Letter it states, "On July 11 customers will begin to receive the corporate response letter, Attachment 1, a letter targeted to clinicians, delivered by their Lilly sales

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representative. The letter is written on behalf of Lilly and signed by Doctor Alan Breier. Market research on the letter was conducted July 2-3 and was very positive."
And my question to you, sir, is Exhibit 9201 a copy of that letter that was referred to in Exhibit 995?
THE WITNESS: Take a look at this.
A. It appears to be the case.
Q. Okay. And to your understanding -- oh, by the way, this letter that is Exhibit 9201, is that something that was actually prepared by you or did someone else draft it?
MR. BOISE: Object to the form of the question.
A. I take accountability for the content of this letter. I've signed it. This was a communication that had input from others.
Q. Who? Which others?
A. I'm not recalling who, specifically, may have contributed. It's not

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unusual when we have a document that we circulate it for input and comments, and I'm quite certain that we did that with this.
Q. Did anyone from the marketing department review and comment?
A. Certainly we would have circulated it to members of marketing, particularly given the fact that it was going to be going to the sales force and then to physicians. But I'm not recalling precisely, precisely who.
Q. Would Cassandra Mehlman have reviewed this?
A. I'm not recalling that name. I have no idea.
Q. How about Jack Jordan or Mike Bandick?
A. I would assume that both of them would have reviewed it, again, given the fact that it was going to be going to the sales force to then to be circulated through that particular channel.
Q. Okay. How about Denice Torres?

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A. I would assume she would.
Q. Would have reviewed it?
A. She would have been one of the people that would have looked at this document, yes.
Q. Did you come up with the first draft of this letter?
A. My recollection is that I sent a voicemail that touched on some of these themes, but for internal use, and that that particular message was found to be helpful and that that then began sort of the thinking that perhaps then a different document or another document might be helpful.
So, as I recall, that was the genesis of this document. I don't recall if I actually wrote the first draft of this specific document.
(Whereupon, Plaintiff's Exhibit(s) 3909, previously marked, was presented to the witness.)
MR. SUGGS: Let me hand you

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what's been previously marked as Exhibit 3909, which is an e-mail dated -- well, it's an e-mail string but you started it off with one dated May 6, 2003, which then got forwarded on to Alan, pardon me, to Denice Torres, who then sent it to -- I'm assuming that's some marketing group within Lilly.
QUESTIONS BY MR. SUGGS:
Q. Is that a fair assumption given that top e-mail address?
THE WITNESS: The "to marketing at Lilly?"
MR. SUGGS: Yes.
A. I assume so. I'm not familiar with that header.
Q. Is this e-mail that you're referring to here, is this that genesis that you were referring to?
A. Again, my recollection is that I sent a voicemail attempting to summarize some facts on this topic. I believe this might have been a transcript of

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that voicemail.
Q. Oh, okay.
A. And that then was found to be helpful in terms of particular context.
I think then that activity then led to some thinking that maybe a different kind of communication that also looked at important questions might be helpful for the external environment.
MR. ALLEN: Just for clarification of the record because it's not clear when you said --
MR. SUGGS: I was going to get there.
MR. ALLEN: This --
MR. SUGGS: I'm getting there.
MR. BOISE: One at a time.
QUESTIONS BY MR. SUGGS:
Q. You made some gestures with your hands, and I want to track through and make sure I understand the process.
It's your recollection and understanding that you initially left a

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lengthy voice mail discussing the issue of Zyprexa and diabetes. That, somehow that got converted into this e-mail that's reflected in Exhibit 3909?
A. I'm not a hundred percent sure, but that's my recollection.
Q. Okay. And then the exhibit, the material that's in Exhibit 3909 became the basis for or the genesis for what then turned into the letter which we see reflected in Exhibit 9201; is that correct?
MR. BOISE: Object to the form.
A. What I'm recalling is that the approach I took in what I believe was a voicemail of posing a specific question, providing the scientific information, was found to be helpful. And that led to then the thought that a similar kind of format might be helpful to the external, to clinicians who might be having the same kinds of questions.
Q. Do you recall who it was that would have actually taken the material that

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was reflected in Exhibit 3909, the e-mail, and converted it to the letter that we see in Exhibit 9201?

MR. BOISE: Object to the form of the question.

A. I don't recall.

Q. Okay. Would it have been someone in the marketing department?

MR. BOISE: Object to the form of the question. Foundation.

A. I don't recall.

Q. Okay. The letter, though, was clearly intended for marketing purposes. Because as you said, it was going to be distributed by sales reps to physicians out in the field, correct?

MR. BOISE: Object to the form of the question.

THE WITNESS: You're talking about this document?

MR. SUGGS: Exhibit 9201.

A. This was intended for doctors. It was intended to raise questions that we understood were on some of their

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minds and then provide scientifically-based answers to those questions.

Q. Okay. The format of your letter, Exhibit 9201, is, after the introductory paragraph, there are other paragraphs that lead off with a question in bold and then your response to that, to those questions, correct?

A. Yes.

Q. Okay. And do you know if, in fact, this letter was distributed by the sales reps to physicians?

A. It's my understanding that it was.

Q. Okay. And do you have any even ballpark kind of estimate as to how many physicians would have received this from the Lilly sales reps?

A. No.

Q. Okay. Was it the intent that the letter would be distributed by Lilly sales reps to every potential Zyprexa prescriber?

MR. BOISE: Object to the

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form of the question.

A. I don't know.

Q. Okay.

You start off in the initial paragraph of your letter, Exhibit 9201, by stating at the end of that paragraph, "We believe it's in the best interest of patients to set the record straight." Correct?

A. You've read that correctly.

Q. And you intended for physicians to believe that what you were stating in here was the truth, the whole truth, and nothing but the truth, correct?

MR. BOISE: Object to the form.

A. I would state that these were facts. That they were expressed in an honest, straightforward and clear manner.

Q. With no spinning, correct?

MR. BOISE: Object to the form.

A. Correct.

Q. Okay.

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Because if you did spin the facts in a letter to doctors, especially when you've said here that it's in the best interest of patients to set the record straight, that would be wrong, wouldn't it, sir?

MR. BOISE: Object to the form of the question. Lack of foundation.

A. Spinning of facts as we're talking about it now would be inappropriate. It's something that we wouldn't do, I didn't do, and what I'm looking at here are a very clear articulation of the data.

Q. In the letter that went out to the doctors, Exhibit 9201, the second question there is, "Does Zyprexa cause diabetes?" And the answer starts off by saying, "The available data do not establish a causal link between diabetes and Zyprexa -- or any other antipsychotic, for that matter."

Is that correct?

A. Yes, it does.

Q. It goes on to say, "We have

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been intensely investigating this question for several years from multiple vantage points: Preclinical studies, head-to-head clinical trials, epidemiological surveys, and endocrinological challenge or clamp studies. Our conclusions have been confirmed by studies conducted by others from around the world. Two clamp studies conducted by Lilly found that Zyprexa did not decrease pancreatic insulin release or, unlike other medicines (prednisone, protease inhibitors) have a direct effect on insulin insensitivity. It is clear that this important area requires more research, and Lilly is committed to staying on the forefront of this scientific inquiry."

Did I read that correctly?

A. Yes, you did.

Q. Okay. So your basic message to the doctor was Zyprexa does not cause diabetes, correct?

MR. BOISE: Object to the form of the question.

A. Every word that you read in

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that paragraph is scientifically accurate and states the case "The available data do not establish a causal link between diabetes and Zyprexa -- or any other antipsychotic, for that matter." That is a true reflection of the totality of scientific information.

MR. FIBICH: Objection, nonresponsive.

Q. Sir, you knew, and even told other people at Lilly, that the weight gain caused by Zyprexa could push some patients over in becoming diabetic, correct?

MR. BOISE: Object to the form of the question. Foundation.

A. Be very clear, we don't have data that links weight gain as a causative factor of diabetes. Moreover, this exact same point has been clearly rearticulated by the FDA after looking at not only the data from our studies, but from all sponsors' studies. So that is a comprehensive view.

We, throughout the course of this investigation of this particular topic, as we note in this paragraph, were

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continuously posing hypotheses and attempting to answer them. That's the way science works and that's how we conducted ourselves. That was our culture --

MR. FIBICH: Objection. Nonresponsive.

A. -- raise questions, design experiments, and let the data lead the way.

MR. SUGGS: Move to strike as nonresponsive.

QUESTIONS BY MR. SUGGS:

Q. My question was, you knew and told other people at Lilly that the weight gain caused by Zyprexa could push some patients over in becoming diabetic, did you not, sir?

MR. BOISE: Object to the form of the question.

A. That's an important hypothesis to examine. There's no data that confirms that relationship, and we looked very, very, carefully and very, very hard at that exact point, and the data available does not prove that point.

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Q. Sir, do you deny that you told --

MR. ALLEN: Are we out of tape or something?

THE VIDEOGRAPHER: We have five minutes.

MR. SUGGS: Go ahead and switch the tape.

MR. BOISE: We're going to take a lunch break then.

MR. SUGGS: I'd rather proceed on.

MR. BOISE: We're going to take a lunch break.

MR. SUGGS: Let's finish this tape then.

MR. BOISE: I have no objection to that.

MR. SUGGS: Okay.

QUESTIONS BY MR. SUGGS:

Q. Sir, do you deny that the weight gain caused by Zyprexa can push some patients over into becoming diabetic?

MR. BOISE: Object to the

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form of the question.
A. We have no data to support that.
Q. Let me show you what's been -- well, let me refer you to Exhibit 3909, the e-mail that you wrote in-house. There you have some numbered questions in bold and you have some answers after that. And the first one, the first question was "Does Zyprexa cause diabetes?"
This is the e-mail that got sent to the marketing people in May of 2003, a couple months ahead of the letter that went out to physicians, correct?
MR. BOISE: Object to the form.
A. I don't recall focusing this to the marketing group. It was focused at a more cross-functional group, including scientists on the team, and statisticians.
Q. In any event, this e-mail of yours was dated about two months before the letter that went outside of the company to physicians, correct?

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A. I believe that's correct. I don't see a date on this particular message but I do see the date you're referring to on the e-mail.
Q. Well, we know, for example, from Exhibit 995, that you told the policy committee that this letter that you wrote was going to be distributed beginning on July 11th, 2003?
A. And I'm not recalling precisely when it actually went out.
Q. Okay. Directing your attention back to Exhibit 3909, the first numbered paragraph says, "1. Does Zyprexa cause diabetes?" And your first part of your response says, quote, "The most straightforward answer is we do not think so. Why do I not say Zyprexa definitively does not cause diabetes? In part, because it is very difficult to prove a negative. When anyone develops diabetes in the general population it is often impossible to say definitively why they developed diabetes."
Do you see that language,

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sir?
A. I do.
Q. And then you go on in point two to say, "Why do I say no direct link as opposed to any link at all?" And then you wrote, quote, "We know and have well characterized that Zyprexa and all antipsychotics causes weight gain and weight gain is an established risk factor for diabetes. Thus in some patients the weight gain of Zyprexa could predispose them to diabetes, particularly if those patients have other risk factors for diabetes. However, and this is very important, most people who gain weight do not develop diabetes. Diabetes is an illness with multiple pathways leading to and contributing towards its development. Thus a patient who gains weight on Zyprexa or other antipsychotic drugs and mood stabilizers is probably, like anyone else who gains weight, the general population. For the vast majority of individuals their pancreases are healthy and the weight gain will not precipitate

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diabetes. For those in the minority whose pancreases are functioning suboptimally, weight gain could push them over to diabetes."
Do you see that language, sir?
A. I do.
Q. And if your weight gain --
MR. SUGGS: Let's stop right there, I guess.
THE VIDEOGRAPHER: This marks the end of tape No. 3. We're off the record at 12:27.

(A lunch recess was taken by the parties at this time.)

AFTERNOON SESSION
THE VIDEOGRAPHER: Back on the record. Beginning of tape No. 3

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of the deposition of Alan Breier.
It's 1:26.
QUESTIONS BY MR. SUGGS:
Q. Dr. Breier, I have just a few questions before I complete my questioning at this time.
If I could direct your attention to Exhibit 3909.
A. Yes.
Q. I'd like to direct your attention to some particular language in your numbered Paragraph 2 and also numbered Paragraph 3.
And in numbered Paragraph 2, three lines up from the bottom you state, "For those in the minority whose pancreases are functioning suboptimally weight gain could push them over to diabetes."
Do you see that language, sir?
A. Um-hum.
Q. And then numbered Item 3 states, "Okay, then how can I tell if

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a patient's pancreas is functioning suboptimally?" And your answer was, "The most efficient and practical way to get a handle on this is easy, just get a fasting glucose level."
Did I read that correctly?
A. You did.
Q. And, in fact, that is what had been recommended in the Japanese label change about a year and-a-half earlier, or about a year earlier in 2002, correct?
A. I'm attempting to recall if they specified fasting glucose or just glucose.
Q. But in any event, the Japanese regulatory authorities said to Japanese physicians -
MR. SUGGS: Strike that.
QUESTIONS BY MR. SUGGS:
Q. The Japanese regulatory authority made Lilly tell physicians in Japan to get a blood test for glucose before a patient started on Zyprexa, correct?
MR. BOISE: Object to the

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form.
A. The part of the label language were to get a blood glucose prior to starting treatment.
Q. Okay.
A. That's correct.
Q. And those, that language that we just talked about here that was in Exhibit 3909 is not contained in the letter 9201 that went out to physicians in the U.S. that was distributed by Lilly sales representatives, isn't that correct, sir?
A. You are correct.
Q. Thank you.
A. These are two different documents. This document, the first document we talked about was an internal document upon which, in addition to other, sharing other facts, we talked about hypotheses, areas that we were interested in looking into.
This was a statement of facts. This was not a letter. The one I'm referring to now is the one that went out to the external community, was not a

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reiteration of treatment guidelines or a how-to manual. There were a variety of other programs underway at that time in the U.S. Affiliate, including more specifics around management guidelines, treatment guidelines, we had endocrinologists in the field, et cetera.
So I just want to make it clear that these two documents were separate documents and had different purposes.
MR. SUGGS: Move to strike the nonresponsive portion which is everything after "you are correct."
QUESTIONS BY MR. SUGGS:
Q. Dr. Breier, who was it that made the decision not to include that language that was in 3909 in the internal e-mail, in the letter that went out to the public in Exhibit 9201? Who made that decision?
MR. BOISE: Object to the form of the question.
A. I'm the author of both. I take responsibility for both.

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MR. SUGGS: Okay. I have no further questions at this time.
MR. ALLEN: We need to go off the record so we can change.
THE VIDEOGRAPHER: Off the record.
(At this time, there was a brief recess taken, after which the following proceedings were had:)
THE VIDEOGRAPHER: We're back on the record.
EXAMINATION
QUESTIONS BY MR. ALLEN:
Q. Good afternoon.
A. Good afternoon.
Q. Dr. Breier, could you state your name for the record, please, sir?
A. My name is Alan Breier.
Q. Yes, sir. Dr. Breier, my name is Scott Allen, and I'm from Houston, Texas. Other than this deposition, you and I have never met before; is that correct?
A. That's correct.

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Q. Okay. You hesitated. Did you think we met before?
A. No.
Q. Okay. All right. Dr. Breier, I heard you testify yesterday at the outset when Mr. Suggs started asking you questions that you take this process seriously or something along those lines. Do you recall that?
A. That's correct.
Q. Okay. I want you to know that I do also. And I'm going to be asking you some questions today. You and I are on the opposite side of the lawsuit, you understand that?
MR. BOISE: Object to the form.
A. Yes.
Q. Okay. The questions I'm going to ask you I'm certain we'll have some disagreements, but I want you to know it's nothing personal, but it's my job as a lawyer to investigate the facts on behalf of my clients. Do you understand that?

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A. Yes.
Q. Okay. I'm going to cover some of the things that Mr. Suggs covered and I'm going to ask some questions that he didn't and try to probe some of your answers that you have given previously in the last day. All right?
The first thing I want the jury to understand, sir, is you are a psychiatrist, correct?
A. That's correct.
Q. Okay. Do you specialize in any other field of medicine or have you ever specialized in any other field of medicine?
THE WITNESS: Outside of psychiatry?
MR. ALLEN: Yes, sir.
A. No.
Q. You were the Zyprexa product team leader, correct?
A. I was.
Q. Who assigned you to that task?
A. That decision would have been

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made by key members of upper management, including John Lechleiter.
Q. Okay. So the -- let me ask this. I don't think we've exactly talked about, to my knowledge, in a succinct form where the jury could understand, what is the product team that you were the leader of for Zyprexa. What does a product team do?
A. Product team is an organization of cross-functional professionals focused on a specific late-stage molecule.
There are many different people that are members of a product team and they have different tasks. The majority of people on a product team are focused on science and medicine, I call it research and development, so those would include physicians, statisticians, data managers, research assistants.
On the Zyprexa Product Team that constituted, I would guess, somewhere between 80-85 percent of people, so those people were involved in examination of

important scientific questions, new indications, new line extensions, of this nature.

In addition, we were, up until, again, somewhere in the '02 time frame, there was a global marketing team. This global marketing team was responsible for the high level understanding of the molecule in terms of the scientists collecting the information and then working with marketing to kind of capture the major themes. The global marketing team then would convey those themes to local affiliates who had their own sales and marketing organization, who then were in charge of translating that theme in the context of their own local geography, and then the implementation through sales, marketing, and other venues.

In addition, there were a number of people who were members of the team but didn't have reporting lines into the team such as regulatory scientists, members from manufacturing, and people of that nature.

Q. Okay. So on the product team that you were head of, and you were assigned by Dr. Lechleiter, who is currently the COO of Lilly; is that right?

MR. BOISE: Object to the form.

Q. Dr. Lechleiter, COO of Lilly?

A. That's correct.

Q. Who assigned you to be the head of the Zyprexa Product Team, on the Zyprexa Product Team were people that were physicians and people that were marketers, correct?

A. In addition, among all the other people that I indicated.

Q. Yes, sir. And on the marketing side, as you've indicated, there was a global marketing team and that was headed up by Denice Torres, correct?

MR. BOISE: Object to the form. Time period?

A. When I began as product team leader at the beginning of 1999, Roland Powell was the medical director for two

years. Denice Torres then assumed the position when Roland Powell rotated into a new position.

Q. Thank you, sir.

MR. SUGGS: He said medical director.

THE WITNESS: Oh, I'm sorry, did you say medical or marketing?

MR. ALLEN: I said marketing.

QUESTIONS BY MR. ALLEN:

Q. When you say "Roland Powell," you meant he was Marketing Director and then Denice Torres took over?

A. That's right.

Q. Since Lilly appointed her to be local marketing director, that would involve issues involving marketing?

A. That's correct.

Q. And she would know, obviously, those things that could affect marketing of a product. She would know those things, that would be her job?

A. Her background was in marketing, and she had an expertise in

marketing, correct.

Q. In fact, she testified in a deposition I took of her, I think it was right before Christmas, sometime shortly before Christmas, that before she became the global marketing director at Lilly, one of her jobs had been in the past she'd been a sales representative, I think in the Chicago area.

Were you aware Denice Torres had been a sales representative at one time, a detail person?

MR. BOISE: You're making a representation about her testimony and then asking him a question?

MR. ALLEN: Yes, I am.

MR. BOISE: Just making it clear.

MR. ALLEN: Yeah.

A. I don't recall that part of her background, but it is not unusual for people in marketing to assume, even sometimes for short period of time, a sales role.

Q. Right. I think even in the case as I recall it, and the evidence will be

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what the evidence is, I think Jack Jordan testified he had been a sales representative. Did you know that?

A. Similarly, I don't recall that specific part of his background, but I, again, would say it was not uncommon.

Q. Yes, sir. Now, back to Denice Torres. As an expert, she testified to me -- and I want to see if it was your understanding of this, too -- she testified to me under oath that it was common knowledge that a warning on a drug product could affect sales. Were you aware of that?

MR. BOISE: Object to the form of the question.

THE WITNESS: Was I aware that she held that view?

MR. ALLEN: Well, let me rephrase it.

QUESTIONS BY MR. ALLEN:

Q. First of all, yes, were you aware she held that view?

MR. BOISE: Object to form.

A. I don't recall discussing

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that with her having that, knowing of that view.

Q. Let me ask this: You understood as the Zyprexa product -- what was your title, Zyprexa -- I have a hard time. Tell me what your title was again and I'll try to remember it exactly.

A. Zyprexa Product Team leader.

Q. I'll screw that up later but let me ask this: Did you understand as Zyprexa Product Team leader that a warning on drug products can affect the sales of the drug?

MR. BOISE: Object to the form. Foundation.

A. My best answer to that is I think it would depend on what the warning was. I think, ultimately, what's going to affect the sales of a product would be the overall attributes, which includes potentials for warning, other situations, as well as the efficacy of a product, and then the degree of unmet need that it has to address.

Q. So what you're saying in a

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Scott Allen or layman's language is there's many things that can affect the sale of a product, but you agree with the fact that one of those things that can affect the sale of a drug product is whether or not it can be a factor. One of the things that's a factor is the warning on a drug?

A. Again, I think it would depend on the content of the warning. I say that because at the time of launch there was a warning for neuroleptic malignant syndrome, for example, I don't think that had a bearing one way or the other on the sale of the product. So I think, again, I would go back to my best answer would say it would depend.

Q. You made a very good point. I think that's a very good point that you made. A warning may affect the product of a drug depending on the content of the warning. That's what you're telling the jury?

MR. BOISE: Object to form.

A. Again, I go back to my original answer. I think it would be the balance between what the content of the

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warning was, balanced by the potential of what the efficacy was, and then the degree of unmet need, and then, again, different options for treatment.

MR. FIBICH: Object. Nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. But of course, in this case in this setting with Zyprexa, you know for a fact, not just as a matter of opinion, you know as a matter of a fact that a warning on diabetes, blood monitoring, and diabetic ketoacidosis, those things would have affected the sales of a product? You know that as a fact?

MR. BOISE: Object to the form of the question. Compound. Foundation.

A. No.

Q. Didn't you have facts in your possession, your own personal possession, that a warning about diabetes, diabetic ketoacidosis, blood monitoring, would have a very profound effect on the sales of Zyprexa?

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MR. BOISE: Object to the form.

A. I would say that it's very difficult to predict what would or would not have a bearing. And it would relate to the other factors that I talked about.

Q. Yes, sir. I understand. You said it's difficult to predict, but you knew at least by the summer of 2002 that it was clear that a label change on Zyprexa concerning diabetes and blood monitoring would have a very profound effect on the sales of the product? You knew that as a fact?

MR. BOISE: Object to the form of the question.

A. I would say no to that. I would disagree that, to know something as a fact is to know something with certitude. Back at that time period, I would suspect that there was speculation and a variety of different scenarios. But to call something a fact I think would be too strong.

Q. Didn't you have actual

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evidence, empirical evidence by the summer of 2002, you, that a warning about diabetes and blood monitoring would for certain have a very profound effect on the sales of Zyprexa?

A. Again, I'm going to answer no.

Q. Okay, thank you, sir.

A. And what I would just use as an example, there was a warning precaution on diabetes and hyperglycemia in the European label, and to the best of my knowledge, that had no bearing on sales.

Q. You raise an --

MR. ALLEN: I object to everything after, I think it was "no", as nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. You raised a point in your testimony with Mr. Suggs, and I want to get it clear, and we can move off this and straight into the matter I was discussing, but just so the jury understands, by 2002, by the summer of 2002, the European label on Zyprexa had a precaution and a warning on

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diabetes, correct?

A. It had a -- it had language about hyperglycemia and diabetes in the one warning and precaution section in Europe. As I mentioned earlier, warning precautions are melded into one section.

Q. Yes. And just for the record, by the summer, actually, the spring, but by the spring of 2002, the Japanese label had a warning on diabetes and hyperglycemia in the Zyprexa label, true?

A. That's correct.

Q. And in the summer of 2002, while the warnings were in the European label and the Japanese label, there was no warning in the U.S. label, correct?

MR. BOISE: Object to the form.

A. That's correct.

Q. And you knew in the summer of 2002 that if a warning on diabetes and hyperglycemia were put into the label, it would clearly have a very profound effect on sales?

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MR. BOISE: Objection. He's asked and answered the question.

Q. Correct?

A. I'll state my answer again. There were, I'm sure, discussions, scenario planning, looking at impact, but did I believe that there would be a profound effect on the label? Did I have certitude on that point? I would say no.

Q. Okay. I'm going to hand your lawyer and you -- somewhere in this stack you've already seen this exhibit but instead of finding it again --

MR. ALLEN: Do we have any exhibit stickers?

I'll hand you what I've marked as Breier Exhibit No. 6 and one for your counsel.

(Whereupon, Deposition Exhibit(s) 6 duly received, marked and made a part of the record.)

MR. ALLEN: This is the summary of the Japan trip that you

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took over to Japan from June 23rd to 27th with Dr. Lechleiter.
QUESTIONS BY MR. ALLEN:
Q. You've seen this earlier in the deposition. You've already read it, correct?
A. Yes.
Q. And you've seen earlier that by this time the Japanese label had changed, you discussed that with Mr. Suggs, and it warned of diabetes, diabetic ketoacidosis, death, and also advised to do blood glucose monitoring in the warning. And the warning or the new label in Japan also suggested that for patients with diabetes, or who were at risk for diabetes, should not be prescribed Zyprexa, correct?
MR. BOISE: Object to the form.
A. One part I'm going to refresh my memory, on your last point, if you had a diagnosis of diabetes, then Zyprexa was contraindicated by the label language, I don't recall risk for diabetes as being a

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contraindication.
Q. Thank you, sir. Other than with that modification, you agree with what I said?
MR. BOISE: Same objections.
A. Yes.
Q. Thank you. Now in this trip summary which we've marked as Breier Exhibit No. 6.
MR. BOISE: Scott, it's also Breier 5. It's the same document.
MR. ALLEN: It may be, I don't know. That's why I'm just using my own number so we don't have to be confused.
QUESTIONS BY MR. ALLEN:
Q. In Breier No. 6 -- why did you all go over to Japan after the label change, you and Dr. Lechleiter?
A. It was Mr. van den Bergh and I --
Q. I'm sorry. I'm sorry.
A. -- went.
MR. BOISE: Hang on. He's

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withdrawing the question.
QUESTIONS BY MR. ALLEN:
Q. You and Dr. -- is it Mr.?
A. Yes.
Q. You and Mr. van den Bergh went over to Japan?
A. Yes.
Q. Why did you all go over to Japan?
A. We wanted to assess how the affiliate was doing, the Japanese affiliate was doing with the label change, to review their approach to this and their implementation plan, and that was the primary reason.
Q. So the purpose of the trip was to assess how the Japanese affiliate was doing after the label change?
A. I think that would be fair. We -- there was a group that was charged with implementing the recommendations from the Japanese regulatory group. This was going to have an impact on staffing and a variety of others in the affiliate.

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There were also discussions about beginning some new prospective trials and data assessments in that area. So it had to do with matters like that.
Q. Right. And then when you got back, at least according to Exhibit No. 6, Mr. van den Bergh and you prepared a memoranda, it's called "memo" at the top, Neuroscience Products, dated July 1st, 2002, to Dr. Lechleiter, Mr. Mayr; is that right?
A. Mayr's, correct.
Q. And Mr., can you pronounce that word for me, Mr. Mascarenhas?
A. Mascarenhas.
Q. And who is Mr. Mayr?
A. At this time I believe he was in charge of global sales and marketing.
Q. That's right. So you sent this to global sales and marketing.
And who's Mr. Mascarenhas?
A. He was the country manager of Japan.
Q. Okay. And Dr. Lechleiter at this time was whom?

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A. Dr. Lechleiter was in charge of the product teams.
Q. And, in fact, I guess the best way to say it, since he's the one that appointed you to be the head of the Zyprexa Product Team, he was your boss?
A. I reported to Mr. van den Bergh, and Mr. van den Bergh reported to Dr. Lechleiter.
Q. And just for the record, Dr. Lechleiter is now the chief operating officer of the entire Lilly company?
A. That's correct.
Q. And I know without a doubt, because in my job, in any job, and the jury will understand, that when you're reporting to your superior concerning a trip to Japan, you're going to try to be as accurate and as truthful as you possibly can be so your superior will have true and accurate information upon which to make his or her decision that needs to be made, right?
MR. BOISE: Objection. Asked and answered.

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A. We would convey our impressions as accurately as possible.
Q. And you told us at least one of the reasons you went to Japan was to assess how the affiliate was doing in Japan after the label change, right?
MR. BOISE: Objection. Asked and answered.
A. That's correct. We wanted to assess their implementation of the guidelines.
Q. Yes, sir. And if you look at Paragraph 1, and I will read it into evidence so it will be easier than making you read it. Here's the first paragraph of what you tell Dr. Lechleiter and Mr. Mayr, the head of global sales and marketing. You say this: "This is a summary of issues and proposed actions in follow-up to our previous update on Japan. It is clear that the impact of the label change in Japan has had a" very profound. We concluded, we, keep going on, you left out -- what word should have come after profound?

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MR. BOISE: You left out a word before very.
MR. ALLEN: Yes, I did. Let me read it again.
QUESTIONS BY MR. ALLEN:
Q. "It is clear that the impact of the label change in Japan has been very profound. We concluded we have lost substantial ground and trust in our relationship with the MHLW."
That's the Japanese equivalent of the FDA, correct? Sir?
A. Yes.
Q. "Market research shows we have also lost quite a bit of credibility with prescribers and opinion leaders. Basically, because they felt left in the dark with what they perceived as the late sharing of safety information. As a result, there has been a 75 percent drop in new patients who are being put on the drug and a continuing fairly high drop-out rate. That's going to lead to a significant performance impact. Probably, over and above the

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10 percent assumed on the sales line in the short term. Although we think we will be able to stem the tide and turn this around."
Did I read that correctly?
A. Yes.
Q. So you knew as a fact that a label change concerning diabetes, a warning concerning diabetes, as a fact, would have an impact on sales, correct?
MR. BOISE: Object to the form of the question.
A. What was, I think, a bit surprising was first the number of patients who were not put on the drug initially which, correct, had an impact on sales, but what's not conveyed in this e-mail was how rapidly the sales performance returned to normal and then actually went quite a bit beyond normal.
So our history is that it's very difficult to predict an impact of a label change and Japan is a good case in point.
MR. FIBICH: Objection. Nonresponsive.

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MR. ALLEN: I join, of course.

QUESTIONS BY MR. ALLEN:

Q. All right, sir, and just for the record, this memo that you wrote says, "It is clear that the impact of the label change in Japan has had a very profound effect."

Those use of the word "clear" and "very profound" were your words, not my words, correct?

A. You've read those words correctly.

MR. FIBICH: Objection, nonresponsive.

Q. I've read the words correctly. Just so the jury understands, the words "clear" and "very profound" are words you selected, not Scott Allen, correct?

MR. BOISE: Object.

A. That's correct.

Q. Thank you, sir.

Sir, I take scribbly notes, you can look at my pad and see nothing's

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really in that order, but I have it written down here. We're going to go off that subject now and go on to another, all right?

We've been talking about diabetes and hyperglycemia in different contexts throughout the deposition as you probably expected when you came here, right?

A. I knew the topic of the deposition.

Q. Right. And you knew the topic was Zyprexa. And you certainly understood that during the time Zyprexa was on the market, hyperglycemia was one of the main issues that Lilly had to address in regard to Zyprexa, right?

A. Investigating hyperglycemia as it related to Zyprexa, determined if there was an association, et cetera, was a topic and a focus of the team.

Q. Yes, sir. And just for the record, I understand that answer and I agree with what you just said, but also there was on the team people who were specifically assigned in what they call the Marketplace

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Management. You know who the Marketplace Management people are? You know that department?

MR. BOISE: Object to form.

Q. Matt Pike and Cassandra Mehlman and others?

A. I'm not a hundred percent clear on the term "Marketplace Management" or how that's being referred.

Q. Okay. Well, tell me how you're not clear because I think -- I want you and I to communicate, and I'm doing the best job I can, and I'd like you to help me and the jury. I've also heard it referred as Issues Management. Does that help you at all?

A. For a period on the team we had a group called an Issues Management team.

Q. Right. Thank you. And one of the main things the Issues Management team had to do was address the issue of hyperglycemia?

A. One of the topics for this team was to examine information around

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hyperglycemia.

MR. ALLEN: Thank you, sir. And I'm going to put in, and I don't want to spend any time on it, but just so the jury understands and I think you can, probably, help us understand, I'm going to hand you Breier Exhibit No. 7.

(Whereupon, Deposition Exhibit(s) 7 duly received, marked and made a part of the record.)

MR. ALLEN: Which is a document from Denice Torres's deposition. You do not need to read the whole thing, you just need to turn to the second page and go to the top where the name Mr. Mike Bandick is listed at the top of the second page.

QUESTIONS BY MR. ALLEN:

Q. You see where it says "Mike Bandick will assume the role of Director, Marketplace Management"?

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Do you see that?
A. I do.
Q. Does that help you help me and help the jury understand what Marketplace Management is? Marketplace Management was one of the people on the Zyprexa Product Team, correct?
MR. BOISE: Object to the form.
A. I, in terms of -- obviously, seeing the sentence they refer to, I don't doubt that that was the title that Mr. Bandick assumed.
A Marketplace Management team or a Marketplace Management organization is something that I'm not familiar with.
Q. Okay. All right. Nevertheless, we'll move on.
Tell the jury since he was on the -- you knew Mike Bandick when you are -- are you still head of the Zyprexa Product Team?
A. No.
Q. Okay. You're medical

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director now?
A. No.
Q. What's your title exactly, I'm sorry?
A. I'm Chief Medical Officer and Vice-president of Medical.
Q. Okay. Back when you were head of the Zyprexa Product Team, you knew Mike Bandick. Mike Bandick was a friend of yours professionally?
MR. BOISE: Object to the form.
A. No.
Q. You never dealt with Mike Bandick?
MR. BOISE: Object to the form.
A. You had two parts of your question: One, did I know Mike Bandick? The answer to that is yes. The second part of your question was were we friends.
Q. Professional friends.
A. No.
Q. Okay. How did you know Mike

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Bandick when you were head of the Zyprexa Product Team?
A. He joined as a member of the team.
Q. Tell the jury what he did for your team that you were head of?
A. Mr. Bandick, his background in marketing, he joined as part of Denice's team in the marketing area and was focused on issues management.
Q. Focused on issues management. That's where we all started this conversation. And one of the issues that you at Eli Lilly had to address on the Zyprexa Product Team was hyperglycemia and diabetes, correct?
MR. BOISE: Object to the form.
A. Correct. That was one of a number of topics that that team worked on.
Q. Thank you. All I asked about was that was one of them, wasn't it? Just so the jury understands. I'm not asking you whatever else they worked on. I'm focusing

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on hyperglycemia and diabetes. You can tell the jury that one of the issues that had to be addressed by the Marketplace Management/Issues Management department was the issue of hyperglycemia and diabetes, true?
A. You're correct.
Q. Thank you, sir.
I've been sitting here all day, and hyperglycemia, what is that?
THE WITNESS: Are you asking for a definition?
MR. ALLEN: Sure, sir.
A. Hyperglycemia would refer to glucose levels that are above a normal value.
Q. Glucose levels where?
A. Technically speaking, in bodily fluids. Blood, I would assume that would apply also to urine, but traditionally we think about it as in blood.
Q. In blood. That's right. Traditionally we do.
So what -- if I'm trying to determine if a person has hyperglycemia, how

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do I make that determination?
A. One would measure glucose levels in blood.
Q. Therefore, blood monitoring would be required?
MR. BOISE: Object to the form.
THE WITNESS: Blood monitoring would be required to determine if someone had higher glucose levels in their blood?
MR. ALLEN: Right.
A. Yes.
Q. Thank you. And prior to the time of the label change that took place in March, I think the day was March 17, 2004, prior to that time, there was no recommendation in the Zyprexa label for blood monitoring to test glucose levels, correct?
MR. BOISE: Object to the form. Foundation.
A. If you're referring to the class labeling change, that occurred in the fall of '03.

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Q. Well, sir, I don't want to quibble with you so we have too much time. I disagree with you about when the actual label change. But let's use, for the sake of not arguing with you, using your words in the fall, prior to the fall of 2003, according to you at least, there was no statement in the Zyprexa label requiring blood monitoring, correct?
A. That's correct.
Q. And not only was there no statement requiring blood monitoring in the Zyprexa label prior to the change that you just discussed, the lack of the need to do blood monitoring was used as a selling point for Zyprexa?
MR. BOISE: Object to the form of the question. Foundation.
A. I'm going to have to disagree with you and provide just a minute of context because I think I know what you're referring to but I'd like to check it.
Q. What am I referring to? Tell the jury. Tell the jury, please, what do you

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think I'm referring to?
A. Okay, I'll take a stab at it.
Q. I'll tell you what I'm referring to. Let me save you some time. I'm referring to the 3 by 3 message. Do you recall that message?
A. No.
Q. Well, let me see if I can help you. As head of the Zyprexa Product Team, you recall the three by three message that said mood, thought and behavioral disorders, broad spectrum efficacy, superior safety, and ease of use. Does that help you at all?
MR. BOISE: Object to the form. Foundation.
A. I can relate to those terms. I'm not relating to a -- of the terminology three by three.
Q. You said you can relate to those terms. Where did you hear that?
A. We can take one at a time and I can give you the context.
Q. I want -- ease of use, I want

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to know where you heard that?
A. Well, it's not where I heard it. That would be an accurate description of one of the attributes of Zyprexa.
Q. There, I think you and I are then agreeing. Maybe it's just a matter of terminology.
MR. BOISE: Were you done with your answer?
THE WITNESS: No.
A. What it refers to is that many antipsychotic drugs, clozapine, for example, requires blood monitoring. Clozapine, specifically, requires blood monitoring for a side effect called agranulocytosis, which is a drop in white blood cells.
Olanzapine and clozapine have some similarities in their chemical structure, although there are significant differences also, and one of the hypotheses at the time of launch was that, was the question will Zyprexa have a drop in granulocytes, if so, that would require blood

monitoring. The evidence came forward to indicate that Zyprexa was not associated with agranulocytosis, therefore, blood monitoring would not be required.

So particularly in the early years after launch, the indication of ease of use as it relates to blood monitoring was that no blood monitoring was required for Zyprexa like it was required for clozapine.

I won't go on too much further other than to say dose titration is another area. Clozapine and other antipsychotic drugs require very slow long building up of the dose. Zyprexa is a drug that is well-tolerated from that perspective and does not require that. So those are the features that would contribute to ease of use.

Q. Sure. And I'll show you a document in a minute, and there's tons of them in your files, how you all describe ease of use, but you've made a good start.

By the way, in my little notes here I had HGFU and then you described

it as an olanzapine plus mood stabilizer study. Do you recall telling Mr. Suggs about that?

A. Yes.

Q. Okay. Olanzapine plus mood stabilizers. What mood stabilizers?

A. In that particular study, if I recall it correctly, were Depakote and lithium.

Q. Depakote, what kind of drug is that? Is that an antipsychotic?

A. No. It's classified as an anticonvulsant and mood stabilizer.

Q. Where did it get that classification?

A. I'm not sure I know what you mean.

Q. You used the word "classified", I didn't. You said it's classified as an anticonvulsant and mood stabilizer. So I asked you "Where did it get that classification" using your word?

A. Based on its efficacy, its ability to decrease seizures, anticonvulsant. The ability to stabilize mood, mood stabilizer.

Q. And it's not an antipsychotic?

A. It's not classified as an antipsychotic.

Q. Classified by whom, the FDA?

A. I've not reviewed the label of Depakote in a long while, but I would bet that it is not classified as an antipsychotic.

Q. Doctor, whether you reviewed the label or not, you're a psychiatrist. You know that Depakote's not an antipsychotic? You know that?

MR. BOISE: Object to the form. Asked and answered.

A. Your question was narrowed to the FDA, and one goes to the label then to determine precise classifications. But you're right, my clinical knowledge is that it's used as an anticonvulsant and a mood stabilizer.

Q. And then you said the HGFU

also is olanzapine plus lithium. And lithium's not an antipsychotic?

A. That's correct.

Q. Okay. So why were you doing a study with olanzapine plus two different mood stabilizers?

A. We had an indication for acute mania in bipolar. There are three phases of bipolar: The manic phase, the maintenance phase, and the depression phase. Lithium and Depakote are two drugs commonly used for the maintenance phase. And that -- those studies were an attempt to determine if the combination of olanzapine with one of those mood stabilizers would be an effective treatment.

Q. By the way, olanzapine or Zyprexa is not a mood stabilizer, is it?

MR. BOISE: Object to the form.

A. Yes.

Q. You agree with me?

A. No.

Q. Okay. Well, Zyprexa had very

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limited indications in the package insert as approved by the FDA. You agree with that?
MR. BOISE: Object to the form.
A. No.
Q. Tell me the indications. So you think -- that's interesting. You think Zyprexa had -- do you think Zyprexa had many wonderful indications?
MR. BOISE: Object to the form.
A. I can state to you the indications it has today.
Q. Go right ahead. Tell the jury -- I'm sorry, sir. Let me repeat the question so the question's clear in my mind before you answer it.
Tell the jury, please, the indications as approved by the FDA that Zyprexa has?
A. Okay. It has an indication for schizophrenia. It has an indication for bipolar mania. It has an indication for use in bipolar along with lithium and Depakote.

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It has an indication for maintenance of bipolar. It has an indication along with Prozac for treatment of bipolar depression. It's got an indication for maintenance of response/relapse prevention in schizophrenia.
Q. You need to slow down and say that again. You were mumbling or at least I couldn't hear you. What was that last one?
A. Maintenance of response in schizophrenia.
It has an indication in the IM for agitation that occurs in schizophrenia and in bipolar. We just received an indication this week for adolescent and child bipolar and adolescent child schizophrenia.
I think I quoted them all.
Q. I think you did, too. Now you're going to go back and you're going to help the jury even more. You want to help the jury, don't you, understand? Let me ask this, do you want to help the jury understand Zyprexa?
MR. BOISE: Object to the form. He's here to answer your questions.
QUESTIONS BY MR. ALLEN:
Q. I'm here trying a case. And I'm asking the witness, do you want to help the jury understand Zyprexa, yes or no?
MR. BOISE: If you will give him a chance to answer the questions, he will.
MR. ALLEN: No, you just need to object to form.
MR. BOISE: I object to the form of that question.
MR. ALLEN: Thank you.
QUESTIONS BY MR. ALLEN:
Q. Do you want to help the jury understand Zyprexa?
A. My purpose here is to answer your questions as fully and directly and honestly as I possibly can.
Q. And you understand I'm here because I'm a trial lawyer and we may have to go to trial and the jury will be at trial, right? You understand that?
A. Yes.

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Q. So you understand your testimony, the questions I'm asking and you're answering are, the ultimate people that are going to hear these are a jury. You understand that?
A. Yes.
Q. Okay. And my question is in answering my questions, do you want to help the jury understand Zyprexa?
MR. BOISE: Object to the form of the question.
A. I'm giving my testimony to be direct, honest and forthright for who all is exposed to this testimony.
Q. Okay. Now we're going to go over the indications that you just described.
When was Zyprexa indicated for schizophrenia?
A. 1996.
Q. When did it get the indication for bipolar mania?
A. 2000.
Q. When did it get the indication for bipolar maintenance?

A. I believe that was 2002, but I'm not a hundred percent positive.
Q. 2002, okay. Now you talked about an indication for Zyprexa for bipolar disease with lithium for depression. When did it get that indication?
MR. BOISE: Object to the form.
A. Again, I believe it was in the 2002 time frame. I don't remember the exact year.
Q. Okay. You said it got an indication. Was there a particular product that's this Zyprexa with lithium? Is there a brand name for that?
MR. BOISE: Object to the form. I think your --
MR. SUGGS: It's what he said.
MR. BOISE: You mischaracterized his prior testimony.
Q. Let me ask you. I want to make sure I didn't. Didn't you tell me one

of the indications, and help the jury, help me understand because I don't. I'm trying to figure this out.
Tell the jury when it got this -- didn't you tell me it had an indication for bipolar with lithium for depression?
A. No.
Q. Okay, what were you saying? You said something along those lines. Help me understand what you were saying.
A. It has an indication for the use of Zyprexa with lithium and Depakote. It also has an indication for bipolar depression along with Prozac.
Q. Okay. You know what, I probably did misspeak, and that's why I need your help.
When did it get this indication for bipolar disease with lithium and Depakote?
A. Lithium and Depakote -- again, I'm thinking it was in the '02 time frame.

Q. Okay. And lithium and Depakote are the mood stabilizers, right?
A. That's correct.
Q. Okay. When did Zyprexa get the indication with Prozac for depression?
A. I believe that was near the end of '03.
Q. Is that Symbyax?
A. Symbyax.
Q. Okay, I'm sorry. When you said it got the indication with Prozac for depression, that's Symbyax?
A. That's correct.
Q. Okay. That's an entirely different product that you had to put in a new NDA on, right?
A. Yes.
Q. That is not Zyprexa, is it?
A. It appears in the Zyprexa label along with the Prozac label.
Q. Just for the record, because Denice Torres has already testified under oath, unless she's was wrong, she testified clearly as did, I think, other witnesses,

that Zyprexa has never been indicated for bipolar depression. Isn't that true, that Zyprexa has never been indicated for bipolar depression?
A. Mono-therapy or single use of Zyprexa is not indicated for bipolar depression, the combination is.
Q. The "combination" being Symbyax?
A. Yes. The combination of Prozac plus olanzapine.
Q. Which is a different drug. It's called Symbyax, right?
A. That's correct.
Q. That's right. After "that's correct" we don't need to do anything else. If I have any other questions, I'll ask you.
A. Okay.
Q. Let me go back to the other drug. Zyprexa with lithium and Depakote, is that another drug product?
A. No.
Q. That's just a drug therapy?
A. It's a type of use of the two

drugs.
Q. Now the IM, that means intramuscular Zyprexa, right?
A. Correct.
Q. You were very clear, I think, in your answer, but I want to make sure I understood it. IM, intramuscular Zyprexa, is indicated for schizophrenia-related agitation and -- excuse me, let me rephrase it.
Intramuscular Zyprexa is indicated for agitation associated with either schizophrenia or bipolar mania, correct?
A. It is for agitation in schizophrenia, and I'm trying to recall if it was agitation only bipolar mania or other parts of bipolar as well, I'm not remembering that, but bipolar disorder.
Q. We're not going to spend a lot of time, but I want to make sure that the intramuscular Zyprexa is indicated for agitation associated with schizophrenia and bipolar?
A. Yes.

Q. It's not indicated for agitation alone?
A. That's correct.
Q. Right. And I'm not trying to be -- I'm really not trying to be cute or funny here because I don't know how else to ask the question. I mean, witnesses get agitated, lawyers get agitated, we've had some agitation in the room over the past two days, in fact, haven't we?
MR. BOISE: I don't think so.
Q. Haven't we?
A. No.
Q. Well, that's good. So you're not agitated with me then?
A. I am not.
Q. Okay. Good. But just for the record, and it could be important to me, doc, that's why I'm asking, I really am asking because it's important. Zyprexa is not and has never been indicated for agitation that is not related to either schizophrenia or bipolar disease, correct?
A. That's correct.

Q. Okay. And you said last week Zyprexa received a new indication for bipolar disease or was it bipolar mania in adolescents and children?
A. I believe it's bipolar mania.
Q. Okay. And that was last week. That's 2007, right?
A. That's correct.
Q. Okay. And we have now covered all the indications for Zyprexa, or a product containing Zyprexa, since it came on the market in 1996 up to 2007, right?
A. I think I included in my initial answer our maintenance to response in schizophrenia. And maintenance in bipolar mono-therapy, single use meaning. And I'm not recalling any other uses or indications.
Q. Thank you. I forgot to ask the question I always ask, or not always, but I ask a lot of witnesses just so we have a clear record, and it's my time to ask questions, and you understand you're under oath testifying, you know that?
MR. BOISE: He's taken the

oath.
Q. I know. You understand it, though?
MR. ALLEN: You're entitled to ask it, it's one of the key questions in a case.
QUESTIONS BY MR. ALLEN:
Q. You understand you're under oath?
A. Yes.
Q. You understand the effect of that oath?
A. Yes.
Q. And we have to depend upon your testimony to be truthful and accurate, you understand that?
A. Yes.
Q. Is there any reason in your testimony of either yesterday or today, is there any reason physically why your testimony could not be truthful and accurate? Is there any ailment or anything that you're suffering from that would make that impossible to do?

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A. No.
Q. Are you today or were you yesterday on any medication?
A. Yes.
Q. What medication, if you don't mind me asking?
A. I take Crestor.
Q. For cholesterol?
A. Yes. I take low dose aspirin.
Q. As a cardiovascular prophylaxis?
A. Yes.
Q. Sir?
A. Yeah.
Q. Is there any medication that you're on that would interfere with your ability -- those two medications --
MR. ALLEN: Let me finish. I understand, I just want to make a clear record.
QUESTIONS BY MR. ALLEN:
Q. The Crestor and the aspirin, they would not interfere with your ability to

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give truthful testimony, correct?
A. Correct.
Q. Is there any medication that you're on that would interfere with that?
A. No.
Q. Okay, thank you.
Why did Mr. Bandick get fired?
MR. BOISE: Object to the form. Foundation.
A. My understanding, he was separated from the company because of inappropriate activities with a vendor or vendors.
Q. Tell me what those are.
MR. BOISE: Object to the form.
A. I don't know.
Q. Mr. Bandick was on the Zyprexa Product Team. We've seen him described in the document I gave you as Marketplace Manager. He was, actually, also the brand manager at the time of the Zyprexa primary care physician launch, right?

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A. Yes.
Q. Mr. Bandick worked on your Zyprexa team. And we know he was fired. And you're telling this jury you don't know why he was fired --
MR. BOISE: Object to form.
Q. -- other than, quote, "some inappropriate activity with vendors?"
MR. BOISE: Object to the form.
A. My understanding is he was separated from the company because of inappropriate activities with a vendor or vendors.
Q. Tell the jury, help the jury understand, help me understand, what would be some examples of inappropriate activities with vendors?
MR. BOISE: Object to the form.
A. I don't know.
Q. You don't know? As an executive at Eli Lilly you don't know what would constitute inappropriate activities

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with vendors?
MR. BOISE: Object to the form.
A. That's correct.
Q. Well, can you have inappropriate activities with vendors that result in your termination from Eli Lilly?
MR. BOISE: Object to the form.
Q. Evidently you can because Mr. Bandick had that.
MR. BOISE: What is your question?
Q. My question is, Dr. Breier, where did you learn that Mr. Bandick was fired because of inappropriate activities with vendors?
MR. BOISE: Object to the form.
A. I had -- it occurred after I left the team. I had heard after the fact. And I was notified by a person in the human resource department.
Q. Who?

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A. Diedre Connolly.
Q. Who?
A. Diedre Connolly.
Q. Where did Ms. Connolly notify you? How did that come about?
A. She gave me a call and told me.
Q. Why did she call you?
MR. BOISE: Object to the form.
A. It was for my information.
Q. Why did you need that information?
MR. BOISE: Object to the form.
A. I didn't.
Q. Okay. Diedre Connolly, what's her title?
A. She is now in charge of the U.S. Affiliate.
Q. In charge of the U.S. Affiliate?
A. Um-hum.
Q. Sir?

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A. Yes.
Q. And I just want to make sure, and I think I understand, but I want to make sure I understand and the jury understands that if she's in charge of the U.S. Affiliate, she'd be president of the U.S. Affiliate?
A. I believe that's her title.
Q. Okay. When Ms. Connolly called you to tell you that Mike Bandick had been fired, what was her title then or what was her job then?
MR. KANTRA: Objection. Foundation.
A. She was in charge of human resources.
Q. Okay. So Diedre Connolly, who was in charge of human resources and is currently President of the U.S. Affiliate of Lilly, called you to inform you Mike Bandick had been fired?
A. As I recall our conversation, she indicated that he was separated from the company. I don't know if he was asked to resign, fired. I don't know the circumstances.
Q. Nevertheless, Ms. Connolly picked up the phone and called you in your office to give you this information, right?
MR. BOISE: Object to the form.
A. She called me and gave me that information.
Q. Right. I bet -- this is Scott Allen thinking, you tell me if I'm wrong. I bet she didn't call -- did she call you Alan or did she call you Dr. Breier?
A. Calls me Alan.
Q. And you call her Diedre?
A. Yes.
Q. I'm thinking that she didn't just call you and say, "Alan, this is Diedre. Mike Bandick has been separated from the company. Got to go now," and hung up. I'll bet that's not the way the conversation went. I bet there was some body to that conversation. Am I accurate?
MR. BOISE: Object to the form.

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A. My recollection is it was very brief. She indicated he had been separated from the company. I believe she indicated, I don't recall if I heard it from her or maybe heard it someplace else, that it related to inappropriate behavior with vendors. There was really no more discussion about it other than that.
Q. It went like this, "Alan, this is Diedre. I'm calling to tell you Mike Bandick has been separated from the company for some activities with vendors. Got to go now," and hung up?
MR. BOISE: Objection to the form. It's been asked and answered two times.
A. I don't recall any other content.
Q. And you didn't ask any questions. You didn't go, "You know, Diedre, I was head of the product team on Zyprexa and Mike Bandick had been the marketplace manager, he had also been the brand manager at the time Zyprexa had come on the PCP

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launch, and I want to know why was he fired?"
You didn't ask any questions?
MR. BOISE: Object to the form.
A. I recall it being a very brief conversation. And I recall the content regarding Mike Bandick what I had conveyed to you.
Q. Using your good logic, I'm sure. I think you taught at Yale. Did you teach at Yale?
A. I trained in psychiatry there.
Q. Okay. I'm thinking you're a logical man. Do you consider yourself a logical man?
A. Yes.
Q. Okay. You're logical enough to, in your own mind, understand why Diedre Connolly would be calling you. But using your logic, why do you think Diedre Connolly, who was head of human resources, called Dr. Breier about Mike Bandick when Mike Bandick got let go? What's your logical

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answer why you were called?
MR. BOISE: Object to the form of the question.
A. I recall it being purely informational. It's common when personnel changes occur at Lilly, movement of one person to another, someone leaves the company, a promotion, that there's an informational network about those events before they come out more publicly. And my understanding was she was just calling me for my information.
Q. Had nothing to do with Zyprexa or did it have something to do with Zyprexa?
MR. BOISE: Object to the form. Foundation.
A. No.
Q. No what?
A. It did not have to do with Zyprexa.
Q. How do you know? Did you ask her? So you must have made an inquiry. You said it didn't have anything to do with

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Zyprexa, so you must have asked "did it have anything to do with Zyprexa?"
MR. BOISE: Objection. Mischaracterizes his testimony.
Q. So the conversation must have included more content than you've told us about.
MR. BOISE: Objection.
What's your question?
Q. Did you ask her, did it have anything to do with Zyprexa?
MR. BOISE: Objection. Asked and answered.
A. No.
Q. Well, how do you know it didn't have anything to do with Zyprexa according to you?
MR. BOISE: Objection. Mischaracterizes his testimony.
A. Perhaps I misunderstood your question. I thought you were asking me something differently than what apparently you were. If you could rephrase your question, I'll answer it directly.

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Q. You know as a fact that Mike Bandick's separation from the company, and I'm going to call it a firing, occurred due to his activities surrounding Zyprexa. You know that?
MR. BOISE: Objection. Asked and answered.
A. My knowledge of what happened was that there was some inappropriate behavior with vendors. I don't know the details of it beyond that. It occurred when I was no longer on the team. And that's the extent of my knowledge.
Q. Okay. What vendors?
MR. BOISE: Objection, foundation.
A. I don't know.
MR. BOISE: Scott, let's take five.
MR. ALLEN: I'll take five because I like you. But I find this a little incredible, but I'll take five.
THE VIDEOGRAPHER: This is

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the end of tape three, we're off the record.

(At this time, there was a brief recess taken, after which the following proceedings were had:)

THE VIDEOGRAPHER: Back on the record. This is beginning of tape No. 4 of the deposition of Alan Breier.

QUESTIONS BY MR. ALLEN:

Q. Dr. Breier, we're back on the record and we have a lot of ground to cover, but I want to go back to this Diedre Connolly conversation regarding Mike Bandick. I want to make sure you and I are communicating and I have the full information on the Diedre Connolly conversation about Mr. Bandick.

As reflected in Exhibit No. 7, Denice Torres was head of global marketing, and as you testified previously, she was on the Zyprexa Product Team, right?

A. Yes.

Q. And as reflected in

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Exhibit 7, and based upon your own personal knowledge separate and apart from Exhibit 7, Mike Bandick worked as Director of Marketplace Management --

THE OPERATOR: Alika Moitra has joined the conference.

Q. And as reflected in Exhibit 7 and from your own personal knowledge, Mike Bandick was also a member of the marketing team and the Zyprexa Product Team, correct?

A. Yes.

Q. And you received a call in your office one day from Diedre Connolly, who was then head of human resources at Eli Lilly and who is now the president of Eli Lilly USA, and she called you, who had formerly been the head of the Zyprexa Product Team, and told you that Mike Bandick, who was also at one time on the Zyprexa Product Team, was, in your words, quote, "separated from the company for inappropriate behavior with a vendor." And that was the extent of the conversation and your knowledge concerning why Mike Bandick was separated from the

Page 569

company?

MR. BOISE: Objection. Asked and answered.

A. That's my recollection of the conversation.

Q. Okay. Have you, and you did not make any inquiry, it's your testimony, that you did not make any further inquiry as to what the inappropriate behavior was; is that correct?

MR. BOISE: Asked and answered.

A. That's my recollection.

Q. You didn't ask who the vendors were?

MR. BOISE: Objection. Asked and answered.

A. That is my recollection.

Q. You didn't ask, was this about Zyprexa?

MR. BOISE: Objection. Asked and answered.

A. That is my recollection.

Q. You didn't ask Diedre, "Why

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are you calling to tell me this?"

A. Correct.

Q. And after that phone call occurred with Diedre Connolly, you made no investigation or inquiry of any kind since then to find out why Mike Bandick got separated from the company?

A. Not to my recollection.

Q. So you were informed -- let's see if I get it right -- that a member of the Zyprexa Product Team who was Brand Manager at the time of the primary care physician launch occurred had been separated from the company for inappropriate behavior, and you have never made an inquiry as to what the behavior was?

MR. BOISE: Object to the form of the question.

A. I have no recollection of making any further inquiries.

Q. Were any other members of the Zyprexa Product Team -- while you were head of the Zyprexa Product Team, have any other members of that team ever been terminated or separated from the company due to

Page 571

inappropriate behavior?
MR. BOISE: Object to the form of the question.
A. I don't recall anyone else --
Q. Okay.
A. -- being separated from the company.
Q. So the only person that you recall ever being separated from the company, using your words, who was on the Zyprexa Product Team, was Mike Bandick. It was for inappropriate behavior. And you've never tried to find out what it was, right?
MR. BOISE: Object to the form of the question.
A. That is my recollection.
Q. And I guess if I take Diedre Connolly's deposition and ask her about the conversation, her recollection will be the same as yours?
MR. BOISE: Object to the form of the question.
A. I can only speak to my recollection.

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Q. You've seen Diedre and you call her by her first name and she calls you Alan. You've seen her since the time of this telephone conversation. I'm sure you have, haven't you?
A. Yes.
Q. Have you ever discussed this again?
A. I have no recollection of having any further conversations with her about this topic.
Q. Did you know whether or not -- have you ever testified before?
A. Have I ever testified before?
Q. Yes.
A. Have I ever had a deposition?
Q. Testified either in a courtroom, a Grand Jury room, in a deposition, on a sworn -- let's leave it at that. Grand Jury, trial or deposition, have you ever testified before?
A. This is my first deposition. I did appear as an expert witness in a trial many years ago.
Q. Before you were with Eli Lilly?
A. Yes.
Q. Okay. Other than the deposition as an expert -- who did you testify for, a doctor, drug company, who?
A. I testified for a plaintiff, I guess that would be the correct --
Q. What happened to that plaintiff?
A. It was a young man with schizophrenia who committed a crime, and I was asked as an expert, as a psychiatrist in schizophrenia, to testify on his behalf.
Q. Okay. And other than that testimony -- that was a criminal proceeding?
A. Yes.
Q. And other than that testimony and this deposition, you've never given any other testimony; is that correct?
MR. BOISE: Object to the form.
Q. Sir?

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A. That's correct.
Q. Have you ever been involved in any federal investigations or state investigations as a witness or has anybody interviewed you regarding Zyprexa concerning federal or state investigations?
MR. BOISE: Object to the form.
A. Outside of preparing for this deposition with my lawyers, no.
Q. Okay. Do you consider yourself an expert in schizophrenia?
A. Yes.
Q. Okay. Which I think brings me to a question I had in mind for you. You talked about the Zyprexa Product Team. And as I understand it, Zyprexa was in the Neuroscience division of Lilly; is that right? Help the jury and me understand that.
A. Yes.
Q. Okay. And I really want the jury to understand, I need to understand, there's a Neuroscience division of Lilly?
A. Yes. There was a

Page 575

Neuroscience division for late-stage molecules that included Zyprexa, and there's a Neuroscience division in early state that was involved in discovering the next generation, the new drugs for neuroscience disorders.

Q. Okay. And so Zyprexa is a neuroscience product?

A. Yes.

Q. Okay. Now in my memory, and I can go look at my notes but I'm sure you can help me with this, Lilly also has, and I've seen it in some of the e-mails and things, has diabetes care products, doesn't it?

A. Yes.

Q. And I can, if I wanted to work the computer, you can hit Eli Lilly on here and they call themselves a diabetes care company. You've seen that?

A. Diabetes is one of the major therapeutic areas that we are involved in.

Q. Yes, sir, that's getting close. But not only is it one of the major

Page 576

therapeutic areas that Lilly is involved in, Lilly often refers to itself as the diabetes care company, doesn't it, sir?

A. I'm not familiar with the terminology as you stated it. I would interpret that to be more of an exclusive focus on diabetes. Whereas, we're very strong on neuroscience, we're strong on diabetes, we're strong on oncology and areas of that nature. And diabetes is one of the areas that we're particularly invested in.

Q. If we had enough time I'd show you one of the documents that came out of the Zyprexa Product Team that referred to Lilly as the diabetes care company. We may not get to it, but we might, and I'll show it to you. Enough of that.

So the diabetes care drugs, I don't need to list every one of them, and I'm going to try to remember the Lilly diabetes drugs. Is one of them Humalog?

A. Yes.

Q. Okay. So the diabetes -- we have the Neuroscience division which contains

Page 577

Zyprexa. What do they call the portion of the company that deals with diabetes, what do they call that portion?

A. Endocrine.

Q. The endocrine. Okay, would it be called the Endocrine division, sir?

A. Yes.

Q. And that's where the diabetes drugs are?

A. Yes.

Q. Okay. Now when they started the Zyprexa Product Team and you were appointed by Dr. Lechleiter to head that team up, do you know or do you have an opinion as to why they chose a psychiatrist to head up the Zyprexa Product Team?

MR. BOISE: Object to the form.

A. I think they look at multiple different qualities of an individual. Having a background in psychiatry would be advantageous in running a Zyprexa Product Team.

Q. Why?

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A. Because the illnesses, primary illnesses that we were focused on included illnesses that would be familiar to a psychiatrist.

Q. Okay. Now you've already testified under oath that one of the issues that confronted Zyprexa during the time you were head of the Zyprexa Product Team was the issues of hyperglycemia and diabetes, correct?

A. Yes.

Q. So who did you, Dr. Breier, as head of the product team, consult with from the Endocrine division, that's the diabetes care side of the company? Who did you begin to consult with to advise you about Zyprexa and diabetes and hyperglycemia when this issue arose?

MR. BOISE: Object to the form.

A. There were contacts and communications with scientists in the endocrine part of the company relatively early on. Some of the people that we worked

Page 579

with included Jamie Dananberg.
Q. Jamie?
A. Jamie Dananberg. Skip Vignati.
Q. Let's take one at that time. Jamie Dananberg, is that a doctor?
A. Yes.
Q. What kind of doctor?
A. Endocrinologist.
Q. Then you went to the next name, Vignati?
A. Skip Vignati.
Q. Doctor?
A. Yes.
Q. What kind of doctor?
A. Endocrinologist.
Q. Who else from the Endocrine division you consult with?
A. José Caro.
Q. What kind of specialty?
A. Endocrinologist.
Q. Who else from the endocrine division?
A. John Holcombe.

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Q. What kind of doctor?
A. Endocrinologist.
Q. Who else from the endocrine division you consult with?
A. Will Dere.
Q. What kind of doctor?
A. I believe he's an endocrinologist.
Q. Who else from the endocrine division you consult with?
A. Margaret Sowell.
Q. What kind of doctor?
A. Endocrinologist.
Q. Who else from the endocrine division you consult with?
A. Mark Himen.
Q. What kind of doctor?
A. He is a Ph.D., a basic scientist with an expertise in endocrinology.
Q. Who else do you consult with from the Endocrine division?
A. I'm not recalling other names at this time.
Q. That's fine. That's fine.

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Doctor, I don't mean this to be disrespectful, I really don't. I'll tell you my perspective right now so you understand I'm not being disrespectful. I'm a trial lawyer, you understand that?
A. Yes.
Q. Okay. And I'll tell you right now I don't do corporate finance or securities. I don't do real estate transactions and I don't do divorces, okay? I don't have expertise in those areas. So if somebody wanted to buy a bank or restructure a land deal, I'd be the last person to come to. I'm just giving that as background to show I'm not trying to be rude to you.
But the fact of the matter is, with all due respect to you, sir, as a psychiatrist, you're not an expert, never have been, and it would be improper to even imply to a jury that you are, in diabetes; isn't that true?
MR. BOISE: Object to the form. Is he an expert in diabetes, is that the question?

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MR. ALLEN: Right.
A. No.
Q. You're not an expert in diabetes, are you?
A. No.
MR. ALLEN: Okay. We have a double negative in the record and I'm going to try to correct it. I think you and I are communicating, but let me ask this way.
QUESTIONS BY MR. ALLEN:
Q. Are you an expert in diabetes?
A. No.
Q. Are you an expert -- well, were you ever in private practice? I didn't -- were you ever in private practice?
A. Yes.
Q. Okay. Did -- if you got a call from somebody that said, "Dr. Breier, I have diabetes, or I think I have diabetes, and I need some care and treatment for it. I need you to diagnose it. I need you to help me determine what caused it. Can I make an

Page 583

appointment in your office today at ten?" You would have told the patient or prospective patient, "You know, you don't need to be coming to see me. I don't have any expertise in that area. You need to go see an endocrinologist." Isn't that what you would have done?

A. If their only concern is what you described, diagnosis, mechanism, I think you indicated also treatment management, they had no other needs, I might well refer them to an endocrinologist or an internist primarily.

Q. All right. I'm certain in your psychiatric practice, you probably treated people who had diabetes, right, but you're treating them as a psychiatrist, correct?

MR. BOISE: Object to form.

A. Yes.

Q. I mean, I'm not trying to be facetious. Just so the record's clear, you probably treated people in your psychiatric practice with the mumps and the measles,

Page 584

flu, with broken hips, but you specialized your treatment in psychiatry, right?

A. That's correct.

Q. Right. And I know you had some academic background, and I understand you had teaching positions and research positions and things of that nature, whatever they may be, you never taught diabetes care and treatment, you never taught diabetes diagnosis, you never taught mechanisms of the cause of diabetes or any subject area like that, did you, sir?

MR. BOISE: Object to the form.

A. Those were not my primary areas of expertise.

Q. Doctor, I'm a lawyer. When you say something like that to me "that's not my primary area of expertise," my question was, did you teach in that area in any regard?

A. Yes.

Q. Tell me what you taught.

A. Give an example. We -- when I was an associate research professor at the

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University of Maryland, I ran a research clinic which I referred to yesterday.

Q. Okay.

A. We investigated a variety of different questions. Some of the -- this was a clinic primarily for schizophrenia. And we would also not only investigate aspects of the psychiatric syndromes but some of the co-morbid medical conditions. And I recall a study where we looked at the relationship between weight gain and clinical efficacy. That was data that we ultimately published. That was data that I then presented in lectures, things of that nature.

So I guess what I would like to do is qualify myself not as a primary expert in endocrinology, but as a psychiatrist who has had fairly extensive clinical experiences. I've encountered the medical problems of my patients. Sometimes those work their way into research questions and then we would write manuscripts and present that data.

Q. Tell me the name of that

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paper?

A. I would need to actually look at my CV to get the exact title.

Q. Give me your best shot.

A. It would be something like Clozapine Induced Weight Gain. Its Relationship to Clinical Symptoms.

Q. What journal was it published in?

A. I believe that was published in "Biological Psychiatry."

Q. What year, approximately? Approximately?

A. Yeah, I don't recall the exact year.

Q. I didn't ask for an exact year that's why I said approximate.

A. I'd say in the '90s, perhaps second half of the '90s.

Q. Thank you. Any other article? Any article that you in any way relate to diabetes?

A. Yes.

Q. Tell me the name. Give it a

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shot.
A. I'm a co-author on PCS analysis. The PCS analysis was an epidemiology study of diabetes. It examined rates of diabetes across a variety of antipsychotic treatments, both typical and traditional. Typical and atypical antipsychotic drugs in the general population.
Q. What journal is that published in?
A. I think it's in "Clinical Epidemiology."
Q. Approximately, what year?
A. I would say somewhere in the 2001/2002 time frame.
Q. While you were at Lilly?
A. Yes.
Q. Was the other article published before you got to Lilly, right?
A. The work was done before I got to Lilly.
Q. And it was published when you got to Lilly?

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A. I believe it was published before --
Q. Any other articles?
A. -- I got to Lilly.
MR. BOISE: Let him finish.
Q. I'm sorry. I'm sorry.
Any other articles?
A. There were two clamp studies.
Q. Let me stop you there. Any other article you published or listed as an author on occurred after you got to Eli Lilly?
A. Related to?
Q. This issue of diabetes.
A. We did a number of mechanistic studies --
Q. Sir, sir, sir, I didn't ask what you did. I said any other articles you're listed as author on dealing with the issue of diabetes occurred after you got to Lilly? That's my only question.
A. After I got to Lilly or before?
Q. Well, you've told me about

Page 589

before. You've told me the clozapine article, right?
A. Um-hum.
Q. Sir, you need to say yes or no.
A. Yes.
Q. You told me about the PCS study, right? Say yes or no. You have to for the record.
MR. BOISE: He's waiting for a question.
Q. You told me about the PCS study, correct?
A. Yes.
Q. Okay. And you told me that both of those were published after you were at Lilly, correct?
A. I was unclear when the clozapine-related article was published. The work was done prior to me coming to Lilly, but I don't recall the exact year it was published.
Q. Okay. And all I'm asking, any other articles that you are listed as an

Page 590

author on dealing with the issue of diabetes, other than those two, any other ones occurred after you were at Eli Lilly, correct? Just a yes or no.
A. Yes.
Q. Thank you.
And now when you were a psychiatrist, what area of psychiatry did you practice in?
A. My area of specialization was in the more severe forms of psychiatric disorders such as schizophrenia.
Q. Okay. So, did you practice general psychiatry?
A. I had clinical responsibilities for the patients who are in our research clinics both at the NIH and at the University of Maryland.
While I was at the NIH, I had a private practice in addition to my work at NIH where that was a general psychiatric practice.
Since I've come to Lilly, I've had a faculty position at the University

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of -- of Indiana University. And I make clinical rounds through my faculty appointment and see a range of patients through those activities.

Q. Do you ever prescribe Zyprexa to anybody?

A. Yes.

Q. How many patients?

A. When we --

Q. My question is simply how many patients? I know you can't give specifics, just how many approximately?

MR. BOISE: Can you approximate a number?

Q. That's my only question. Where you are the prescribing physician for Zyprexa.

A. This is a very rough approximation. I will say between 25 and 50.

Q. Somewhere between 25 and 50. Were they all patients who had either schizophrenia or bipolar mania?

A. No.

Q. What other conditions did the

Page 592

people that you prescribed Zyprexa for have?

A. I'm recalling two patients that had primary mood disorders that were not in the bipolar area.

Q. So you have two -- excuse me, sir, between this rough estimate of 25 and 50, other than those two patients who had primary mood disorder, were the rest of the patients you prescribed Zyprexa to people who had either schizophrenia or bipolar mania?

A. I don't recall.

Q. Well, sir, I'm asking you because this is going to be an issue in the case. So I'm asking, the jury and me are asking you for your best recollection. Do you recall any other patients to whom you have prescribed Zyprexa for things other than schizophrenia or bipolar mania, other than the two patients you discussed who had primary mood disorder?

MR. BOISE: Objection. Asked and answered.

A. I don't recall.

Q. So the two for primary mood

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disorders are the only two you recall that were off-label; is that correct?

MR. BOISE: Object to the form of the question.

A. I don't recall.

Q. Sir, you do recall -- because you just testified that you can recall two for primary mood disorder. Other than those two, can you recall any others?

MR. BOISE: Objection. Asked and answered.

A. I don't recall.

Q. Did you ever prescribe Zyprexa for dementia?

A. I don't recall.

Q. Did you ever prescribe it for depression?

A. Yes.

Q. Okay. Is that one of the two patients with primary mood disorder?

A. Yes.

Q. Have you ever prescribed Zyprexa for -- well, let me go at it this way. The two patients with primary mood

Page 594

disorder, who you do recall prescribing Zyprexa to, what did they have? Let's go with patient No. 1 first.

A. My best recollection is they had forms of depression.

Q. Both of them, sir?

A. Yes.

Q. Forms of depression unrelated to schizophrenia and/or bipolar mania, correct?

A. That's my recollection.

Q. Yes. So those would be off-label prescriptions, is that true?

A. Yes.

Q. And when did those prescriptions occur, approximately, before or after you came to Eli Lilly?

A. I had a private practice when I was at the NIH before I came to Eli Lilly. So that would have been prior to 1997. In my role at Indiana University as a professor of psychiatry there, and when I make rounds, I'm not the prescribing physician but I'm involved in the

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clinical assessment of, of many patients.
Q. With due respect that's nonresponsive. My question to you only was: Those two patients to whom you prescribed Zyprexa for depression unrelated to schizophrenia or bipolar mania, did that occur before or after you came to Eli Lilly?
MR. BOISE: Object to the form.
A. Before.
Q. Okay. Since you came to Eli Lilly, have you ever prescribed Zyprexa in an off-label fashion?
MR. BOISE: Object to the form.
A. No.
Q. Why not?
MR. BOISE: Object to the form.
A. Because my clinical duties are as a consultant and teacher as opposed to a primary prescribing physician.
Q. Okay. Now you just talked about the fact you make rounds at the

Page 596

University of Indiana, and I guess people work underneath you.
A. No.
Q. Okay. Let me ask it this way: Have you ever been a physician on a team for a patient, either singularly as a one-person team being Dr. Breier, or as Dr. Breier with other doctors, since you got to Eli Lilly, where that patient, who either you're treating or your team is treating, has been prescribed Zyprexa in an off-label fashion?
A. Yes.
Q. How many times?
MR. BOISE: Object to the form.
A. This is a very rough approximation -- 20.
Q. Okay. Now do any of these patients, any of the patients that you ever prescribed Zyprexa to or you've been on a team where Zyprexa's been prescribed, did any of those patients gain weight with respect to Zyprexa?

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MR. BOISE: Objection to the form.
A. Yes.
Q. How many? I'm talking -- let's clarify, clinically significant weight gain. Let me rephrase the question.
In any of the patients to whom you've ever prescribed Zyprexa and/or you've been on a team where the patient was prescribed Zyprexa, did any of those patients have clinically significant weight gain which you felt was secondary to Zyprexa?
MR. BOISE: Object to the form.
A. Again, this is a very rough approximation, but I would -- I would approximate that approximately half of the patients that I'm aware of have had clinically meaningful weight gain associated with their treatments with Zyprexa.
But I must add that particularly since I've been at the Indiana University where I see very sick patients, nearly all of those patients have been on

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other medicines as well, sometimes multiple medicines. So it can be difficult to tease out or to sort out exactly what may or may not have been contributing to weight gain.
Q. But at least as an approximation for the jury at least 50 percent of the patients to whom you have prescribed Zyprexa and/or your team has prescribed Zyprexa, you have seen in those patients clinically significant weight gain?
MR. BOISE: Object to the form.
A. Again, it's a rough approximation --
Q. Thank you.
A. -- but I would say that of the patients that I have seen in clinical settings who have been treated with Zyprexa, I've seen weight gain, but in particularly the patients that I've seen since I've been in Indianapolis who tend to be very, very ill, those patients tend to be treated with multiple different medications over very long periods of time, and it's very difficult to

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kind of sort out in terms of what the association means.

MR. ALLEN: Objection. Nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. I understand, sir, what you're trying to say, and I'm just asking a real simple question of numbers. We can talk about those other issues if you like if your lawyer wants to ask you.

I want you to listen to the question because it's really an easy question. Of those patients to whom you've prescribed Zyprexa and/or you've been on a team where those patients have been treated with Zyprexa, according to you, 50 percent of those patients you had seen had clinically significant weight gain, as an approximation, true?

A. Again, I just want to qualify that this is a very rough approximation.

Q. Okay. Was the rough approximation 50 percent?

A. Yes.

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Q. Thank you. Now of those patients, the 50 percent of patients that had clinically significant weight gain, how many of those patients ended up developing diabetes?

MR. BOISE: Object to the form.

A. Again, I want to just be precise in my answer. You said at one point how many of those patients had clinically significant weight. And your second question as I heard it, maybe I misunderstood it, related to weight gain. And so what I need to describe, so it's clear,is that my response was at Indiana University as a consultant I'll come in and see a case, usually very, very ill, who is being treated with multiple medicines.

The ones I'm thinking about now with Zyprexa I'm saying, approximately, half of those had weight, were overweight. I don't know when the weight gain started or if it occurred temporally with the start of Zyprexa or before or after.

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But I just want to be very clear that I don't see patients over a longitudinal period of time, week after week, to be clear about the actual trajectory of the weight.

But walking in, seeing a case in cross-section, about half of those that I've seen on Zyprexa and other medicines have had weight gain.

Q. To the patients where you have prescribed Zyprexa or you've been on a team where a patient was prescribed Zyprexa, how many of those have gained clinically significant weight that you believed was related to the Zyprexa?

A. As I think back to my private practice, I can think of a small number of patients. My experience at I.U. is not, it's difficult to --

Q. Sir, you know what, really, I swear, you're thinking. You're letting me hear your thinking. I just need a number, okay.

Give me an approximation of

Page 602

the percentage of patients to whom you prescribed Zyprexa or you've been on a team that the patient got Zyprexa, a percentage of patients who had clinically significant weight gain that you, yourself, related to the Zyprexa? A number, please.

MR. BOISE: Object to the form of the question.

A. Very rough, very rough percentage, 10 percent.

Q. Okay. Of those patients, how many developed diabetes?

MR. BOISE: Object to the form.

A. None that I know of.

Q. Okay. When they gained the clinically significant weight gain after you administered Zyprexa, did you do blood glucose monitoring?

MR. BOISE: Object to the form of the question.

Q. Yes or no is the answer or you don't know.

A. In my private practice where

Page 603

I was the primary psychiatrist and primary treating physician, no.
Q. Okay.
A. At I.U., my role was not one to follow along patients.
Q. Thank you, sir.
All right. Sir, do you remember when the primary care physician launch occurred? You remember that?
MR. BOISE: The question is does he remember?
MR. ALLEN: Yes. That's the question. These are easy questions.
MR. BOISE: I want to make sure I understood the question.
That you were done.
QUESTIONS BY MR. ALLEN:
Q. You recall that, do you not?
A. Yes.
Q. Thank you, sir. As a matter of fact, you were at, was it Orlando, Florida, when Viva Zyprexa primary care physician launch occurred, weren't you? Yes.
A. I was at the launch meeting,

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I believe it was in Orlando.
Q. And you spoke at the launch meeting, the primary care physician launch meeting with the sales representatives. Yes?
MR. BOISE: Object to the form.
A. Yes.
Q. And at the time a decision was made to do the primary care physician launch, you were part of the team that made the decision to do the primary care physician launch, correct?
MR. BOISE: Object to the form of the question.
A. No.
Q. Okay. So who was on that team that made the decision to launch in the primary care physician market?
MR. BOISE: Object to the form of the question.
Q. Just tell me who's on the team. There's no explanation. If you don't remember, tell me you don't remember.
A. They would have been senior

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management in the U.S. Affiliate. I couldn't tell you the names.
Q. So senior management in the U.S. Affiliate made the decision to do the primary care physician launch, correct?
MR. BOISE: Object to the form.
A. Yes.
(Whereupon, Deposition Exhibit(s) 8 duly received, marked and made a part of the record.)
THE WITNESS: All right, here's Exhibit 8, Breier 8. I think it's been marked previously but I don't want to go back and look for it. You read it already in this case. It's called Zyprexa Primary Care Implement Strategy and Overview.
QUESTIONS BY MR. ALLEN:
Q. You recall that document, do you not?
A. Just looking at the title, I

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don't recall it.
Q. Sir, you've read it already in the last two days.
MR. BOISE: Object to the form.
Q. Okay. You've already read it.
A. I need to read it.
Q. If you don't recall reading it in the last two days, we're going to go through it and read it together.
Sir, under "Background" -- do you see the word "Background" at the top? The answer's yes, you see it.
MR. BOISE: Let him find it.
Just let him find it.
MR. ALLEN: It's easy, it's right there.
QUESTIONS BY MR. ALLEN:
Q. Do you see it, doc?
A. Yes.
Q. Let me read for you. It says, "Following several months of study by the Lilly U.S.A. Zyprexa brand team." That would

be the team you're head of, isn't it?
MR. BOISE: Object to the form.
A. No.
Q. Why, because it's limited to the USA brand team?
MR. BOISE: Object to the form.
A. The Lilly U.S.A. Zyprexa brand team is part of the U.S. Affiliate, not the product team.
Q. Okay. Let me go on. "Following several months of study by the U.S.A. Zyprexa Brand Team the affiliate approved the recommendation that Lilly actively promote Zyprexa to selected current primary care prescriber targets."
Did I read that correctly?
A. Yes.
Q. Yes, thank you. Go down to "Current Situations."
MR. BOISE: Let him answer.
Q. It's just so easy.
MR. BOISE: For you.

Q. You see "Current Situation"?
A. Yes.
Q. And it says "PCPs," that's primary care physicians, right?
A. That's correct.
Q. Okay. "PCPs account for about 18 percent of retail antipsychotic prescriptions. Risperdal holds a 29 share compared to 18 for Zyprexa. Typical agents such as Haldol account for another 40 plus percent. Nearly half of all PCP antipsychotic prescriptions go to patients age 65 plus," which is 65 and above, correct?
MR. BOISE: Object to the form. Correct what?
Q. Did I read that correctly?
MR. BOISE: No.
A. You've read that paragraph correctly.
Q. Thank you, sir. Now --
(Whereupon, Deposition Exhibit(s) 9 duly received, marked and made a part of the record.)

MR. ALLEN: I'm marking Breier No. 9, the Zyprexa launch meeting. I'm asking you to turn to Page 86. Let me just get it for you, I'm going to help you out. Eighty-six, the launch meeting agenda day one.
QUESTIONS BY MR. ALLEN:
Q. Just so the record reflects that the general session that you're reflected, General Session Olanzapine Medical, A. Breier, MD.
You spoke at the launch meeting, right?
MR. BOISE: Objection. Asked and answered.
Q. "Yes, Mr. Allen, I spoke at the launch meeting."
MR. BOISE: You can ask him the question without the document. You asked him with the document.
MR. ALLEN: Yes.
MR. BOISE: He's answered that question.

MR. ALLEN: I'm trying to refresh his recollection.
QUESTIONS BY MR. ALLEN:
Q. You spoke at the launch meeting as reflected in this document, correct?
MR. BOISE: His recollection wasn't needing refreshing.
He already answered that question.
Q. Help me out, sir.
A. I spoke at the launch meeting.
Q. Okay. Now, you were involved in the Zyprexa primary care physician launch, were you not?
MR. BOISE: Object to the form. He testified at length about this yesterday.
MR. ALLEN: I understand.
QUESTIONS BY MR. ALLEN:
Q. Just were you not?
MR. BOISE: Object to the form.

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A. I spoke in the general session of the primary care launch.
Q. Right. And they recorded your comments so that they could be put on audio cassette tapes so they could continue to train the sales representatives after the launch meeting, correct?
MR. BOISE: Object to the form.
A. It is my understanding that my remarks were audiotaped and made available.
Q. To the sales representatives?
MR. BOISE: Object to the form.
A. I don't know who all in the U.S. Affiliate it was made available to. I assume it was the sales representatives.
Q. Now if you look on page -- prior to today, you've certainly seen what we've marked as Bandick -- I mean, excuse me, Breier No. 9, the document in your hand. You have seen this exhibit before, have you not?
A. I don't recall seeing it

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before.
Q. Well, let's just go through some of the paragraphs in the -- is it Breier 8? Get Breier 8 out. It's right over there. See Breier 8 and Breier 9, put them together. We're going to look at them together.
MR. SUGGS: Could you read off the exhibit number in the left corner at the bottom.
MR. ALLEN: The left hand corner?
MR. SUGGS: Yes.
MR. ALLEN: It's Plaintiff's Exhibit No. 85046.
QUESTIONS BY MR. ALLEN:
Q. Now, look under the last thing we read is "nearly half of all PCP antipsychotic prescriptions go to patients age 65 plus."
Do you recall reading that with me?
A. Yes.
Q. Okay. Now go to page -- and the page number, sir, I'm talking, we're

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going to look at the page numbers on Breier 9 that are in the bottom right-hand corner, okay? And go to Page 69. Let's go to 68, first. Okay? Let's go to 68 first. Okay. Are you with me, sir? It's real easy just turn to Page 68, are you there?
MR. BOISE: Let him be.
Q. That's all I'm asking. Are you there at Page 68?
A. Yes.
Q. Okay. Now I know you can do this because you're an educator, you've taught at Yale, you've been at NIH, you've held academic positions and you're head of Zyprexa Product Team.
If you look at Exhibit 8 to your left, and while you're still holding 9 in your right hand, look at 8. You see No. 8 over there to your left? All right.
MR. BOISE: Don't be condescending.
MR. ALLEN: I'm not. I'm trying to -- he can do this.
MR. BOISE: You don't have to

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load it up with that. You know you don't.
MR. SUGGS: I understand, but he can do this.
MR. BOISE: You know you don't.
QUESTIONS BY MR. ALLEN:
Q. Look at "Current Situation" in Exhibit 8. It says "PCPs account for nearly 18 percent of all retail antipsychotic prescriptions," right?
MR. BOISE: Object to the form.
A. I'm reading the words over here that you just --
Q. Yes, sir.
A. -- indicated.
Q. Right. And that's contained in the Zyprexa Primary Care Strategy and Implementation Overview, Breier No. 8. And then we go to Page 68 of the Zyprexa Launch Meeting document. And if we look at it, the third bullet point on Page 68 says "PCPs account for 18 percent of antipsychotic

Page 615

market. More than half is composed of older, vulnerable agents."
Did I read that correctly?
A. You read that bullet point correctly.
Q. Yes, sir. Now, if you go to Page 69.
THE WITNESS: Excuse me, could we take a short break at a point that's conducive?
MR. ALLEN: You need to take a break for the restroom or something?
THE WITNESS: Yes.
MR. ALLEN: Go right ahead. We'll take it right this second.
THE WITNESS: Sure. I'll make it quick.
THE VIDEOGRAPHER: We're off the record.
(At this time, there was a brief recess taken, after which the following proceedings were had:)

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THE VIDEOGRAPHER: Back on the record. Beginning of tape No. 5.
QUESTIONS BY MR. ALLEN:
Q. Doctor, we took a break at your request. Are you ready to proceed?
A. I am.
Q. I'm not going to ask you anything more about that Viva Zyprexa, okay? We're going to go on to another subject.
All right. Doctor, we've discussed and Mr. Suggs discussed with you at some length the issue of the Japanese label, you recall that?
A. Yes.
Q. And I'm just trying to put this in context. You and I discussed the fact of hyperglycemia and the fact it was one of the issues confronted by the Zyprexa Product Team, and, in particular, was discussed by the Issues Management people.
MR. BOISE: Object to form.
A. I wouldn't characterize it that way.

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Q. Characterize it for the jury as succinctly as possible.
A. Okay. Hyperglycemia, trying to understand is it/is it not associated with Zyprexa was an important scientific focus. And there were multiple groups on the team that were involved with that, primarily, from RD perspective.
The Issues Management team was a team, let's say a subteam on the team, that looked at a range of issues as well. But your characterization that was primarily, maybe I'm misunderstanding and misquoting, but your characterization that the Issues Management team was the primary group focusing on hypoglycemia would not have been correct.
Q. Okay. Nevertheless, we know -- maybe I should rephrase my questions better. The Issues Management team, which was part of the marketing people, right? They were a marketing department.
A. It did not have a primary marketing focus, it had a primary medical

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focus.
Q. That's fine. So you're saying the Issues Management team that was headed up by Michael Bandick had a primary medical focus?
A. No. It was not headed by Michael Bandick.
Q. I don't want to argue with you but get out Exhibit 7, please.
MR. ALLEN: Let me have the stack, I'll find it. There it is. I saw it go right through your hand. I think I'll recognize it right when I see it. It's going to be one of these. Here it is.
QUESTIONS BY MR. ALLEN:
Q. Sir, Breier No. 7, it's called "Restructuring the Marketing Component For Zyprexa Product Team." Second page, top of the second page, it says "Mike Bandick will assume the role of Director of Marketplace Management."
Did I read that correctly?
It's very simple.

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A. Yes, you did.
Q. Okay. And Marketplace Management was the department that handled marketing issues and messaging as one of its roles, correct, or you don't know, or no?
A. I wouldn't characterize it that way.
Q. Okay, sir. Thank you. We'll just rely on the testimony of the people that were in that department.
Now, I'm going to hand you what's been marked as Breier No. 10.
(Whereupon, Deposition Exhibit(s) 10 duly received, marked and made a part of the record.)
Q. I'm not going to ask you about the whole document. This is something called Zyprexa Implementation Guide.
Turn to the second page of Exhibit 10 where it says "Key Message Elements." Do you see that? Right in kind of the top third of the page, the heading "Key Message Elements."

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A. I see that.
Q. All right. And I'm going to read underneath it. It says -- this is from the Zyprexa Implementation Guide. And if we go back to the first page briefly. Will you do that for me, sir? Back to the first page, please. Under the heading "Strategy Overview." You see the heading "Strategy Overview"?
A. Yes.
Q. Here's what it says. "Welcome to the primary care resource guide. This guide will function as your resource for our launch of the primary care message. Our vision is to expand the market of Zyprexa by redefining how primary care physicians help reduce mood, thought, and behavioral disturbances."
Did I read that correctly?
A. Yes.
Q. Go to the second page. So this document was created, it's very clear, as a part and parcel of the primary care physician launch. Do you agree with that?
MR. BOISE: Objection to the form.

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A. I don't know.
Q. Okay. If you don't know, we'll go to the second page and we'll let the jury determine what they think about that. Go to the second page. You see where it says "Key Message Elements." About the top one-third of the page.
A. I see that.
Q. Okay. I'm going to read and you follow along. "In essence, the Zyprexa primary care message has a, quote, 'three times three', closed quotes, component to it. The three set of disturbances we need to focus on are mood disturbances, thought disturbances, and behavioral disturbances."
Did I read that correctly so far?
A. Yes.
Q. Continuing. "We then have three components to our message." And it has three bullet points, correct?
A. Yes.
Q. Okay. "The three components

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to the message" -- I want to address each one separately -- "broad efficacy (refer to three patient types: Martha, David, Christine.)"
Did I read that correctly?
A. Yes.
Q. Okay. The next component to the message is safety. And I'll read it. It says "Safety (Proven: 5 years 5 million patients, low risk of certain serious medical complications.)"
Did I read that correctly?
A. Yes.
Q. Now I want to focus on the third bullet point of the message. "Ease of use (5 milligrams to start, QD"--
That means once a day, doesn't it, QD?
A. You're correct.
Q. "5 milligrams to start, QD at bedtime with or without food, no blood monitoring." Did I read that correctly?
A. Yes.
Q. Okay. So if this document is correct, the Zyprexa implementation guide

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says that the three components to the message that we're going to give doctors are that Zyprexa has broad efficacy, proven safety, and ease of use. And as part of the ease of use message you're going to tell doctors, there's no need for blood monitoring, correct?

MR. BOISE: Object to the form.

A. I'm reading the words as we go along on this page. I have not reviewed this entire document, but the document from what I've seen so far is not one that I'm familiar with. I cannot then determine from or answer your question along the lines as you said -- something of the effect -- this is something that we're going to. And I don't have the context to answer yes or no to that.

I can talk to some of these points from a clinical perspective if you'd like, but I don't have enough context to talk about this specific document and these points in the context of this document.

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Q. Let me ask this question, Dr. Alan Breier, former head of Zyprexa Product Team, can you testify whether or not one of the messages you gave to doctors was ease of use, and included within that message was the fact that doctors did not need to do blood monitoring? Can you testify to that or not?

MR. BOISE: Object to the form.

A. As I stated earlier this afternoon, I can provide the background on the --

Q. I didn't ask you to provide the background. I didn't ask you to provide the background.

A. Then I'll have to say that I don't know the context that this information would be conveyed to a doctor.

Q. So you don't know whether or not, as the head of the Zyprexa Product Team, you don't know that doctors were given the message that Zyprexa was easy to use, you could give patients five milligrams to start,

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you'd only have to take it once a day at bedtime with or without food, and there was no need for blood monitoring? You don't know whether that message was given to doctors or not?

A. As stated here, I do not.

MR. ALLEN: Okay. Can you hand me the document?

MR. BOISE: Were you done with your answer?

THE WITNESS: No.

MR. ALLEN: Go ahead, finish. Go ahead and finish your answer.

A. Again, we spoke a little bit about this before. The product team's responsibilities is one not involved in implementation, sales force activities, et cetera; however, I can speak to each one of these points from a clinical perspective.

MR. ALLEN: I'm not asking you to do that. See, your lawyer's going to ask you that. Hand me the document. We'll put it here. We're not going to talk about it.

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QUESTIONS BY MR. ALLEN:

Q. Can you, Alan Breier, tell this jury that one of the messages given to doctors by Lilly sales representatives was Zyprexa is easy to use, you have once a day dosing at bedtime with or without food, and there's no need to do blood monitoring, yes or no?

MR. BOISE: Objection. Asked and answered.

A. Again, I can talk to the data that would support each one of those points. I think each one of those points has validity and can be supported by the medical data. I don't know precisely what verbatims were given to sales reps, how they framed it, what those kind of interactions went to.

Q. That's your best answer to my question?

A. Yes.

Q. Okay. You used some words just then in your answer. You said "I don't know about the specific verbatims and how they framed it." Do you recall saying that?

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Those are your words, not mine.
Do you recall just saying "I don't know the specific verbatims and how they framed it." Do you recall saying that?
A. Yes.
Q. What's a verbatim?
MR. BOISE: Objection. Asked and answered.
A. Verbal product.
Q. What's "framing" mean?
A. Context.
Q. And you do know that sales representatives were trained in verbatims that they were to relay to doctors and they were taught how to frame those verbatims? You do know that, don't you?
MR. BOISE: Object to the form.
A. Yes.
Q. Okay. And why were sales representatives given verbatims and then told how to frame the verbatims when they went and met with doctors?
MR. BOISE: Object to the

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form.
A. My best understanding of that is that the sales, members of the sales force had varied background. Some had deeper science background than others. So in order to get the communication of the data accurate and precise, having training and what information to deliver, if it's accurate, not accurate, supported by data, et cetera, so there would be a training on how you present the information.
Q. Makes common sense. The sales representatives are not all doctors, they're not all pharmacists, they're not scientists, they're not epidemiologists, they're not endocrinologists. They may be, we may find one that is somewhere. What you're telling this jury in Scott Allen language is the sales representatives have to be trained by the company so we make sure that they're giving the people that they talk to truthful and accurate information they can count on, right?
A. I agree with that, your

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statement.
Q. I thought you would. And that's why if you see on some of the documents, sir, I'm sure you've seen it and you've seen the phrase "Lilly, Answers that matter." That's kind of a corporate slogo of you alls. Slogo. Corporate slogan of you alls, isn't it?
MR. BOISE: Can we translate?
MR. ALLEN: Yeah, let me rephrase it.
QUESTIONS BY MR. ALLEN:
Q. You've seen the phrase "Lilly, Answers that matter." That's kind of a corporate slogan of your company's, is it not?
A. Yes.
Q. Yeah. Just for example, I'm looking right here on the memo you wrote after your trip to Japan, you wrote it on stationery that says, "Lilly," down at the bottom right here preprinted, it says, "Answers that matter," right?

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A. Yes.
Q. And so when you trained your sales representatives to give answers to doctor's questions, for example, you knew that those answers mattered to the doctors and to the patients?
MR. BOISE: Object to the form.
A. Yes. We as a company strove to get the most meaningful and accurate information to prescribers, doctors.
Q. And you knew that that information could be and was likely to be relayed to patients?
MR. BOISE: Object to the form.
THE WITNESS: I'm not sure -- I didn't fully understand your question. Could you repeat it?
QUESTIONS BY MR. ALLEN:
Q. You understood whatever Lilly told doctors could be, and you suspected would be, related to patients?
MR. BOISE: Object to the

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form.
Q. Who did doctors -- let me put it this way, and then if you don't want to agree with me -- you know doctors treat patients?
A. Yes.
Q. And you know doctors talk to patients?
A. Yes.
Q. And you know patients ask questions about the drugs that they're going to be prescribed?
MR. BOISE: Object to the form.
A. They certainly, certainly they often do.
Q. Yes. And you know doctors will try to answer the patient's questions if they can. You know that?
A. Yes.
Q. And you know that your sales representatives talk to doctors about Zyprexa?
A. Yes.

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Q. And you know that the doctors who are talking to your sales representatives, as you said, are entitled to answers that matter that are truthful and accurate, true?
MR. BOISE: Object to the form.
A. I agree with what you said.
Q. Thank you. Now, and you know your sales representatives are trained to answer the doctor's questions so you as a company can make sure that your sales representatives are acting appropriately when they talk to the doctors, right?
A. That's correct. There's a diversity of background. So in order to make sure there's a uniformity in conveying the data, we have very rigorous policies and procedures around training. We have a function called MLR that reviews very carefully all the information that a sales rep conveys.
Q. And the MLR process that stands for medical, legal, and regulatory

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departments, they have to approve, for example, all of the written material that may be passed out to physicians or to PBMs, pharmaceutical benefit managers. Any written material that comes out of Eli Lilly on Zyprexa has to go through this review process, correct?
MR. BOISE: Object to the form. Foundation.
A. That's correct.
Q. Thank you, sir.
A. I also believe they have to review, I'm not a hundred percent sure about this, but I also believe they have to review and approve any sort of training aids.
Q. Okay, good. Now, I'm going to hand you 10, which I'm going to say is called the Zyprexa Implementation Guide, and I'm going to assume it is a training aid.
And if you go to Page 11, they have Frequently Asked Questions. Okay, do you see Frequently Asked Questions?
MR. BOISE: I missed the page, Scott.

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MR. ALLEN: Page 11.
A. I see that.
Q. Okay. Then they have questions and answers to help train the sales reps. We're going to get to particular questions, Doctor. I appreciate it if you stay with me on Page 11 right now. Here's the questions, then they gave the answers. I'm not going to read all the answers.
Just to put into context, question one is "How do I switch from other psychotropics to Zyprexa?" Question two is "What about the cost? Then gives an answer. Question three is "How does Zyprexa compare to Haldol?"
Do you see those questions, sir?
A. Yes.
Q. Now go to the next page. On Page 12 they have the question "Do I need to do any blood monitoring with Zyprexa?" Let me rephrase. On Page 12 of the Zyprexa Implementation Guide the question is asked "Do I need to do any -- excuse me -- "Do I

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need to do any blood monitoring with Zyprexa?" That's the question. Is that correct?
A. You've read that correctly.
Q. What's Lilly's answer?
A. The answer stated here is "no."
Q. Thank you, sir. Let's go to the next question. The next question is "I have heard that Zyprexa causes diabetes. Has this been your clinical experience?"
That's the question, right?
A. You've read those words correctly.
Q. Okay. Read the answer to that question that Lilly gave.
MR. BOISE: Object to the form of the question. Foundation.
Q. Can you read it out loud for the jury, please?
A. In a large, (n = 5,022) retrospective analysis, the incidence of treatment-emergent glucose elevations with Zyprexa was comparable to placebo,

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(3.1 percent versus 2.5 percent.) Further, the incidence of developing diabetes while on Zyprexa is not statistically different from the population at large. I can supply you with a medical letter that can provide further details."
Q. Okay, sir. So in this question, the question is asked "I have heard that Zyprexa causes diabetes. Has this been your clinical experience?" The answer that Lilly has in the Zyprexa Implementation Guide for primary care physicians is "The incidence of treatment-emergent glucose elevations with Zyprexa was comparable to placebo."
Correct?
A. You've reread that sentence correctly.
Q. Right. So you were training the sales representatives -- let me ask this. Is it true that treatment-emergent glucose elevations with Zyprexa are comparable to placebo?
MR. BOISE: Object to the form.

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THE WITNESS: Before answering that question, I'd like to get a little more context and look at a little bit more of the document.
MR. ALLEN: No. This is a scientific question. You can put the document down. You can hand me the document, please, sir. I'm going to ask you a scientific question.
QUESTIONS BY MR. ALLEN:
Q. Is it true that treatment-emergent glucose elevations with Zyprexa are comparable to placebo?
MR. BOISE: Object to the form.
THE WITNESS: Could you repeat the question?
MR. ALLEN: Is it true that the incidence of treatment-emergent glucose elevations with Zyprexa are comparable to placebo?
A. The differences in glucose

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levels between placebo and Zyprexa are, from large datasets of that nature, would be coming from the clinical trial dataset. Those are random samples. The differences are relatively small between Zyprexa and placebo and not outside of the normal range.
We've done analyses that have showed statistically significant differences between Zyprexa and placebo, but, again, those have to be interpreted both with the fact that they're random samples, that the differences were small.
And I think to fully understand this issue, one has to look at the totality of medicine. I think the reference to a medical letter is a way of appropriately bringing in -- our medical letters are very thorough -- in bringing all of the information on this particular topic.
MR. ALLEN: We'll have to argue about this later, but with all due respect, this is nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. I don't want you to consider

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Breier No. 10. We're not talking about Breier No. 10. I'm asking, as we sit here today, January the 12th, 2007, is it true that treatment-emergent blood glucose elevations with Zyprexa are comparable to a placebo?

MR. BOISE: Objection. Asked and answered.

A. I would need to give you my same answer again.

Q. The one you just gave?

A. Yes.

MR. ALLEN: Thank you, that's all I needed to know.

QUESTIONS BY MR. ALLEN:

Q. Is it true the incidence, in your opinion, sitting here today, are you telling me the incidence of developing diabetes on Zyprexa is the same as the population at large?

MR. BOISE: Objection to the form. Asked and answered.

THE WITNESS: Could you repeat the question?

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QUESTIONS BY MR. ALLEN:

Q. Are you telling me -- have you ever heard of a consensus statement dealing with second generation antipsychotics?

THE WITNESS: ADA consensus statement?

MR. ALLEN: Yes.

A. Yes.

Q. Do you agree with that consensus statement, yes or no?

A. There are parts of it I agree very much with, and there are parts I disagree with.

MR. ALLEN: That's all I need to know. All right.

QUESTIONS BY MR. ALLEN:

Q. Now, who's Donna?

A. I don't know.

MR. ALLEN: Let me rephrase the question because, you know, I've gotten that answer every time I've asked it.

QUESTIONS BY MR. ALLEN:

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Q. In relation to Zyprexa, who's Donna?

A. I'm not sure.

Q. In relation to Zyprexa, who's Mark?

A. I don't know.

Q. In relation to Zyprexa, who's Martha?

A. I believe that Martha is a -- if this is what you're referring to, I'll test it -- is a patient profile that exhibits specific symptoms.

MR. ALLEN: Okay. Thank you. I'm going to hand you what's been marked as Breier 11. Give your counsel a copy.

(Whereupon, Deposition Exhibit(s) 11 duly received, marked and made a part of the record.)

QUESTIONS BY MR. ALLEN:

Q. You knew there was a diabetes sell sheet, hyperglycemia and diabetes sell sheet. You knew that, didn't you?

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A. Yes.

Q. Okay. And you, in fact, were involved in developing the hyperglycemia/diabetes sell sheet, weren't you?

MR. BOISE: Object to the form. Foundation.

A. I don't recall.

Q. Okay. On Exhibit 11, it's called Hyperglycemia/Diabetes Sell Sheet Implementation --

MR. SUGGS: Could you read the Plaintiff's Exhibit number?

MR. ALLEN: Yeah, I'm sorry. It's hard for me to read this number it's so small. 01962.

QUESTIONS BY MR. ALLEN:

Q. As a matter of fact, on Exhibit 11 we see the logo "Lilly, Answers that matter." And we go to the second page, it says, "Proper implementation is key!" Do you see that?

A. Yes.

Q. Underneath that it says, "Our

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goal and focus is on creating a market with Donna. The competition wins if we are distracted into talking about diabetes."

Did I read that correctly?

A. You read the two sentences on the page correctly.

Q. Right. Now, does that help you recall who Donna is?

A. No.

Q. Thank you, sir. While you were -- sir, we're through with that.

While you were Zyprexa Product Team leader, that was your position, right?

A. Yes.

Q. Okay. I have a hard time remembering that exact terminology. I apologize, all right?

You recall that at times you would get or you would be involved in a process where people were wondering, people on the Zyprexa Product Team were wondering whether or not certain questions about the safety and efficacy of Zyprexa were available

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from the company in the form of a standby statement? Do you recall that process?

MR. BOISE: Object to the form of the question. Foundation.

A. No.

Q. Okay. Do you know what a standby statement is?

A. I have an understanding of standby statement.

Q. Tell the jury what a standby statement is.

A. My assumption is -- there's probably different meanings for that and different ways that a standby statement can be used -- it would be --

Q. I didn't ask how it would be used. My question is -- I apologize to interrupt -- my only question is, what is a standby statement?

A. Again, I think there's probably several different meanings depending on the context.

Q. Okay. Then give the jury --

MR. ALLEN: Let me show you

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Exhibit 13, it might help you.

(Whereupon, Deposition Exhibit(s) 13 duly received, marked and made a part of the record.)

MR. BOISE: You skipped 12.

MR. ALLEN: Yeah, I did skip 12 because I happened to have been another standby statement.

MR. SUGGS: Can you read the plaintiff's exhibit number?

MR. ALLEN: I'm sorry. I swear to God I can barely read it. It's 06128.

QUESTIONS BY MR. ALLEN:

Q. Have you ever seen this document before, sir?

THE WITNESS: I'll take a look.

Q. Yes, sir. It's an e-mail string.

Sir, I'm going to direct your attention to the third page of this document, okay? Go to the third page. If you look,

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it's an e-mail by Ernie Anand. Do you know who Ernie Anand is?

A. Yes.

Q. Tell the jury who he is.

A. He is a Lilly employee who works out of London. He worked on issues related to Zyprexa. Quite frankly, I don't know what his title was or his level.

Q. That's fine. And then he says in the e-mail on the -- on Page 3. Did you stay with me? Yeah, you did. It's to Patrick Johnson and others. It says, "Olanzapine and cardiovascular risk. Dear all. Thought you'd like to be aware of this article." And it references a publication below. "In my opinion it's yet another example of how we are becoming quickly associated into this whole area -- arena -- into this whole arena of cardiovascular risk due to cholesterol/weight gain/diabetes as key causative factors; comments have also been made in the last two week from very independent sources as well, e.g., -- which means for example -- Professor Nicholas Moore

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at the February 28 Diabetes Advisory Board meeting in London and Professor John Camm at the March 7th, QTc meeting organized by LillyUK, also in London. It's very clear to me that our whole cardiovascular message needs to be further refined to help differentiate positioning versus QTc, hypotension/bradycardia and obesity/weight as CVS risk factors. Welcome your thought/comments. Regards, Ernie."

Did I read that correctly?

A. Yes.

Q. And then it references a publication below and it's, the publication date's March 5, 2001, and it has a summary of the publication, summary of the text. Do you see that?

A. I see the summary of the text.

Q. Okay. Now, Ernie sends this e-mail out, and if you go back to Page 3, he also sends another e-mail to Andrea Smith. Do you know who Andrea Smith is, sir?

A. Yes.

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Q. Who's Andrea Smith?

A. I believe Andrea Smith is a Lilly employee who works in the communications department.

Q. Right. The e-mail's then carbon-copied to Patrick Johnson and Suni Keeling. You know Suni Keeling, do you not? She's been deposed in this case?

A. I don't recall who that is.

Q. Okay. Nevertheless, let's read Ernie Anand's e-mail of March 12, 2001 -- no, it's probably not. It's December the 3rd, 2001. It's probably going to be the European way.

MR. BOISE: Did you take that deposition?

MR. ALLEN: I will.

QUESTIONS BY MR. ALLEN:

Q. It says, "Dear Andrea. Do we have a standby statement to clarify our position here, e.g.," -- in this case it means regarding -- "Do we have a standby statement to clarify our position here," and here's the position, "That Zyprexa can cause

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cardiovascular complications due to weight gain/diabetes, which are clinically recognized risk factors."

Did I read that correctly?

A. You read the words on the page correctly. It's clearly not the position of the company or supported by data.

Q. No --

A. It's words on the page.

Q. I didn't even think, sir -- you know what, I don't think that is the position of the company. If it is, then we wouldn't need to be here.

I think what they're saying here is if somebody asked whether or not Zyprexa can cause cardiovascular complications due to weight gain/diabetes and whether or not that's a clinically recognized risk factor, do we have a statement in response? That's the way I read it. Let's assume that's the way I read it, all right? Okay?

A. Okay.

Q. Now, you know Dr. Charles

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Beasley, do you not?

A. Yes.

Q. You worked closely with Dr. Beasley on Zyprexa while you were head of the Zyprexa Product Team?

A. That's correct.

Q. Okay. It would be accurate and truthful to say that you and Dr. Beasley were close professional colleagues involved in Zyprexa when you all worked together on Zyprexa Product Team, right?

A. We were colleagues who worked together on the Zyprexa Product Team, yes.

Q. Sir, and I don't know this but it just makes common sense, to me it does, you tell me if I'm wrong, I bet you and Dr. Beasley would also see each other after work. I bet you all had dinner together. I mean, you all -- you all are not -- you all are friends probably, I would think.

MR. BOISE: Object to the form.

A. I wouldn't classify ourselves as social friends.

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Q. Okay. So you're just business colleagues on Zyprexa?
A. Yes.
Q. Who's your best social friend at Eli Lilly that you worked on with Zyprexa? I'm sure you have some friends. When you work on a big team, some of those people you work with end up being your friends. Who's your friend in that regard?
A. I didn't really have social friends from the Zyprexa Product Team.
Q. Okay. Thank you.
Now let's go to Page 2 in regard to this issue of the standby statement. And there's an e-mail from Dr. Beasley right in the middle of the page. All right? Do you see that?
A. Yes.
Q. And we know it's dated March 15, 2001 to Andrea K. Smith, who you believe was in communications, right?
A. That's correct.
Q. Dr. Beasley also carbon copies Mr. or Dr. Anand, who is over in

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London, Dr. Cavazzoni, we know who Dr. Cavazzoni is you worked with her on Zyprexa, correct?
A. Correct.
Q. Carbon-copied Margaret Sowell. You testified, you know, within the last hour, Dr. Sowell was an endocrinologist that worked on Zyprexa, correct?
A. Yes.
Q. And Anna Thornton. Who is Anna Thornton? I don't know who that is. I'm sure you do. Who's Anna Thornton?
A. The name rings a bell. I believe she worked on the Zyprexa Product Team, perhaps a medical writer, but I'm not 100 percent sure.
Q. Right. Nevertheless, this is an e-mail from Dr. Beasley to people, at least the names you do know -- Cavazzoni and Sowell and Andrea Smith -- you do know were on the Zyprexa Product Team, right?
MR. BOISE: Object to form.
A. Andrea Smith was not a member of the Zyprexa Product Team.

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Q. Cavazzoni and Sowell for certain were, weren't they?
A. At the time of this e-mail, yes.
Q. Okay. Dr. Beasley, who was also on the product team writes as follows: "Subject: Re: Olanzapine and cardiovascular risk." Quote, "Unfortunately, I believe it will be a while before we have a clear, definitive position developed regarding hyperglycemia, hyperlipidemia, obesity, the metabolic syndrome long-term cardiovascular risk and olanzapine. We have two physicians primarily dedicated to these issues and a host of others working on them as well. One thing that we can say definitively is that olanzapine causes weight gain and for approximately 50 percent of patients in trials who remained on the drug for greater than six months, the amount of weight gain was greater than 10 pounds. Some patients in clinical trials gained as much as 80-plus pounds. Lacking empirical data to the contrary, it would be ludicrous to state that

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such a patient is not at a long-term, increased cardiac risk relative to prior to gaining that weight, especially, if in temporal association with that weight gain the patient developed an increase in fasting glucose and lipid levels. Therefore, much research is ongoing."
Did I read that correctly?
A. Yes, you did.
MR. ALLEN: Okay. Now you can put that e-mail aside. We're not going to talk about that exhibit number anymore, okay?
QUESTIONS BY MR. ALLEN:
Q. I have a -- Scott Allen, I come to you as a psychiatrist. But when I walk in the door, I have my medical records from my GP with me and I want to bring them with me, I want to show them to you. It shows that I have put on 80 pounds in the last six weeks, my fasting glucose levels have been elevated, and I ask you this question, I say, "Doctor, am I at increased risk of getting diabetes?" What's your

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answer?
THE WITNESS: Just to be a hundred percent clear. You said you are a psychiatrist coming to see me?
MR. BOISE: Are you a patient or psychiatrist?
MR. ALLEN: Oh, I'm sorry, you got me. But let me rephrase the question.
QUESTIONS BY MR. ALLEN:
Q. Assume a patient walks in your office. Patient walks in your office and says, "Look, I have gained 80 pounds in the last six weeks. My fasting glucose blood levels show I have hyperglycemia. Am I at increased risk for getting diabetes?" What's your answer?
A. You have two risk factors that are -- have been associated with the development of cardiovascular disease.
Q. And then I ask you, I said, "Okay, I think I understood your answer, doc, but I need -- as a layman I want to know am I at an increased risk above the general

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population?"
A. You have two risk factors, so that would put you at -- you would be an individual with added risk.
Q. Okay. And I say, "Okay, doc, I'm really trying to understand. You said I'm an individual at added risk. Does that mean I'm more likely than other people to get diabetes, is that what you're saying?"
What's your answer?
MR. BOISE: Object to the form of the question.
A. Well, did you already say that you had elevated fasting glucose levels?
Q. Yes, sir.
A. Above 126?
Q. Yes, sir.
A. So that, yes, you are at high risk of diabetes. In fact, you might have it already.
Q. Okay. Now let's say I walk into your office, and I'm just a patient now, not a lawyer in a courtroom, a patient that just really wants to know. Say, "Doctor, I

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have put on clinically significant weight gain in the last 6 weeks of about 20 pounds. Does that put me at risk of any diseases?" What's your answer?
MR. BOISE: Object to the form of the question.
A. Well, the mere fact that you've gained 20 pounds does not necessarily pose a risk factor. If that 20 pounds puts you into a significantly overweight category, an obese category, then you'd have a risk factor.
Q. And what would my risk factors be for? I'm saying, "Doc, what risks are those, what risk are you talking about?" What's your answer?
A. Being obese is a risk factor for diabetes and it's also a risk factor for cardiovascular complications.
Q. That's just common knowledge, isn't it?
MR. BOISE: Object to the form.
A. I think given the obesity

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epidemic in the United States and the numerous publications, Time magazine, et cetera, et cetera, yes, I would say it is probably common knowledge.
Q. Let me ask you, say, "Doctor" -- I'm a patient. I'm looking forward to taking care of my health. I'm saying, "Doctor, assume I have one risk factor for getting diabetes." No, let me ask it this way. I say, "Doc, I'm thinking about my future health and I have a family history of diabetes. Am I at an increased risk?" What's your answer?
MR. BOISE: Of diabetes?
MR. ALLEN: Yeah.
THE WITNESS: Would you repeat that?
QUESTIONS BY MR. ALLEN:
Q. I'm a patient. I'm not a lawyer I'm just a patient. I say to you, "Doctor, I have a family history of diabetes. Am I at an increased risk of getting diabetes?" What's your answer?
A. You have a risk factor,

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that's correct. A family history is a risk factor for diabetes.

Q. Doc, I wish I could get a straight answer to my question. My question to you is this: "I have a family history of diabetes. And I'm not asking you if I have a risk factor, I'm asking you am I at an increased risk of getting diabetes over the people who don't have a family history?"

MR. BOISE: Object to the first part of your question.

A. Well, when you say "people who don't have a risk," do the people have other risk factors?

Q. This is how you talk to a patient?

MR. BOISE: Object to the form.

Q. Let me ask this. I walk in the door and I say "I have a family history of diabetes, am I at an increased risk of getting diabetes?" What would your answer be, yes or no?

MR. BOISE: Object to the

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form. Incomplete hypothetical.

A. Again, I would say you have a risk factor, a well-recognized risk factor for the development of diabetes.

Q. All right. Then I say, "You know, doc, not only do I have a family history of diabetes, but I have gained clinically significant weight of 7 percent or greater in the last six weeks. Is that an additional risk for getting diabetes?" What would your answer be?

A. If the weight gain took you to a phase of being overweight or obese, then I would say you now have an additional risk factor, so you have two. If the increase in weight took you to a normal weight, then it would not be a risk factor.

Q. Okay. So assume it took me to obese, obesity, the weight gain. And I say to you, "Okay, doc, I have a family history. The 7 percent weight gain was clinically significant. It did cause me to fall in the range of obesity. You've told me now I have two risk factors, right?"

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A. Correct.

Q. Now I say to you, "Doc, I'm not a doctor. Why does that 7 percent weight gain that made me obese put me at additional risk for diabetes?" What's your answer?

MR. BOISE: Object to the form.

Q. What is it about the weight gain that puts me at additional risk?

A. I would say that the understanding, the scientific data of how significant amounts of weight gain actually leads to the development of diabetes is poorly understood.

Q. Okay. So, doc, are you telling me you don't know how it happens, you just know that it does happen?

MR. BOISE: Object to the form.

A. We know that it's a risk factor. We can't explain when an individual gets diabetes, even if they have risk factors, why and how they got diabetes.

Q. Okay. And I'll tell you, and

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now I'm going to go back to being a lawyer for a second. It's like cigarette smoking and lung cancer, we know that those are statistically and epidemiologically associated, don't we?

A. I don't think it's a good parallel.

MR. ALLEN: I didn't ask you whether you thought it was a good parallel. With all due respect, I object as nonresponsive.

QUESTIONS BY MR. ALLEN:

Q. We know that cigarettes are statistically and epidemiologically associated with lung cancer, don't we?

A. Yes.

Q. But we don't know the mechanism of action how cigarette smoking causes lung cancer, do we? There's theories, hypotheses, but there's no known mechanism of action.

MR. BOISE: Object to the form of the question.

A. I'm not an expert in that

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area. I thought there were, but I would not qualify myself as an expert.
Q. The fact of the matter is, though, that is what the field of epidemiology does. It can identify associations such as cigarette smoking and lung cancer that are accepted by the medical community, although the mechanism of action may not be known. You know that as a fact, don't you?
MR. BOISE: Object to the form. Compound.
A. I would agree with your comment that if you only have epidemiological evidence, you cannot prove cause and effect. You'll need many more other lines of evidence that would allow one to prove cause and effect.
So my understanding, although I'm not an expert, with cigarette smoking and lung cancer, is there have been those refined studies in animals and cell cultures with tumor cells that have been able to take the epidemiological finding and actually

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demonstrate mechanistic cause and effect.
Q. That's your opinion at least. Let's go on.
I'm back to being a patient. I now have a family history of diabetes. And I have clinically significant weight gain that has made me obese. You've now told me I have two risk factors, all right?
A. Yes.
Q. I ask you, I say, "Doc, is it better to have the additional risk factor of weight gain or should I -- and should I try to lose weight or should I maintain my weight, does it matter?" What would your advice be?
MR. BOISE: Object to the form of the question.
A. You're the patient, I'm the physician. I would say that any risk factors that you can decrease, if we're talking about those alone and in isolation, then I would say please decrease them. Do what you could to decrease them.
Q. Why would you want to

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decrease my risk factors?
MR. BOISE: Object to the form.
A. Because we believe that the fewer risk factors you have, the better.
Q. Okay. According to your company, at least, and we don't need to get in debate, I'm just asking, is this your company's position that having schizophrenia or bipolar mania is a risk factor for diabetes? Is that your company's position or not?
MR. BOISE: Object to form.
A. We know that schizophrenia and bipolar carry an increased risk for diabetes. In schizophrenia, it's two to fourfold higher, and bipolar we think it's two to three and-a-half times more. So those illnesses alone are associated with increased risk for diabetes.
Q. That's your company's position you just stated?
MR. BOISE: Object to form.
A. That's what the data says.

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MR. ALLEN: Objection. Nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. I'm not asking you for the reason of your company's position. You just stated -- I just want to know, is your company's position what you just stated, that patients with schizophrenia and bipolar mania are at increased risk for diabetes? Is that your company's position or not?
MR. BOISE: Object to the form.
A. Our company, when it comes to a scientific issue, will rest its position and opinions on the strength of the scientific data.
MR. ALLEN: Objection nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. Doctor, I'm not even asking -- doctor, I swear we're not even quibbling right now. I'm just asking is it your company's position that people with schizophrenia and bipolar mania are or are

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not at increased risk of diabetes?
A. They are at increased risk.
Q. Okay. Now, I'm a patient with schizophrenia/bipolar mania and a family history of diabetes. Am I at an increased risk of getting diabetes over and above that of the normal population?
MR. BOISE: Object to the form of the question.
THE WITNESS: If you have schizophrenia/bipolar and a family history?
MR. ALLEN: Of diabetes.
A. You have -- let's say you've got two risk factors. Although the ADA has not necessarily recognized schizophrenia/bipolar as risk factors. So let's assume you have two risk factors. You would have an increased risk over individuals who have no risk factors.
Q. You made a very interesting point. The American Diabetes Association has never said that schizophrenia and bipolar mania are risk factors for diabetes. They

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have not said so, have they?
MR. BOISE: Object to the form of the question. Foundation.
A. To the best of my knowledge, the ADA has not listed chronic mental illnesses as one of their formal risk factors. Although in the ADA consensus statement you referenced earlier, they were fairly clear in indicating that, at least the consensus group for the ADA saw evidence that both schizophrenia and bipolar were populations at increased risk.
MR. ALLEN: Objection.
Nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. The ADA guidelines on diabetes have never listed severe mental illness and/or schizophrenia and/or bipolar mania as increased risk factors for diabetes, have they? Yes, no, or you don't know?
A. To the best of my knowledge, I believe you're correct.
Q. Okay. Now, but your company --

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MR. BOISE: Just go back on that. Yes, no, I don't know, you're correct.
MR. ALLEN: Okay.
QUESTIONS BY MR. ALLEN:
Q. Doc, the American Diabetes Association guidelines do not list severe mental illness, schizophrenia or bipolar mania as risk factors for diabetes, do they?
A. That is my understanding.
Q. Thank you.
Now, however, your company's position is that schizophrenia and bipolar mania is a risk factor for diabetes. That's your company's position, right?
MR. BOISE: Object to the form of the question.
A. Again I'll give you my same answer. That's what's reflected by the data and that is, you know, articulated by the -- so it's, no, it's not the company's position, it's the scientific data.
MR. ALLEN: Objection.
nonresponsive.

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QUESTIONS BY MR. ALLEN:
Q. See, I'm not in an argument. I'm not asking you why your company's position is what it is. I'm not asking -- you know, I see the house -- you ever drive by a house and it's red, okay? And I ask you what color it is and it's red, what would your answer be?
MR. BOISE: Objection.
MR. ALLEN: No, I want you to know this is especially good. I'm trying to follow up.
MR. BOISE: Ask the next question, Scott.
QUESTIONS BY MR. ALLEN:
Q. Let me give you the example. We're driving by a house and I say it's a red house and I say, doctor, what color is it? You'd say "red." You wouldn't say "Red. And the reason it's red, Mr. Allen, is because Sherwin Williams developed that color, they put it in a bucket, they shipped it to town, three painters picked up brushes and spatulas and rollers and they came on a Wednesday and

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they painted the house red." You'd just say "red," okay? You understand what I'm telling you here?

MR. BOISE: Start asking your questions.

MR. ALLEN: Okay. All right.

QUESTIONS BY MR. ALLEN:

Q. With that as background, with that as background, is it your company's position that schizophrenia and bipolar mania are risk factors for diabetes? Is it your company's position?

MR. BOISE: Object to the form of the question.

A. Yes.

Q. Okay. Now, I am a patient. I have a family history of diabetes, and I have schizophrenia. According to you, Dr. Breier, and your company, I have two risk factors for diabetes, correct?

THE WITNESS: I'm sorry. You've got schizophrenia and which other one? Family history?

MR. ALLEN: Family history.

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A. Yes.

Q. Okay. Now --

THE WITNESS: I don't mean to interrupt, but -- and I don't want to cut you in midstream, but can we finish this line and then take a short break? Keep going. I just want to lodge that as a request within the next 5 to 10 minutes.

MR. ALLEN: Okay. I heard you. I'm a fair and honest man and I'll let you take a break in just a second.

QUESTIONS BY MR. ALLEN:

Q. I've got the two risk factors. I've got family history and a history of schizophrenia. I say, "Doctor, I'm thinking about gaining about 30 pounds and it's going to put me and make me obese. How's that going to affect my risk of factor of diabetes? Am I going to increase my risk factor, am I going to lower it, or is it not going to make any difference?"

What's your answer?

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A. I would say if you went and did that, you'd have three risk factors.

Q. I'm asking you, "Is it a good idea I put on those 30 pounds or is it a bad idea?"

MR. BOISE: Object to form.

A. If we're talking about weight gain in only isolation in this very abstract example, with no other considerations, particularly clinical considerations, then I would say it's not a good thing and not advisable.

Q. Why?

A. As we spoke before, the fewer risk factors the better.

Q. Right. Now I say to you: "Doctor, I've got a family history of diabetes. I have a disease state" -- doesn't matter what it is. We call it disease state X -- "that puts me at additional risk for diabetes, and I need to take a medicine for disease state Y."

So are you following me? This is just logic, okay?

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"I have family history of diabetes. I also have disease state X, and I need to take a medication to treat disease state X." You follow me?

A. Yes.

Q. Okay. I have a choice, though, I've gone to my doctor and I can take several medications for disease state X. One that adds additional risk factor of obesity or one that doesn't add the additional risk factor for obesity, and I'm trying to avoid diabetes which I have a family history of, should I take the medicine that's going to make me overweight and obese or should I take the medicine that's not going to make me overweight and obese?" What's your answer?

MR. BOISE: Object to the form of the question.

A. This is a very abstract example. Most conditions that you take medicines for are very complex. And it's a doctor's job to always weigh risk/benefit of every medication choice. And if your medical -- if the condition, I believe you

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called condition X, is a very severe complicated illness, there won't be a simple answer of a yes/no that you could pursue. You would have to look at how severe is the primary illness we're treating? What other medications has that person been tried on? How successful have they been? Is the person's medical condition very, very severe?

And it's that balance between the severity of the illness, the past background of medicines that have been tried, and the potential side effects that doctors have to make a decision about every day. So you can't reduce it to a simple yes/no right/wrong, but you have to look at all of the data in making those decisions.

Q. Well, sir, I keep on seeing, and I don't want to go back and look at any documents, I've seen throughout y'all's documents there at Eli Lilly that y'all said that Zyprexa had superior efficacy of the other second-generation antipsychotics. Didn't your company take that position?

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MR. BOISE: Object to the form.

A. Yes.

Q. Okay. So that means although Zyprexa is in a class of drugs called second-generation antipsychotics, your company takes the position that on the efficacy side of the equation there's something about y'all's molecule that makes it more efficacious when it's taken by patients. Isn't that the position you take, there's something different about your molecule?

MR. BOISE: Object to the form.

A. I want to make two points about that.

Q. No, that's not my question. My question is --

MR. BOISE: He's answering your question.

THE WITNESS: I'm going to answer very directly.

MR. ALLEN: All right.

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A. Point No. 1 is there are several studies that have demonstrated that Zyprexa is superior to a number of other atypical antipsychotic drugs, that's one thing.

No. 2, when you're talking about the treatment of schizophrenia and bipolar, each patient is quite unique and different. And the importance of tailoring the medicine to the patient becomes critical. A patient may not respond to drug A in a class and respond beautifully to drug B. And that's the clinical reality of treating these conditions.

Q. Well, that's interesting. What was that word -- counterdetailing. You call it counterdetailing. Is that the term you used, counterdetailing?

A. I'm familiar with that term.

Q. You used it earlier. Tell me and tell the jury what it is again, counterdetailing?

MR. BOISE: Objection. Asked and answered.

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Q. Short and succinct and to the point, what is counterdetailing?

MR. BOISE: Let him answer the question.

MR. ALLEN: It's easy. Answer it.

A. Again, I think it's a term that probably has a range of meanings depending on the context. When I think of counterdetailing, what I think of is competitive companies that may have products in a similar class will provide contrary messaging to a competitor drug.

Q. Contrary messaging to a competitor drug. And you told Mr. Suggs yesterday that you thought there was a lot of counterdetailing going on by your competitors trying to relate Zyprexa to weight gain and diabetes. Didn't you tell Mr. Suggs that?

MR. BOISE: Objection.

A. I don't recall --

Q. Let me ask you this: Did you think there was a lot of counterdetailing going on by your competitors against Zyprexa

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trying to relate Zyprexa with weight gain, yes, no, or you don't know?
A. There was a lot of counterdetailing regarding Zyprexa-related weight changes, yes.
Q. Right. And by the way, though, just so the record's clear, Lilly did a lot of counterdetailing against the other drugs in the class, and it counterdetailed against Geodon on QTc, it counterdetailed on Depakote, which was not an antipsychotic, but it counterdetailed on Depakote concerning black box warning, it counterdetailed against lithium, it counterdetailed against Abilify, it counterdetailed against Seroquel, and it counterdetailed against Risperdal, didn't it?
MR. BOISE: Objection to form.
A. Not that I'm aware of.
Q. So to your knowledge Lilly never counterdetailed against any of the other drugs in the second-generation antipsychotic class?
MR. BOISE: Object to the

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form.
Q. Is that your knowledge?
MR. BOISE: Object to the form.
A. I'm not an expert in this area. My area --
Q. I'm just asking do you know.
A. Let me share my understanding. When I think of counterdetailing, I think of a message element that's taken out of context. So it would be a biased message, perhaps of one characteristic without putting it in the context of the rest of the data and making it as if it's a one-issue detail as opposed to a detail that may look at a liability of a medicine, but to do that in the context of the data. And we're a data-driven company so we --
MR. ALLEN: Objection, nonresponsive. Are you through? Go ahead. Are you through with that answer?
THE WITNESS: Yes.

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MR. BOISE: Are you done with this line because we do have to break.
MR. ALLEN: No. No, I'm not. We're going to be done with the deposition. No, I'm not going to give him a break.
Objection, nonresponsive.
Hold on. Hold on. You've taken like three and I've only been examining -- just give me -- I'm almost done.
QUESTIONS BY MR. ALLEN:
Q. You've already testified previously what counterdetailing is. You gave us a definition, it's on the record.
My only question to you is, do you know whether or not Eli Lilly counterdetailed against other second-generation antipsychotics? Yes, no, or you don't know?
A. My understanding is that we would put other products in a comparison context with Zyprexa, but we would do that

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with not looking at one data element but do that in the context of all of the available or more available data so that it would be a more balanced portrayal of the drug. That is my understanding the way we worked in the marketplace.
MR. ALLEN: Objection nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. Let me ask this: You testified, yes, other companies counterdetailed against Eli Lilly/Zyprexa. The answer to that's yes, isn't it?
A. That's my understanding.
Q. Okay. Now, I'm just asking you yes, no, or you don't know, did Lilly, using your definition of counterdetailing you gave us earlier, using that definition, did Eli Lilly counterdetail against other second-generation antipsychotics? Yes, no, or you don't know?
MR. BOISE: Object to the form of the question.
A. I don't believe we did but

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I -- I'll have to leave my answer there. I don't believe we did.
Q. You think counterdetailing is unethical, using your definition of counterdetailing as given in this deposition? You think it's unethical?
MR. BOISE: Object to the form of the question.
A. I think that a detail should be balanced and provide information that's useful to clinicians to treat their patients.
MR. ALLEN: Objection. Nonresponsive.
QUESTIONS BY MR. ALLEN:
Q. Using your definition of counterdetailing that you gave us earlier, I'm asking you whether or not you think counterdetailing is ethical or not?
MR. BOISE: Object to the form of the question.
A. I don't think it's appropriate.
MR. ALLEN: Okay, thank you. Last exhibit, last series of

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questions. We'll be done. Exhibit 14.
(Whereupon, Deposition Exhibit(s) 14 duly received, marked and made a part of the record.)
MR. SUGGS: Can you read the --
MR. ALLEN: I can't read it. According to the folder --
MR. BOISE: I mean with all respect to Mr. Allen, if you do need to stand up and stretch or do something.
MR. ALLEN: This is the last exhibit.
MR. BOISE: I know, but he did ask for a break.
MR. ALLEN: I think it's 02588 but I can't read it really. Unless the exhibit number has to stick up like this one --
THE WITNESS: Fourteen.
MR. ALLEN: -- is 14 I can't

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read it.
MR. BOISE: You understand my instruction, though, if you need to stand up?
THE WITNESS: I'm okay.
MR. ALLEN: Sir, this is -- Breier Exhibit 14 is an e-mail dated August the 12th, 2002. The subject is "Morgan Stanley First Call Note - Zyprexa Conference Call."
QUESTIONS BY MR. ALLEN:
Q. Do you recall being on this conference call with the Morgan Stanley?
A. I'm not recalling it at this moment. If you'd like, I can refresh my memory, take a look at the document.
Q. You know, sir, that would be -- I appreciate that, and I'm trying to get through, and so my only question really -- if we had more time, I would let you, but my only question is, do you recall being on the call with Morgan Stanley?
A. No.
Q. But you do recall that you

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would be on calls with Wall Street at times? You recall being on conference calls with people on Wall Street?
A. I have met with analysts. When I was on the Zyprexa product team, I did meet with Wall Street analysts from time to time.
Q. And why would you do that?
A. Primarily to answer their questions about generally important issues, new studies, data related to Zyprexa.
Q. And how does that relate -- what did Wall Street have to do with that?
MR. BOISE: Object to the form.
A. There are Wall Street firms that invest in pharmaceutical companies. They want to understand the portfolio of products, the data behind them, so that they can determine how they're going to invest.
Q. So Wall Street is interested in the nature and characteristics of pharmaceutical drug products because it will affect their investment. Is that what you're

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telling us?
MR. BOISE: Object to form.
A. Yes.
Q. And negative information about a drug product has the potential to lower the stock price of the pharmaceutical company?
MR. BOISE: Object to the form.
Q. Has the potential, that's my question.
A. It's a hypothetical. It would depend on the drug.
Q. Yes, sir. I agree. There's a lot of factors. My only question is: Assuming there's a lot of factors, negative information about a pharmaceutical company's No. 1 selling product has the potential to decrease that company's stock price?
MR. BOISE: Object to the form of the question.
A. Again, it would depend on the drug. It would depend on what the information were.

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Q. Okay.
A. Many factors would determine that.
Q. Look at Exhibit 14. I'm going to read it. I have to read it a little fast because I have to go catch a plane. You're going to win this.
Right on the first page, "9:18 a.m. Eastern Daylight Time, 12, August 2002, Morgan Stanley," and I'm skipping some words, "Eli Lilly: Power Brunch on Lilly's Antipsychotic Zyprexa PI." PI's package insert, isn't it?
A. I'm sorry, I'm having trouble.
Q. I'll go on. This is an e-mail. "We hosted a conference call with Lilly's Dr. Alan Breier and two outside doctors. The topic was association between Zyprexa and metabolic side effects, an issue that has recently gained more prominence from a study published in 'Pharmacotherapy'."
Next bullet point: "No conclusive data indicates that Zyprexa is associated with diabetes but it appears that

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additional studies have assessed a potential link to all antipsychotics. According to Dr. Breier, patients with schizophrenia are more likely to develop diabetes."
Next bullet point: "No label change for Zyprexa seems imminent. Though the FDA is looking" -- Hum?
A. I'm losing it.
Q. "No label change for Zyprexa seems imminent though the FDA is looking into it. We think the most likely outcome is the addition of precautionary language for the whole class a antipsychotics." It should, probably, be of.
Did I read that correctly, sir?
A. I'm sorry, I'm literally having a hard time --
MR. ALLEN: Here, look at the highlighted. I agree. That's the way it was produced.
QUESTIONS BY MR. ALLEN:
Q. You see the one says "No label change for Zyprexa seems imminent

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though the FDA is looking into it. We think the most likely outcome" --
Sir?
A. I'm just checking the date so I can ground myself in the document.
Q. The date is August the 12, 2002.
A. Okay.
Q. "No label change for Zyprexa seems imminent, though the FDA is looking into it. We think the most likely outcome is the addition of precautionary language for the whole class a antipsychotics." Do you see that?
A. I do.
MR. ALLEN: You can hand that back to me now.
QUESTIONS BY MR. ALLEN:
Q. You knew, Dr. Alan Breier, the head of the Zyprexa Product Team knew that if the label of Zyprexa was changed on diabetes where Lilly warned about diabetes in the package insert, it had the potential to lower the sales of Zyprexa and reduce the

stock price?. You knew that, didn't you?
MR. BOISE: Objection. Asked and answered.
A. No.
MR. ALLEN: Okay, thank you, sir. Nice meeting you. You get to go home now and you take your final break. Okay, thank you very much.
MR. BOISE: You're not going to stay for my questions?
MR. ALLEN: You have questions? I'll stay.
MR. BOISE: I think we're done.
MR. ALLEN: Are you done?
MR. BOISE: Give me two minutes.
MR. ALLEN: Okay.
THE VIDEOGRAPHER: We're off the record.
(At this time, there was a brief recess taken, after which the following proceedings were had:)

(Conducted off the video record)
MR. BOISE: We have no questions.
Does anyone else have any other questions?
MR. FARRELL: No. I have nothing other than just getting one last exhibit number.
MR. BOISE: Okay. I'm sure Mr. Suggs can accommodate that. Thank you very much.
(On video record)
THE VIDEOGRAPHER: That concludes the deposition of Dr. Breier. We're off the record at 5:02. This is the end of tape five of five.
MR. SUGGS: Very good.

AND FURTHER THE DEPONENT SAITH NOT.

_____
ALAN BREIER, M.D.

STATE OF INDIANA)
) SS:
COUNTY OF MORGAN)

I, Rebecca J. Swinney, RMR-FCRR, a Notary Public in and for the County of Morgan, State of Indiana at large, do hereby certify that ALAN BREIER, M.D., the deponent herein, was by me first duly sworn to tell the truth, the whole truth, and nothing but the truth in the aforementioned matter;

That the foregoing deposition was taken on behalf of the Plaintiffs pursuant to the Indiana Rules of Trial Procedure;

That said deposition was taken down in stenograph notes and afterwards reduced to typewriting under my direction, and that the typewritten transcript is a true record of the testimony given by the said deponent; and that the signature of said deponent to his or her deposition was requested;

That the parties were represented by their counsel as aforementioned.

I do further certify that I am a disinterested person in this cause of action; that I am not a relative or attorney of either party, or otherwise interested in the event of this action, and am not in the employ of the attorneys for either party.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 13th day of January, 2007.

_____
Rebecca J. Swinney, RMR-FCRR
CSR No. 94-R-1047
Notary Public

My Commission Expires:
March 9, 2007

County of Residence:
Morgan

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

FILED IN OPEN COURT
Date: 3-10-08
Clerk: MG

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CI

RESPONSE TO STATE'S LETTER MOTION TO THE COURT REGARDING OFF-LABEL PROMOTION

I. INTRODUCTION

Ever since the Court prohibited the State from introducing evidence of off-label promotion, the State has insisted that Lilly "opened the door" to such testimony. Despite the Court's observation that, "if the door has been opened, it's not readily apparent to me,"[1] the State sees in Lilly's opening statement a "door flung wide open."

Rehashing its time-worn refrain, the State forgets that *its* opening was replete with the kind of off-label innuendo that later characterized the testimony of its witness, Dr. John Gueriguian. The State has not been prejudiced, and the subject of off-label promotion has not become independently relevant to the trial as a result of Lilly's opening. Moreover, as the Court instructed the jury, openings are not evidence. Lilly therefore urges the Court to close discussion of this issue and deny the State's letter motion of March 7, 2008.[2]

[1] Vol. 4 Tr. of Proceedings, Mar. 6, 2008, at 11:2-3 (Exh. A).

[2] *See, e.g., Loncar v. Gray*, 28 P.3d 928, 932 n.7 (Alaska 2001) (applying the curative admissibility doctrine only when the original evidence made an otherwise irrelevant issue independently relevant).

II. ARGUMENT

The State mischaracterizes Lilly's opening statement. Using tortured semantics, it complains that "counsel for Lilly engaged in error or extreme inadvertence in opening when she continually referred to Zyprexa's use . . . in 'bipolar disorder,'"[3] but the State ignores the fact that Zyprexa *is* approved for treatment of bipolar I disorder.[4] The State claims that Zyprexa was only approved for treatment of "bipolar mania,"[5] but there is no such thing as a bipolar mania diagnosis.[6] In addition, the State argues that Lilly's statement that "schizophrenic and bipolar patients are at risk of diabetes regardless of what medication they use" skews the risk/benefit analysis that physicians make before prescribing Zyprexa.[7] Again, the State ignores that Lilly's statement is a medical fact supported by the scientific literature cited by Dr. Brancati.[8]

During opening statements, counsel for Lilly did not say or imply, as the State claims, that "23 million [Zyprexa] prescriptions have been for schizophrenia and 'bipolar disorder.'"[9] Rather, Lilly's reference to "23 million people"[10] was a statement of fact that contained no reference or suggestion to the reasons why physicians chose to prescribe Zyprexa.

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[3] Letter from S. Allen to J. Rindner, Mar. 7, 2008, at 3.

[4] *See* Letter from FDA to Lilly, Mar. 17, 2000, which approves Zyprexa for "the treatment of manic or mixed episodes in bipolar disorder," which is also known as bipolar I disorder. Diagnostic and Statistical Manual of Mental Disorders 357-68, 382-97 (4th ed. 2000) (Exh. B); *see also* EL-3800, Letter from FDA to Lilly, Jan. 14, 2004 (Exh. C)

[5] Exh. A, Vol. 4 Tr. of Proceedings, Mar. 6, 2008, at 11:10-15.

[6] Exh. B, Diagnostic and Statistical Manual of Mental Disorders 357-68, 382-97 (4th ed. 2000).

[7] Letter from S. Allen to J. Rindner, Mar. 7, 2008, at 2.

[8] *See, e.g.,* AK-2368, *Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes*, 27 Diabetes Care 596, 597 (2004) (Exh. D).

[9] Letter from S. Allen to J. Rindner, Mar. 7, 2008, at 3.

[10] Exh. A, Vol. 4 Tr. of Proceedings, Mar. 6, 2008, at 121:9-11; 157:8-10.

Nor did Lilly say that Zyprexa "saved '23 million people' with schizophrenia from having 'frontal lobotomies' and [from] being 'robbed of their dignity.'"[11] The State had to shuffle phrases that were scattered across five pages of transcript to concoct this sentence.[12] Lilly's actual statement is a historical fact—divorced from any suggestion that Zyprexa rescued patients from this fact—that the early treatment for schizophrenia and bipolar disorder entailed lobotomies and other treatments.[13]

Finally, the State claims that Lilly opened the door with counsel's statement that "when Lilly received approval from FDA in 2000 for Zyprexa to be used in bipolar disorder, that's why it started to move into calling upon primary care physicians."[14] What the State ignores, however, is that Lilly's opening statement was a rebuttal to *the State's* impermissible references and innuendo to off-label promotion in the primary care field.[15] Lilly's singular statement, which was a benign and passing reference to primary care that occupied no more than ten seconds of an opening statement that lasted for over an hour, simply attempted to cure the prejudice inflicted on Lilly by the State's impermissible opening statement. The issue is closed.[16]

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[11] Letter from S. Allen to J. Rindner, Mar. 7, 2008, at 1.

[12] "Robbed of their dignity" appears on page 117, "frontal lobotomies" appears in the middle of page 120, and "23 million people" appears in the middle of page 121 of the March 6 transcript.

[13] *See, e.g.,* Joel T. Braslow, Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century 169 (1997) (After the introduction of the first generation antipsychotics, lobotomies fell out of common use); VW Swayze, *Frontal Leukotomy and Related Psychosurgical Procedures in the Era Before Antipsychotics (1935-1954): A Historical Overview*, 152 Am. J. Psychiatry 505 (1995).

[14] Letter from S. Allen to J. Rindner, Mar. 7, 2008, at 3.

[15] Exh. A, Vol. 4 Tr. of Proceedings, Mar. 6, 2008, at 93:7-16.

[16] *See United States v. Brown*, 921 F.2d 1304, 1307 (D.C. Cir. 1990) (noting that curative admissibility is a shield, not a sword); *United States v. Winston*, 447 F.2d 1236, 1240 (D.C. Cir. 1971) ("Introduction of otherwise (continued...)

Regardless of how the State distorts the factual statements in Lilly's opening, the State could not have been prejudiced because its witnesses' testimony and several improper remarks made during its opening undermine its position. First, Lilly relied on the State's expert, Dr. Wirshing, to support statements like "[second generation antipsychotics are] the closest thing to magic that I have ever experienced in my professional life."[17] Second, the State developed impermissible testimony from Dr. Gueriguian on direct examination that a Lilly promotional piece was off-label.[18] Third, the State asserted in its own opening statement that it would present evidence concerning the non-superiority of second-generation antipsychotic medications to earlier forms of treatment.[19] Fourth, the State made several comments during its opening statement, the sole purpose of which was to imply off-label promotion: repeated statements like "[Zyprexa] is not indicated for depression or anxiety for children or the elderly with Alzheimer's;"[20] and discussion about Lilly's entry into the primary care market, for example, "we've got to sell it to more people. We've got to get it to more doctors. Had the indications changed? Was it now for something else? No. Their needs had changed; they needed money."[21] These statements sufficiently rebut the State's claimed prejudice.

(continued...)

inadmissible evidence under shield of [curative admissibility] is permitted 'only to the extent necessary to remove any unfair prejudice which might otherwise have ensued from the original evidence.'" (citation omitted)).

[17] Exh. A, Vol. 4 Tr. of Proceedings, Mar. 6, 2008, at 119:1-3.

[18] Vol. 5 Tr. of Proceedings, Mar. 7, 2008, at 182:25 to 183:4 (Exh. E).

[19] Exh. A, Vol. 4 Tr. of Proceedings, Mar. 6, 2008, at 55:1-5.

[20] *Id.* at 44:21-24; *see id.* at 53:21-25; 81:24 to 82:5; 95:1-21.

[21] *Id.* at 93:12-16; *see id.* at 92:6 to 94:2.

For the foregoing reasons, Lilly requests that the Court enter an order preventing ...tate from presenting, on the basis of Lilly's opening statement, evidence described in the ...e's March 7 letter to the Court.

DATED this 10th day of March, 2008.

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Exhibit A

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

VOLUME 4

TRANSCRIPT OF PROCEEDINGS

March 6, 2008 - Pages 1 through 238

BEFORE THE HONORABLE MARK RINDNER
Superior Court Judge

thinking about it, but I just will say that if the door has been opened, it's not readily apparent to me, at least at this point. If the door is opened, we'll take that up, but right now risk benefit analysis in a general sense is still in a general sense and I haven't heard specific differences of risk benefit analysis coming out or any of those kinds of things nor have I heard the statistics or any of that kind of thing.

I don't have that evidence competently put in front of us at this point, and so I'll just tell you that maybe after today's testimony I'll think the door's been open, but based on -- based on the opening, the door may be open to the bipolar mania issue that was discussed and there was a little bit of colloquy between counsel as to whether it was approved or whether it wasn't approved. But right now, that's all I see the door being open.

MR. FIBICH: We would like the opportunity to talk to the Court about that at the conclusion of today's testimony.

MR. LEHNER: Your Honor, we'd be happy to engage in that conversation if it's necessary.

this goes beyond the scope of what's necessary to --

THE COURT: So do I.

MR. KANTRA: Just establishing the boundaries, sir. With that, my only objection would be that he be offered as an expert witness with respect to type 2 diabetes and not type 1, since he's not offering that.

THE COURT: Any objections to that clarification?

MR. SUGGS: No, Your Honor.

THE COURT: Then I'll recognize him as that, as an expert and will be discussing type 2 diabetes.

MR. SUGGS: Your Honor, the State takes the position that Dr. Brancati is clearly an expert with respect to both types of diabetes. We're offering his testimony about type 2 and that's essentially -- you've heard all the testimony we're going to have about type 1.

THE COURT: Okay. I will recognize him for that purpose.

MR. SUGGS: Thank you, Your Honor.

THE COURT: Go, on Mr. Suggs.

Q. (BY MR. SUGGS) Okay. We were talking

decreased calorie expenditure in the form of exercise and so weight deposits and then that weight gain is associated with insulin resistance.

Q. Sorry. I was going to ask you what insulin resistance is.

A. Sure, sure. Well, for the body to maintain a stable label of glucose, the pancreas serves as a bit of thermostat. It senses the level of glucose or sugar in the blood. As that level rises, the pancreas secretes insulin. And then the response of the body depends on a prompt response to the insulin-sensitive tissues to that signal.

What happens is as people gain weight and reach middle age is they'll develop resistance to that insulin signal or it will take more and more insulin to generate the same response of the body to incorporate glucose from the blood into the insulin-sensitive tissues like fat and liver and muscle. As long as the pancreas compensates by making more insulin, by sending out more hormone, the balance is maintained and the glucose levels stay steady. But unfortunately, in many people the pancreas

1 when I'm walking slowly for a block, it's fine
2 but if I walk two blocks quickly, my legs will
3 cramp up. I'll get pain in the calves and I have
4 to rest for five minutes, then I can walk again.
5 Q. What is the end stage of this particular
6 problem in the leg?
7 A. The problem here is that the leg
8 gradually becomes more and more ischemic. It's
9 getting less and less blood and less and less
10 oxygen. And that -- that predisposes to
11 infection and infection can be very severe if the
12 blood -- if the body is unable to deliver oxygen
13 and nutrients and inflammatory cells to the
14 involved area. As the blood supply is closed
15 off, there could even be death of the tissue
16 downstream. So death of tissue due to lack of
17 blood is called gangrene. There's dry gangrene
18 when there's no infection involved and it's just
19 lack of blood and oxygen that kills the tissue;
20 it's called wet gangrene when there's an active
21 infection along with the compromised blood
22 supply.
23 Q. And do you have a picture of the dry
24 gangrene?
25 A. I do.

Q. And what is this picture showing?
A. This is the foot of someone with diabetes. You see here the tips of the toes and in this case the entire toe has essentially just died, turned black, and gradually worn -- worn away because of lack of blood supply.
Q. Okay. So we've now talked about atherosclerosis in the big vessels that can impact the heart, the brain and the limbs.
Have we covered the macrovascular side of the problem?
A. Yes.
Q. Okay. Let's go back and take a look at the microvascular side of this.
This is the slide we looked at earlier. But could you focus on the microvascular portion of the slide and describe for us what is involved in microvascular disease?
A. Sure. Macro is you can see with the naked eye. Microvascular disease is disease of the small vessels; the ones you can only see with the microscope. There are three vessel beds we are particularly concerned about in diabetes; the retina, which is the screen in the back of the eye that lets us see; the kidney and the nerves,

send blood -- say the heart pumps blood to, say, our legs. It pushes all the nutrients, pushes a lot of the fluid out. And then on the return trip it has to have a way to re-collect the fluid and minerals. The only sort of pressure dragging the fluid and minerals back is called osmotic pressure, it's because the protein concentration in the blood of albumin is maintained high enough that it actually sucks that fluid back in. When albumin levels drop, and the blood goes to the leg, the fluid gets pushed out and never comes back and is one of the causes of leg swelling and fluid retention in the legs. That happens in other parts of the body, for example, the chest and it causes shortness of breath and trouble there.

Q. Okay. I interrupted you. Can you go back and explain what you mean by less filtering?

A. So one problem is the leakiness. The other problem is sort of not leaky enough. One way to think about this is using a coffee filter to make coffee. You don't want the filter to be leaky and let the coffee grounds go into the pot. You don't want it that leaky. On the other hand, if the filter doesn't work, if it was made of

linoleum, you wouldn't be able to make coffee because it needs to filter to a certain extent. You need a filter that works just right.

Diabetes creates two problems for the kidney. It makes parts of it more leaky and it makes part of it not leaky enough. So the overall amount of filtering that goes on decreases. This is the bigger problem, because when there's not enough filtering, the waste products accumulate in the blood; acids, other toxins, waste products formed by the normal metabolism of all the cells in the body. When those waste products build up, they can cause illness and if untreated, before we had dialysis, would lead to death.

Q. And you note there early damage shows in blood and urine tests; is that correct?

A. Yeah, current recommendations for the care of people with diabetes include frequent blood and urine testing. Some of that is to check the sugar but some of that is also to check on the kidney. We can -- in the urine we can measure the leakiness of the kidney, how much protein there is. And then in the blood we can measure how waste products are breaking up. We

measure a substance called creatinine, a waste product formed by muscle. When it's normally filtered the level should be low in the blood. And as the filtering system of the kidney begins to deteriorate, we'll start to see levels of this molecule go up. It's not dangerous in itself but it stands for the collection of other waste products that signal trouble.

Q. Okay. I think we had another slide here that further discusses this but I think you may have covered some of the items in there. Let me see if I can pull it up. Okay. Did I do that or did you do that?

Okay. Could you tell us what's involved in this slide, what the later problems are?

A. Sure. Well, early on, kidney disease is pretty asymptomatic. People don't know that they have it and that's why physicians have to check the urine and the blood to get early signs. You wouldn't know you have it at all. One of the reasons we have two kidneys; there's a bit of redundancy there. You can take out a whole kidney. You could lose half your kidney function and not notice it. That's the basis for kidney

transplants. But as kidney function continues to decline, and we go under 50 percent function, down to 30 percent, 20 percent now the problems are more serious than just abnormalities on tests. Now fluid begins to accumulate in the legs and chest, as I mentioned a moment ago. People don't feel right. Fatigue, loss of appetite, nausea. And then waste products begin to accumulate in the blood, especially acids. Our body generates a lot of acids in the course of normal metabolism. If they don't come out in the kidney, they build up in the blood. The pH drops and that's incompatible with life. The thing that keeps people alive, once they develop full-blown kidney failure, is either transplantation or hemodialysis. And diabetes is the leading cause of kidney failure and the need to go on dialysis in the United States.

Q. Okay. And there is, I think, one other element of microvascular disease that we have yet to talk about and that's diabetic neuropathy; is that right?

A. That's right.

Q. Okay. Let me go to that.

If I can. There we go.

example -- other elements of tobacco, for example, chewing tobacco, smoking cigars or most recently, passive smoking; all exposures related to cigarette smoking. But the fact that we knew so much about cigarette smoking made it a little easier to connect the dots in relation to those -- to those other elements of tobacco exposure, whether active or passive.

And, for example, when the -- when the passive smoking literature was developing, the fact that we already knew that direct exposure to cigarette smoke was highly dangerous made it more likely right up front that passive exposure to other people's smoke might be dangerous, albeit somewhat less so.

Q. And then, finally, I think the last factor in the Bradford-Hill criteria is experiment; is that correct?

A. Yes. Experiment is really the acid test. So a few moments ago I talked about the acid test for proving A causes B, which is a large-scale randomized human experiment where you take thousands of people and follow them for decades and then count the occurrence of complications in the two groups. It's easy to

For example, they might not have full-blown emphysema that restricts them to bed and oxygen, but they might have chronic bronchitis which is on the way to developing full-blown emphysema. You could test that in the short-term experiment and that would add to the experimental -- that would add to the evidence base in favor of causality.

Q. Dr. Brancati, regarding diabetes, in particular, and leaving aside for a moment the question of whether Zyprexa is involved in diabetes, are there risk factors for diabetes that are well established and accepted in the field of medicine?

A. Yes, there are.

Q. And let me pull up this next slide, Risk Factors for Type 2 Diabetes. Can you very briefly describe for us the risk factors that are on this slide?

A. Sure. I've grouped them into two categories modifiable and nonmodifiable. It's just the jargon we use to mean the factors we can do something about; the factors we can change or modify, and the factors we can't do anything about. The ones we can't do anything about, we

don't fret too much over them, except that we know that they can be used for risk prediction, identifying which group's at highest risk to go after the modifiable factors.

So the nonmodifiable factors for type 2 diabetes that are well established, one is age. As people get older, they're more and more likely to have type 2 diabetes. Type 2 diabetes is unusual in kids and young adults. Can happen. It's happening more in this country, but it's a strong risk factor.

Another factor is race and ethnicity. It turns out in the United States that people of European ancestry, we get a lot of diabetes, but we get a lot less than people of every other ethnic group in the United States. So, African-Americans are at higher risk, Hispanic Americans are at higher risk, Native Americans, Pacific Islanders, Native Alaskans, all of those other ethnic groups are at higher risk than their European counterparts.

The third there is family history. I think that's something we all know, that diabetes runs in families, especially type 2 diabetes. It's always one of the questions we

ask -- that I ask when someone comes in and they're concerned about getting diabetes. I know their age, their race, ethnicity. I also ask them about a history of diabetes in the family. If there's been a lot of it, I worry that they're at high risk.

Q And then over on the right-hand side you have the modifiable risk factors. Am I correct that those are the ones that can be altered by behavioral changes to some extent?

A. That's correct. These are the ones we have a shot at doing something about. So obesity is the single strongest risk factor for type 2 diabetes. The gradient of risk across the full range of obesity, from lean all the way up to morbidly obese, is well over tenfold. So it's like over the full range of the relationship between cigarette smoking and lung cancer. It is the single biggest risk factor. That's why it's been the target in studies aimed at preventing diabetes and preventing diabetic complications.

Q. Dr. Brancati, how much weight gain does it take to significantly increase the risk of diabetes?

A. That's a good question. It depends

something that's not effective at all. And, again, you know, as we saw before, olanzapine and clozapine up high here in terms of weight gain, and olanzapine up in the range of a 4 kilogram weight gain. A kilo is about 2.2 pounds, so this was on the order of eight or nine pounds of weight gain in ten weeks.

Q. Is that a large amount of weight gain in that short a period of time in your opinion?

A. Sure. That's a lot to gain in a short period, because if you play that out over a year, five times that, 40 pounds in a year. That's a lot.

Q. And it shows that olanzapine and clozapine are at the highest end over there on the right in terms of weight gain of all those other drugs; is that correct?

A. That's correct.

Q. When you were analyzing the data in the studies in terms of the risk for diabetes, where did olanzapine and clozapine stand on the scale there?

A. Right here. Right at the upper end of the scale. That's part of why the relationship between olanzapine and Zyprexa was so plausible

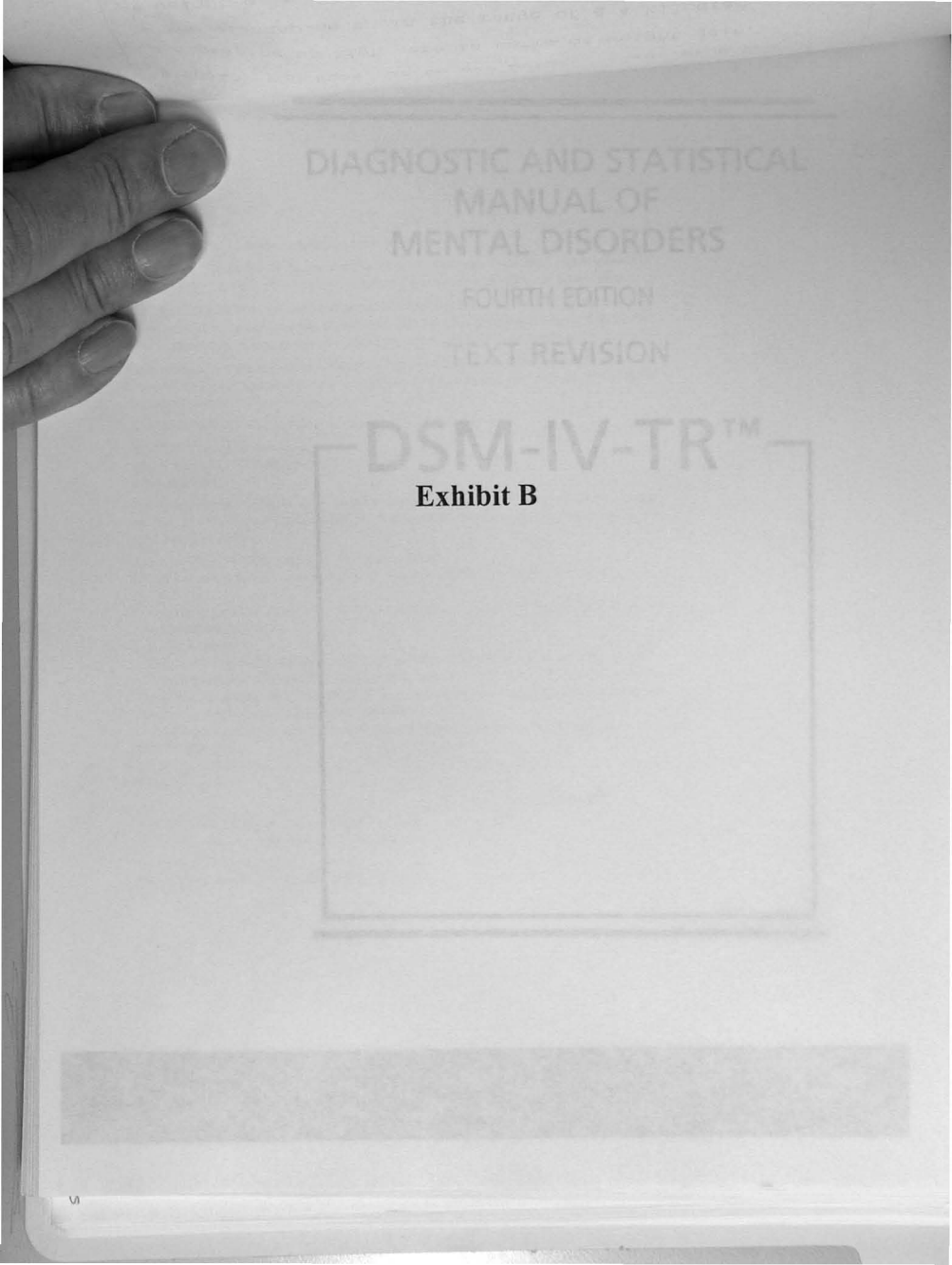
DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS
FOURTH EDITION
TEXT REVISION
DSM-IV-TR™

Exhibit B

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FOURTH EDITION

TEXT REVISION

DSM-IV-TR™

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Manic Episode

Episode Features

A Manic Episode is defined by a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood. This period of abnormal mood must last at least 1 week (or less if hospitalization is required) (Criterion A). The mood disturbance must be accompanied by at least three additional symptoms from a list that includes inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences. If the mood is irritable (rather than elevated or expansive), at least four of the above symptoms must be present (Criterion B). The symptoms do not meet criteria for a Mixed Episode, which is characterized by the symptoms of both a Manic Episode and a Major Depressive Episode occurring nearly every day for at least a 1-week period (Criterion C). The disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is characterized by the presence of psychotic features (Criterion D). The episode must not be due to the direct physiological effects of a drug of abuse, a medication, other somatic treatments for depression (e.g., electroconvulsive therapy or light therapy), or toxin exposure. The episode must also not be due to the direct physiological effects of a general medical condition (e.g., multiple sclerosis, brain tumor) (Criterion E).

The elevated mood of a Manic Episode may be described as euphoric, unusually good, cheerful, or high. Although the person's mood may initially have an infectious quality for the uninvolved observer, it is recognized as excessive by those who know the person well. The expansive quality of the mood is characterized by unceasing and indiscriminate enthusiasm for interpersonal, sexual, or occupational interactions. For example, the person may spontaneously start extensive conversations with strangers in public places, or a salesperson may telephone strangers at home in the early morning hours to initiate sales. Although elevated mood is considered the prototypical symptom, the predominant mood disturbance may be irritability, particularly when the person's wishes are thwarted. Lability of mood (e.g., the alternation between euphoria and irritability) is frequently seen.

Inflated self-esteem is typically present, ranging from uncritical self-confidence to marked grandiosity, and may reach delusional proportions (Criterion B1). Individuals may give advice on matters about which they have no special knowledge (e.g., how to run the United Nations). Despite lack of any particular experience or talent, the individual may embark on writing a novel or composing a symphony or seek publicity for some impractical invention. Grandiose delusions are common (e.g., having a special relationship to God or to some public figure from the political, religious, or entertainment world).

Almost invariably, there is a decreased need for sleep (Criterion B2). The person usually awakens several hours earlier than usual, feeling full of energy. When the sleep disturbance is severe, the person may go for days without sleep and yet not feel tired.

Manic speech is typically pressured, loud, rapid, and difficult to interrupt (Criterion B3). Individuals may talk nonstop, sometimes for hours on end, and without regard for others' wishes to communicate. Speech is sometimes characterized by joking, punning, and amusing irrelevancies. The individual may become theatrical, with dramatic mannerisms and singing. Sounds rather than meaningful conceptual relationships may govern word choice (i.e., clanging). If the person's mood is more irritable than expansive, speech may be marked by complaints, hostile comments, or angry tirades.

The individual's thoughts may race, often at a rate faster than can be articulated (Criterion B4). Some individuals with Manic Episodes report that this experience resembles watching two or three television programs simultaneously. Frequently there is flight of ideas evidenced by a nearly continuous flow of accelerated speech, with abrupt changes from one topic to another. For example, while talking about a potential business deal to sell computers, a salesperson may shift to discussing in minute detail the history of the computer chip, the industrial revolution, or applied mathematics. When flight of ideas is severe, speech may become disorganized and incoherent.

Distractibility (Criterion B5) is evidenced by an inability to screen out irrelevant external stimuli (e.g., the interviewer's tie, background noises or conversations, or furnishings in the room). There may be a reduced ability to differentiate between thoughts that are germane to the topic and thoughts that are only slightly relevant or clearly irrelevant.

The increase in goal-directed activity often involves excessive planning of, and excessive participation in, multiple activities (e.g., sexual, occupational, political, religious) (Criterion B6). Increased sexual drive, fantasies, and behavior are often present. The person may simultaneously take on multiple new business ventures without regard for the apparent risks or the need to complete each venture satisfactorily. Almost invariably, there is increased sociability (e.g., renewing old acquaintances or calling friends or even strangers at all hours of the day or night), without regard to the intrusive, domineering, and demanding nature of these interactions. Individuals often display psychomotor agitation or restlessness by pacing or by holding multiple conversations simultaneously (e.g., by telephone and in person at the same time). Some individuals write a torrent of letters on many different topics to friends, public figures, or the media.

Expansiveness, unwarranted optimism, grandiosity, and poor judgment often lead to an imprudent involvement in pleasurable activities such as buying sprees, reckless driving, foolish business investments, and sexual behavior unusual for the person, even though these activities are likely to have painful consequences (Criterion B7). The individual may purchase many unneeded items (e.g., 20 pairs of shoes, expensive antiques) without the money to pay for them. Unusual sexual behavior may include infidelity or indiscriminate sexual encounters with strangers.

The impairment resulting from the disturbance must be severe enough to cause marked impairment in functioning or to require hospitalization to protect the individual from the negative consequences of actions that result from poor judgment (e.g., financial losses, illegal activities, loss of employment, assaultive behavior). By definition, the presence of psychotic features during a Manic Episode constitutes marked impairment in functioning (Criterion D).

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Associated Features and Disorders

Associated descriptive features and mental disorders. Individuals with a Manic Episode frequently do not recognize that they are ill and resist efforts to be treated. They may travel impulsively to other cities, losing contact with relatives and caretakers. They may change their dress, makeup, or personal appearance to a more sexually suggestive or dramatically flamboyant style that is out of character for them. They may engage in activities that have a disorganized or bizarre quality (e.g., distributing candy, money, or advice to passing strangers). Gambling and antisocial behaviors may accompany the Manic Episode. Ethical concerns may be disregarded even by those who are typically very conscientious (e.g., a stockbroker inappropriately buys and sells stock without the clients' knowledge or permission; a scientist incorporates the findings of others). The person may be hostile and physically threatening to others. Some individuals, especially those with psychotic features, may become physically assaultive or suicidal. Adverse consequences of a Manic Episode (e.g., involuntary hospitalization, difficulties with the law, or serious financial difficulties) often result from poor judgment and hyperactivity. When no longer in the Manic Episode, most individuals are regretful for behaviors engaged in during the Manic Episode. Some individuals describe having a much sharper sense of smell, hearing, or vision (e.g., colors appear very bright). When catatonic symptoms (e.g., stupor, mutism, negativism, and posturing) are present, the specifier With Catatonic Features may be indicated (see p. 417).

Mood may shift rapidly to anger or depression. Depressive symptoms may last moments, hours, or, more rarely, days. Not uncommonly, the depressive symptoms and manic symptoms occur simultaneously. If the criteria for both a Major Depressive Episode and a Manic Episode are prominent every day for at least 1 week, the episode is considered to be a Mixed Episode (see p. 362). As the Manic Episode develops, there is often a substantial increase in the use of alcohol or stimulants, which may exacerbate or prolong the episode.

Associated laboratory findings. No laboratory findings that are diagnostic of a Manic Episode have been identified. However, a variety of laboratory findings have been noted to be abnormal in groups of individuals with Manic Episodes compared with control subjects. Laboratory findings in Manic Episodes include polysomnographic

abnormalities and increased cortisol secretion. There may be abnormalities involving the norepinephrine, serotonin, acetylcholine, dopamine, or gamma-aminobutyric acid neurotransmitter systems, as demonstrated by studies of neurotransmitter metabolites, receptor functioning, pharmacological provocation, and neuroendocrine function.

Specific Culture, Age, and Gender Features

Cultural considerations that were suggested for Major Depressive Episodes are also relevant to Manic Episodes (see p. 353). Manic Episodes in adolescents are more likely to include psychotic features and may be associated with school truancy, antisocial behavior, school failure, or substance use. A significant minority of adolescents appear to have a history of long-standing behavior problems that precede the onset of a frank Manic Episode. It is unclear whether these problems represent a prolonged prodrome to Bipolar Disorder or an independent disorder. See the corresponding sections of the texts for Bipolar I Disorder (p. 385) and Bipolar II Disorder (p. 394) for specific information on gender.

Course

The mean age at onset for a first Manic Episode is the early 20s, but some cases start in adolescence and others start after age 50 years. Manic Episodes typically begin suddenly, with a rapid escalation of symptoms over a few days. Frequently, Manic Episodes occur following psychosocial stressors. The episodes usually last from a few weeks to several months and are briefer and end more abruptly than Major Depressive Episodes. In many instances (50%–60%), a Major Depressive Episode immediately precedes or immediately follows a Manic Episode, with no intervening period of euthymia. If the Manic Episode occurs in the postpartum period, there may be an increased risk for recurrence in subsequent postpartum periods and the specifier With Postpartum Onset is applicable (see p. 422).

Differential Diagnosis

A Manic Episode must be distinguished from a **Mood Disorder Due to a General Medical Condition.** The appropriate diagnosis would be Mood Disorder Due to a General Medical Condition if the mood disturbance is judged to be the direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, brain tumor, Cushing's syndrome) (see p. 401). This determination is based on the history, laboratory findings, or physical examination. If it is judged that the manic symptoms are not the direct physiological consequence of the general medical condition, then the primary Mood Disorder is recorded on Axis I (e.g., Bipolar I Disorder) and the general medical condition is recorded on Axis III (e.g., myocardial infarction). A late onset of a first Manic Episode (e.g., after age 50 years) should alert the clinician to the possibility of an etiological general medical condition or substance.

A **Substance-Induced Mood Disorder** is distinguished from a Manic Episode by the fact that a substance (e.g., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiologically related to the mood disturbance (see p. 405). Symptoms like

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those seen in a Manic Episode may be precipitated by a drug of abuse (e.g., manic symptoms that occur only in the context of intoxication with cocaine would be diagnosed as Cocaine-Induced Mood Disorder, With Manic Features, With Onset During Intoxication). Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment such as medication, electroconvulsive therapy, or light therapy. Such episodes are also diagnosed as Substance-Induced Mood Disorders (e.g., Amitriptyline-Induced Mood Disorder, With Manic Features; Electroconvulsive Therapy–Induced Mood Disorder, With Manic Features). However, clinical judgment is essential to determine whether the treatment is truly causal or whether a primary Manic Episode happened to have its onset while the person was receiving the treatment (see p. 406).

Manic Episodes should be distinguished from **Hypomanic Episodes.** Although Manic Episodes and Hypomanic Episodes have an identical list of characteristic symptoms, the disturbance in Hypomanic Episodes is not sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization. Some Hypomanic Episodes may evolve into full Manic Episodes.

Major Depressive Episodes with prominent irritable mood may be difficult to distinguish from Manic Episodes with irritable mood or from **Mixed Episodes.** This determination requires a careful clinical evaluation of the presence of manic symptoms. If criteria are met for both a Manic Episode and a Major Depressive Episode nearly every day for at least a 1-week period, this would constitute a Mixed Episode.

Attention-Deficit/Hyperactivity Disorder and a Manic Episode are both characterized by excessive activity, impulsive behavior, poor judgment, and denial of problems. Attention-Deficit/Hyperactivity Disorder is distinguished from a Manic Episode by its characteristic early onset (i.e., before age 7 years), chronic rather than episodic course, lack of relatively clear onsets and offsets, and the absence of abnormally expansive or elevated mood or psychotic features.

Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity
(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode (see p. 365).

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Mixed Episode

Episode Features

A Mixed Episode is characterized by a period of time (lasting at least 1 week) in which the criteria are met both for a Manic Episode and for a Major Depressive Episode nearly every day (Criterion A). The individual experiences rapidly alternating moods (sadness, irritability, euphoria) accompanied by symptoms of a Manic Episode (see p. 357) and a Major Depressive Episode (see p. 349). The symptom presentation frequently includes agitation, insomnia, appetite dysregulation, psychotic features, and suicidal thinking. The disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is

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Associated Features and Disorders

Associated descriptive features and mental disorders. Associated features of a Mixed Episode are similar to those for Manic Episodes and Major Depressive Episodes. Individuals may be disorganized in their thinking or behavior. Because individuals in Mixed Episodes experience more dysphoria than do those in Manic Episodes, they may be more likely to seek help.

Associated laboratory findings. Laboratory findings for Mixed Episode are not well studied, although evidence to date suggests physiological and endocrine findings that are similar to those found in severe Major Depressive Episodes.

Specific Culture, Age, and Gender Features

Cultural considerations suggested for Major Depressive Episodes are relevant to Mixed Episodes as well (see p. 353). Mixed episodes appear to be more common in younger individuals and in individuals over age 60 years with Bipolar Disorder and may be more common in males than in females.

Course

Mixed Episodes can evolve from a Manic Episode or from a Major Depressive Episode or may arise de novo. For example, the diagnosis would be changed from Bipolar I Disorder, Most Recent Episode Manic, to Bipolar I Disorder, Most Recent Episode Mixed, for an individual with 3 weeks of manic symptoms followed by 1 week of both manic symptoms and depressive symptoms. Mixed episodes may last weeks to several months and may remit to a period with few or no symptoms or evolve into a Major Depressive Episode. It is far less common for a Mixed Episode to evolve into a Manic Episode.

Differential Diagnosis

A Mixed Episode must be distinguished from a **Mood Disorder Due to a General Medical Condition.** The diagnosis is Mood Disorder Due to a General Medical Condition if the mood disturbance is judged to be the direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, brain tumor, Cushing's syndrome) (see p. 401). This determination is based on the history, laboratory findings, or physical examination. If it is judged that the mixed manic and depressive symptoms are not the direct physiological consequence of the general medical condition, then the primary Mood Disorder is recorded on Axis I (e.g., Bipolar I Disorder) and the general medical condition is recorded on Axis III (e.g., myocardial infarction).

A **Substance-Induced Mood Disorder** is distinguished from a Mixed Episode by the fact that a substance (e.g., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiologically related to the mood disturbance (see p. 405). Symptoms like those seen in a Mixed Episode may be precipitated by use of a drug of abuse (e.g., mixed manic and depressive symptoms that occur only in the context of intoxication with cocaine would be diagnosed as Cocaine-Induced Mood Disorder, With Mixed Features, With Onset During Intoxication). Symptoms like those seen in a Mixed Episode may also be precipitated by antidepressant treatment such as medication, electroconvulsive therapy, or light therapy. Such episodes are also diagnosed as Substance-Induced Mood Disorders (e.g., Amitriptyline-Induced Mood Disorder, With Mixed Features; Electroconvulsive Therapy–Induced Mood Disorder, With Mixed Features). However, clinical judgment is essential to determine whether the treatment is truly causal or whether a primary Mixed Episode happened to have its onset while the person was receiving the treatment (see p. 406).

Major Depressive Episodes with prominent irritable mood and **Manic Episodes with prominent irritable mood** may be difficult to distinguish from Mixed Episodes. This determination requires a careful clinical evaluation of the simultaneous presence of symptoms that are characteristic of both a full Manic Episode and a full Major Depressive Episode (except for duration).

Attention-Deficit/Hyperactivity Disorder and a Mixed Episode are both characterized by excessive activity, impulsive behavior, poor judgment, and denial of problems. Attention-Deficit/Hyperactivity Disorder is distinguished from a Mixed Episode by its characteristic early onset (i.e., before age 7 years), chronic rather than episodic course, lack of relatively clear onsets and offsets, and the absence of abnormally expansive or elevated mood or psychotic features. Children with Attention-Deficit/Hyperactivity Disorder also sometimes show depressive symptoms such as low self-esteem and frustration tolerance. If criteria are met for both, Attention-Deficit/Hyperactivity Disorder may be diagnosed in addition to the Mood Disorder.

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Criteria for Mixed Episode

A. The criteria are met both for a Manic Episode (see p. 362) and for a Major Depressive Episode (see p. 356) (except for duration) nearly every day during at least a 1-week period.

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Hypomanic Episode

Episode Features

A Hypomanic Episode is defined as a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood that lasts at least 4 days (Criterion A). This period of abnormal mood must be accompanied by at least three additional symptoms from a list that includes inflated self-esteem or grandiosity (nondelusional), decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful consequences (Criterion B). If the mood is irritable rather than elevated or expansive, at least four of the above symptoms must be present. This list of additional symptoms is identical to those that define a Manic Episode (see p. 357) except that delusions or hallucinations cannot be present. The mood during a Hypomanic Episode must be clearly different from the individual's usual nondepressed mood, and there must be a clear change in functioning that is not characteristic of the individual's usual functioning (Criterion C). Because the changes in mood and functioning must be observable by others (Criterion D), the evaluation of this criterion will often require interviewing other informants (e.g., family members). History from other informants is particularly important in the evaluation of adolescents. In contrast to a Manic Episode, a Hypomanic Episode is not severe enough to cause marked impairment in social or occupational functioning or to require hospitalization, and there are no psychotic features (Criterion E). The change in functioning for some individuals may take the form of a marked increase in efficiency, accomplishments, or creativity. However, for others, hypomania can cause some social or occupational impairment.

The mood disturbance and other symptoms must not be due to the direct physiological effects of a drug of abuse, a medication, other treatment for depression (electroconvulsive therapy or light therapy), or toxin exposure. The episode must also not be due to the direct physiological effects of a general medical condition (e.g., multiple sclerosis, brain tumor) (Criterion F). Symptoms like those seen in a Hypomanic Episode may be due to the direct effects of antidepressant medication, electroconvulsive therapy, light therapy, or medication prescribed for other general medical conditions (e.g., corticosteroids). Such presentations are not considered Hypomanic Episodes and do not count toward the diagnosis of Bipolar II Disorder. For example, if a person with recurrent Major Depressive Disorder develops symptoms of a hypomanic-like episode during a course of antidepressant medication, the episode is diagnosed as a Substance-Induced Mood Disorder, With Manic Features, and there is no switch from a diagnosis of Major Depressive Disorder to Bipolar II Disorder. Some evidence suggests that there may be a bipolar "diathesis" in individuals who develop manic- or hypomanic-like episodes following somatic treatment for depression. Such individuals may have an increased likelihood of future Manic or Hypomanic Episodes that are not related to substances or somatic treatments for depression.

The elevated mood in a Hypomanic Episode is described as euphoric, unusually good, cheerful, or high. Although the person's mood may have an infectious quality for the uninvolved observer, it is recognized as a distinct change from the usual self by those who know the person well. The expansive quality of the mood disturbance is characterized by enthusiasm for social, interpersonal, or occupational interactions. Although elevated mood is considered prototypical, the mood disturbance may be irritable or may alternate between euphoria and irritability. Characteristically, inflated self-esteem, usually at the level of uncritical self-confidence rather than marked grandiosity, is present (Criterion B1). There is very often a decreased need for sleep (Criterion B2); the person awakens before the usual time with increased energy. The speech of a person with a Hypomanic Episode is often somewhat louder and more rapid than usual, but is not typically difficult to interrupt. It may be full of jokes, puns, plays on words, and irrelevancies (Criterion B3). Flight of ideas is uncommon and, if present, lasts for very brief periods (Criterion B4).

Distractibility is often present, as evidenced by rapid changes in speech or activity as a result of responding to various irrelevant external stimuli (Criterion B5). The increase in goal-directed activity may involve planning of, and participation in, multiple activities (Criterion B6). These activities are often creative and productive (e.g., writing a letter to the editor, clearing up paperwork). Sociability is usually increased, and there may be an increase in sexual activity. There may be impulsive activity such as buying sprees, reckless driving, or foolish business investments (Criterion B7). However, such activities are usually organized, are not bizarre, and do not result in the level of impairment that is characteristic of a Manic Episode.

Associated Features and Disorders

Associated features of a Hypomanic Episode are similar to those for a Manic Episode. Mood may also be characterized as dysphoric if irritable or depressive symptoms are more prominent than euphoria in the clinical presentation.

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Specific Culture and Age Features

Cultural considerations that were suggested for Major Depressive Episodes are relevant to Hypomanic Episodes as well (see p. 353). In younger (e.g., adolescent) persons, Hypomanic Episodes may be associated with school truancy, antisocial behavior, school failure, or substance use.

Course

A Hypomanic Episode typically begins suddenly, with a rapid escalation of symptoms within a day or two. Episodes may last for several weeks to months and are usually more abrupt in onset and briefer than Major Depressive Episodes. In many cases, the Hypomanic Episode may be preceded or followed by a Major Depressive Episode. Studies suggest that 5%–15% of individuals with hypomania will ultimately develop a Manic Episode.

Differential Diagnosis

A Hypomanic Episode must be distinguished from a **Mood Disorder Due to a General Medical Condition.** The diagnosis is Mood Disorder Due to a General Medical Condition if the mood disturbance is judged to be the direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, brain tumor, Cushing's syndrome) (see p. 401). This determination is based on the history, laboratory findings, or physical examination. If it is judged that the hypomanic symptoms are not the direct physiological consequence of the general medical condition, then the primary Mood Disorder is recorded on Axis I (e.g., Bipolar II Disorder) and the general medical condition is recorded on Axis III (e.g., myocardial infarction).

A **Substance-Induced Mood Disorder** is distinguished from a Hypomanic Episode by the fact that a substance (e.g., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiologically related to the mood disturbance (see p. 405). Symptoms like those seen in a Hypomanic Episode may be precipitated by a drug of abuse (e.g., hypomanic symptoms that occur only in the context of intoxication with cocaine would be diagnosed as Cocaine-Induced Mood Disorder, With Manic Features, With Onset During Intoxication). Symptoms like those seen in a Hypomanic Episode may also be precipitated by antidepressant treatment such as medication, electroconvulsive therapy, or light therapy. Such episodes are also diagnosed as Substance-Induced Mood Disorders (e.g., Amitriptyline-Induced Mood Disorder, With Manic Features; Electroconvulsive Therapy–Induced Mood Disorder, With Manic Features). However, clinical judgment is essential to determine whether the treatment is truly causal or whether a primary Hypomanic Episode happened to have its onset while the person was receiving the treatment (see p. 406).

Manic Episodes should be distinguished from Hypomanic Episodes. Although Manic Episodes and Hypomanic Episodes have identical lists of characteristic symptoms, the mood disturbance in Hypomanic Episodes is not sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization. Some Hypomanic Episodes may evolve into full Manic Episodes.

Attention-Deficit/Hyperactivity Disorder and a Hypomanic Episode are both

characterized by excessive activity, impulsive behavior, poor judgment, and denial of problems. Attention-Deficit/Hyperactivity Disorder is distinguished from a Hypomanic Episode by its characteristic early onset (i.e., before age 7 years), chronic rather than episodic course, lack of relatively clear onsets and offsets, and the absence of abnormally expansive or elevated mood.

A Hypomanic Episode must be distinguished from **euthymia**, particularly in individuals who have been chronically depressed and are unaccustomed to the experience of a nondepressed mood state.

Criteria for Hypomanic Episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity
(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.

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3. Recurrent brief depressive disorder: depressive episodes lasting from 2 days up to 2 weeks, occurring at least once a month for 12 months (not associated with the menstrual cycle) (see p. 778 for suggested research criteria).
4. Postpsychotic depressive disorder of Schizophrenia: a Major Depressive Episode that occurs during the residual phase of Schizophrenia (see p. 767 for suggested research criteria).
5. A Major Depressive Episode superimposed on Delusional Disorder, Psychotic Disorder Not Otherwise Specified, or the active phase of Schizophrenia.
6. Situations in which the clinician has concluded that a depressive disorder is present but is unable to determine whether it is primary, due to a general medical condition, or substance induced.

Bipolar Disorders

This section includes Bipolar I Disorder, Bipolar II Disorder, Cyclothymia, and Bipolar Disorder Not Otherwise Specified. There are six separate criteria sets for Bipolar I Disorder: Single Manic Episode, Most Recent Episode Hypomanic, Most Recent Episode Manic, Most Recent Episode Mixed, Most Recent Episode Depressed, and Most Recent Episode Unspecified. Bipolar I Disorder, Single Manic Episode, is used to describe individuals who are having a first episode of mania. The remaining criteria sets are used to specify the nature of the current (or most recent) episode in individuals who have had recurrent mood episodes.

Bipolar I Disorder

Diagnostic Features

The essential feature of Bipolar I Disorder is a clinical course that is characterized by the occurrence of one or more Manic Episodes (see p. 357) or Mixed Episodes (see p. 362). Often individuals have also had one or more Major Depressive Episodes (see p. 349). Episodes of Substance-Induced Mood Disorder (due to the direct effects of a medication, other somatic treatments for depression, a drug of abuse, or toxin exposure) or of Mood Disorder Due to a General Medical Condition do not count toward a diagnosis of Bipolar I Disorder. In addition, the episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. Bipolar I Disorder is subclassified in the fourth digit of the code according to whether the individual is experiencing a first episode (i.e., Single Manic Episode) or whether the disorder is recurrent. Recurrence is indicated by either a shift in the polarity of the episode or an interval between episodes of at least 2 months without manic symptoms. A shift in polarity is defined as a clinical course in which a Major Depressive Episode evolves into a Manic Episode or a Mixed Episode or in which a Manic Episode or a Mixed Episode evolves into a Major Depressive Episode. In contrast, a Hypomanic Episode that evolves into a Manic Episode or a Mixed Epi-

sode or a Manic Episode that evolves into a Mixed Episode (or vice versa), is considered to be only a single episode. For recurrent Bipolar I Disorders, the nature of the current (or most recent) episode can be specified (Most Recent Episode Hypomanic, Most Recent Episode Manic, Most Recent Episode Mixed, Most Recent Episode Depressed, Most Recent Episode Unspecified).

Specifiers

If the full criteria are currently met for a Manic, Mixed, or Major Depressive Episode, the following specifiers may be used to describe the current clinical status of the episode and to describe features of the current episode:

Mild, **Moderate, Severe Without Psychotic Features, Severe With Psychotic Features** (see p. 411)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Manic, Mixed or Major Depressive Episode, the following specifiers may be used to describe the current clinical status of the Bipolar I Disorder and to describe features of the most recent episode:

In Partial Remission, In Full Remission (see p. 411)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

If criteria are currently met for a Major Depressive Episode, the following may be used to describe features of the current episode (or, if criteria are not currently met but the most recent episode of Bipolar I Disorder was a Major Depressive Episode, these specifiers apply to that episode):

Chronic (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)

The following specifiers can be used to indicate the pattern of episodes:

Longitudinal Course Specifiers (With and Without Full Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Recording Procedures

The diagnostic codes for Bipolar I Disorder are selected as follows:

1. The first three digits are 296.
2. The fourth digit is 0 if there is a single Manic Episode. For recurrent episodes, the fourth digit indicates the nature of the current episode (or, if the Bipolar I Dis-

order is currently in partial or full remission, the nature of the most recent episode) as follows: 4 if the current or most recent episode is a Hypomanic Episode or a Manic Episode, 5 if it is a Major Depressive Episode, 6 if it is a Mixed Episode, and 7 if the current or most recent episode is Unspecified.

3. The fifth digit (except for Bipolar I Disorder, Most Recent Episode Hypomanic, and Bipolar I Disorder, Most Recent Episode Unspecified) indicates the severity of the current episode if full criteria are met for a Manic, Mixed, or Major Depressive Episode as follows: 1 for Mild severity, 2 for Moderate severity, 3 for Severe Without Psychotic Features, 4 for Severe With Psychotic Features. If full criteria are not met for a Manic, Mixed, or Major Depressive Episode, the fifth digit indicates the current clinical status of the Bipolar I Disorder as follows: 5 for In Partial Remission, 6 for In Full Remission. If current severity or clinical status is unspecified, the fifth digit is 0. Other specifiers for Bipolar I Disorder cannot be coded. For Bipolar I Disorder, Most Recent Episode Hypomanic, the fifth digit is always 0. For Bipolar Disorder, Most Recent Episode Unspecified, there is no fifth digit.

In recording the name of a diagnosis, terms should be listed in the following order: Bipolar I Disorder, specifiers coded in the fourth digit (e.g., Most Recent Episode Manic), specifiers coded in the fifth digit (e.g., Mild, Severe With Psychotic Features, In Partial Remission), as many specifiers (without codes) as apply to the current or most recent episode (e.g., With Melancholic Features, With Postpartum Onset), and as many specifiers (without codes) as apply to the course of episodes (e.g., With Rapid Cycling); for example, 296.54 Bipolar I Disorder, Most Recent Episode Depressed, Severe With Psychotic Features, With Melancholic Features, With Rapid Cycling.

Note that if the single episode of Bipolar I Disorder is a Mixed Episode, the diagnosis would be indicated as 296.0x Bipolar I Disorder, Single Manic Episode, Mixed.

Associated Features and Disorders

Associated descriptive features and mental disorders. Completed suicide occurs in 10%–15% of individuals with Bipolar I Disorder. Suicidal ideation and attempts are more likely to occur when the individual is in a depressive or mixed state. Child abuse, spouse abuse, or other violent behavior may occur during severe Manic Episodes or during those with psychotic features. Other associated problems include school truancy, school failure, occupational failure, divorce, or episodic antisocial behavior. Bipolar Disorder is associated with Alcohol and other Substance Use Disorders in many individuals. Individuals with earlier onset of Bipolar I Disorder are more likely to have a history of current alcohol or other substance use problems. Concomitant alcohol and other substance use is associated with an increased number of hospitalizations and a worse course of illness. Other associated mental disorders include Anorexia Nervosa, Bulimia Nervosa, Attention-Deficit/Hyperactivity Disorder, Panic Disorder, and Social Phobia.

Associated laboratory findings. There appear to be no laboratory features that are diagnostic of Bipolar I Disorder or that distinguish Major Depressive Episodes found in Bipolar I Disorder from those in Major Depressive Disorder or Bipolar II Disorder.

Imaging studies comparing groups of individuals with Bipolar I Disorder with groups with Major Depressive Disorder or groups without any Mood Disorder tend to show increased rates of right-hemispheric lesions, or bilateral subcortical or periventricular lesions in those with Bipolar I Disorder.

Associated physical examination findings and general medical conditions. An age at onset for a first Manic Episode after age 40 years should alert the clinician to the possibility that the symptoms may be due to a general medical condition or substance use. Current or past hypothyroidism or laboratory evidence of mild thyroid hypofunction may be associated with Rapid Cycling (see p. 427). In addition, hyperthyroidism may precipitate or worsen manic symptoms in individuals with a preexisting Mood Disorder. However, hyperthyroidism in individuals without preexisting Mood Disorder does not typically cause manic symptoms.

Specific Culture, Age, and Gender Features

There are no reports of differential incidence of Bipolar I Disorder based on race or ethnicity. There is some evidence that clinicians may have a tendency to overdiagnose Schizophrenia (instead of Bipolar Disorder) in some ethnic groups and in younger individuals.

Approximately 10%–15% of adolescents with recurrent Major Depressive Episodes will go on to develop Bipolar I Disorder. Mixed Episodes appear to be more likely in adolescents and young adults than in older adults.

Recent epidemiological studies in the United States indicate that Bipolar I Disorder is approximately equally common in men and women (unlike Major Depressive Disorder, which is more common in women). Gender appears to be related to the number and type of Manic and Major Depressive Episodes. The first episode in males is more likely to be a Manic Episode. The first episode in females is more likely to be a Major Depressive Episode. In men the number of Manic Episodes equals or exceeds the number of Major Depressive Episodes, whereas in women Major Depressive Episodes predominate. In addition, Rapid Cycling (see p. 427) is more common in women than in men. Some evidence suggests that mixed or depressive symptoms during Manic Episodes may be more common in women as well, although not all studies are in agreement. Thus, women may be at particular risk for depressive or intermixed mood symptoms. Women with Bipolar I Disorder have an increased risk of developing subsequent episodes in the immediate postpartum period. Some women have their first episode during the postpartum period. The specifier With Postpartum Onset may be used to indicate that the onset of the episode is within 4 weeks of delivery (see p. 422). The premenstrual period may be associated with worsening of an ongoing Major Depressive, Manic, Mixed, or Hypomanic Episode.

Prevalence

The lifetime prevalence of Bipolar I Disorder in community samples has varied from 0.4% to 1.6%.

Course

Average age at onset is 20 for both men and women. Bipolar I Disorder is a recurrent disorder—more than 90% of individuals who have a single Manic Episode go on to have future episodes. Roughly 60%–70% of Manic Episodes occur immediately before or after a Major Depressive Episode. Manic Episodes often precede or follow the Major Depressive Episodes in a characteristic pattern for a particular person. The number of lifetime episodes (both Manic and Major Depressive) tends to be higher for Bipolar I Disorder compared with Major Depressive Disorder, Recurrent. Studies of the course of Bipolar I Disorder prior to lithium maintenance treatment suggest that, on average, four episodes occur in 10 years. The interval between episodes tends to decrease as the individual ages. There is some evidence that changes in sleep-wake schedule such as occur during time zone changes or sleep deprivation may precipitate or exacerbate a Manic, Mixed, or Hypomanic Episode. Approximately 5%–15% of individuals with Bipolar I Disorder have multiple (four or more) mood episodes (Major Depressive, Manic, Mixed, or Hypomanic) that occur within a given year. If this pattern is present, it is noted by the specifier With Rapid Cycling (see p. 427). A rapid-cycling pattern is associated with a poorer prognosis.

Although the majority of individuals with Bipolar I Disorder experience significant symptom reduction between episodes, some (20%–30%) continue to display mood lability and other residual mood symptoms. As many as 60% experience chronic interpersonal or occupational difficulties between acute episodes. Psychotic symptoms may develop after days or weeks in what was previously a nonpsychotic Manic or Mixed Episode. When an individual has Manic Episodes with psychotic features, subsequent Manic Episodes are more likely to have psychotic features. Incomplete interepisode recovery is more common when the current episode is accompanied by mood-incongruent psychotic features.

Familial Pattern

First-degree biological relatives of individuals with Bipolar I Disorder have elevated rates of Bipolar I Disorder (4%–24%), Bipolar II Disorder (1%–5%), and Major Depressive Disorder (4%–24%). Those individuals with Mood Disorder in their first-degree biological relatives are more likely to have an earlier age at onset. Twin and adoption studies provide strong evidence of a genetic influence for Bipolar I Disorder.

Differential Diagnosis

Major Depressive, Manic, Mixed, and Hypomanic Episodes in Bipolar I Disorder must be distinguished from episodes of a **Mood Disorder Due to a General Medical Condition.** The diagnosis is Mood Disorder Due to a General Medical Condition for episodes that are judged to be the direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, stroke, hypothyroidism) (see p. 401). This determination is based on the history, laboratory findings, or physical examination.

A **Substance-Induced Mood Disorder** is distinguished from Major Depressive, Manic, or Mixed Episodes that occur in Bipolar I Disorder by the fact that a substance (e.g., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiological-

Mixed, or Hypomanic Episode may be part of an intoxication with or withdrawal from a drug of abuse and should be diagnosed as a Substance-Induced Mood Disorder (e.g., euphoric mood that occurs only in the context of intoxication with cocaine would be diagnosed as Cocaine-Induced Mood Disorder, With Manic Features, With Onset During Intoxication). Symptoms like those seen in a Manic or Mixed Episode may also be precipitated by antidepressant treatment such as medication, electroconvulsive therapy, or light therapy. Such episodes may be diagnosed as a Substance-Induced Mood Disorder (e.g., Amitriptyline-Induced Mood Disorder, With Manic Features; Electroconvulsive Therapy–Induced Mood Disorder, With Manic Features) and would not count toward a diagnosis of Bipolar I Disorder. However, when the substance use or medication is judged not to fully account for the episode (e.g., the episode continues for a considerable period autonomously after the substance is discontinued), the episode would count toward a diagnosis of Bipolar I Disorder.

Bipolar I Disorder is distinguished from **Major Depressive Disorder** and **Dysthymic Disorder** by the lifetime history of at least one Manic or Mixed Episode. Bipolar I Disorder is distinguished from **Bipolar II Disorder** by the presence of one or more Manic or Mixed Episodes. When an individual previously diagnosed with Bipolar II Disorder develops a Manic or Mixed Episode, the diagnosis is changed to Bipolar I Disorder.

In **Cyclothymic Disorder,** there are numerous periods of hypomanic symptoms that do not meet criteria for a Manic Episode and periods of depressive symptoms that do not meet symptom or duration criteria for a Major Depressive Episode. Bipolar I Disorder is distinguished from Cyclothymic Disorder by the presence of one or more Manic or Mixed Episodes. If a Manic or Mixed Episode occurs after the first 2 years of Cyclothymic Disorder, then Cyclothymic Disorder and Bipolar I Disorder may both be diagnosed.

The differential diagnosis between **Psychotic Disorders** (e.g., Schizoaffective Disorder, Schizophrenia, and Delusional Disorder) and Bipolar I Disorder may be difficult (especially in adolescents) because these disorders may share a number of presenting symptoms (e.g., grandiose and persecutory delusions, irritability, agitation, and catatonic symptoms), particularly cross-sectionally and early in their course. In contrast to Bipolar I Disorder, Schizophrenia, Schizoaffective Disorder, and Delusional Disorder are all characterized by periods of psychotic symptoms that occur in the absence of prominent mood symptoms. Other helpful considerations include the accompanying symptoms, previous course, and family history. Manic and depressive symptoms may be present during Schizophrenia, Delusional Disorder, and Psychotic Disorder Not Otherwise Specified, but rarely with sufficient number, duration, and pervasiveness to meet criteria for a Manic Episode or a Major Depressive Episode. However, when full criteria are met (or the symptoms are of particular clinical significance), a diagnosis of **Bipolar Disorder Not Otherwise Specified** may be made in addition to the diagnosis of Schizophrenia, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

If there is a very rapid alternation (over days) between manic symptoms and depressive symptoms (e.g., several days of purely manic symptoms followed by several days of purely depressive symptoms) that do not meet minimal duration criteria for a Manic Episode or Major Depressive Episode, the diagnosis is **Bipolar Disorder Not Otherwise Specified.**

Diagnostic criteria for 296.0x Bipolar I Disorder, Single Manic Episode

A. Presence of only one Manic Episode (see p. 362) and no past Major Depressive Episodes.

Note: Recurrence is defined as either a change in polarity from depression or an interval of at least 2 months without manic symptoms.

B. The Manic Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Specify if:

Mixed: if symptoms meet criteria for a Mixed Episode (see p. 365)

If the full criteria are currently met for a Manic, Mixed, or Major Depressive Episode, *specify* its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features (see p. 410)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Manic, Mixed, or Major Depressive Episode, *specify* the current clinical status of the Bipolar I Disorder or features of the most recent episode:

In Partial Remission, In Full Remission (see p. 410)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

Diagnostic criteria for 296.40 Bipolar I Disorder, Most Recent Episode Hypomanic

A. Currently (or most recently) in a Hypomanic Episode (see p. 368).

B. There has previously been at least one Manic Episode (see p. 362) or Mixed Episode (see p. 365).

C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Diagnostic criteria for 296.4x Bipolar I Disorder, Most Recent Episode Manic

A. Currently (or most recently) in a Manic Episode (see p. 362).

B. There has previously been at least one Major Depressive Episode (see p. 356), Manic Episode (see p. 362), or Mixed Episode (see p. 365).

C. The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

If the full criteria are currently met for a Manic Episode, *specify* its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features (see p. 413)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Manic Episode, *specify* the current clinical status of the Bipolar I Disorder and/or features of the most recent Manic Episode:

In Partial Remission, In Full Remission (see p. 414)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Diagnostic criteria for 296.6x Bipolar I Disorder, Most Recent Episode Mixed

A. Currently (or most recently) in a Mixed Episode (see p. 365).

B. There has previously been at least one Major Depressive Episode (see p. 356), Manic Episode (see p. 362), or Mixed Episode (see p. 365).

C. The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

If the full criteria are currently met for a Mixed Episode, *specify* its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features (see p. 415)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Mixed Episode, *specify* the current clinical status of the Bipolar I Disorder and/or features of the most recent Mixed Episode:

In Partial Remission, In Full Remission (see p. 416)
With Catatonic Features (see p. 417)
With Postpartum Onset (see p. 422)

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Diagnostic criteria for 296.5x Bipolar I Disorder, Most Recent Episode Depressed

A. Currently (or most recently) in a Major Depressive Episode (see p. 356).

B. There has previously been at least one Manic Episode (see p. 362) or Mixed Episode (see p. 365).

C. The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

If the full criteria are currently met for a Major Depressive Episode, *specify* its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features (see p. 411)
Chronic (see p. 417)
With Catatonic Features (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Major Depressive Episode, *specify* the current clinical status of the Bipolar I Disorder and/or features of the most recent Major Depressive Episode:

In Partial Remission, In Full Remission (see p. 411)
Chronic (see p. 417)
With Catatonic Features (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)
With Postpartum Onset (see p. 422)

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Diagnostic criteria for 296.7 Bipolar I Disorder, Most Recent Episode Unspecified

A. Criteria, except for duration, are currently (or most recently) met for a Manic (see p. 362), a Hypomanic (see p. 368), a Mixed (see p. 365), or a Major Depressive Episode (see p. 356).

B. There has previously been at least one Manic Episode (see p. 362) or Mixed Episode (see p. 365).

C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

E. The mood symptoms in Criteria A and B are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

296.89 Bipolar II Disorder (Recurrent Major Depressive Episodes With Hypomanic Episodes)

Diagnostic Features

The essential feature of Bipolar II Disorder is a clinical course that is characterized by the occurrence of one or more Major Depressive Episodes (Criterion A) accompanied by at least one Hypomanic Episode (Criterion B). Hypomanic Episodes should not be confused with the several days of euthymia that may follow remission of a Major Depressive Episode. The presence of a Manic or Mixed Episode precludes the diagnosis of Bipolar II Disorder (Criterion C). Episodes of Substance-Induced Mood Disorder (due to the direct physiological effects of a medication, other somatic treatments for depression, drugs of abuse, or toxin exposure) or of Mood Disorder Due to a General Medical Condition do not count toward a diagnosis of Bipolar II Disorder. In addition, the episodes must not be better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified (Criterion D). The symptoms must cause clinically significant distress or impairment in social, occupational, or oth-

or important areas of functioning (Criterion E). In some cases, the Hypomanic Episodes themselves do not cause impairment. Instead, the impairment may result from the Major Depressive Episodes or from a chronic pattern of unpredictable mood episodes and fluctuating unreliable interpersonal or occupational functioning.

Individuals with Bipolar II Disorder may not view the Hypomanic Episodes as pathological, although others may be troubled by the individual's erratic behavior. Often individuals, particularly when in the midst of a Major Depressive Episode, do not recall periods of hypomania without reminders from close friends or relatives. Information from other informants is often critical in establishing the diagnosis of Bipolar II Disorder.

Specifiers

The following specifiers for Bipolar II Disorder should be used to indicate the nature of the current episode or, if the full criteria are not currently met for a Hypomanic or Major Depressive Episode, the nature of the most recent episode:

Hypomanic. This specifier is used if the current (or most recent) episode is a Hypomanic Episode.
Depressed. This specifier is used if the current (or most recent) episode is a Major Depressive Episode.

If the full criteria are currently met for a Major Depressive Episode, the following specifiers may be used to describe the current clinical status of the episode and to describe features of the current episode:

Mild, Moderate, Severe Without Psychotic Features, Severe With Psychotic Features (see p. 411)
Chronic (see p. 417)
With Catatonic Features (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Hypomanic or Major Depressive Episode, the following specifiers may be used to describe the current clinical status of the Bipolar II Disorder and to describe features of the most recent Major Depressive Episode (only if it is the most recent type of mood episode):

In Partial Remission, In Full Remission (see p. 411)
Chronic (see p. 417)
With Catatonic Features (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)
With Postpartum Onset (see p. 422)

The following specifiers may be used to indicate the pattern or frequency of episodes:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Recording Procedures

The diagnostic code for Bipolar II Disorder is 296.89; none of the specifiers are codable. In recording the name of the diagnosis, terms should be listed in the following order: Bipolar II Disorder, specifiers indicating current or most recent episode (e.g., Hypomanic, Depressed), severity specifiers that apply to the current Major Depressive Episode (e.g., Moderate), as many specifiers describing features as apply to the current or most recent Major Depressive Episode (e.g., With Melancholic Features, With Postpartum Onset), and as many specifiers as apply to the course of episodes (e.g., With Seasonal Pattern); for example, 296.89 Bipolar II Disorder, Depressed, Severe With Psychotic Features, With Melancholic Features, With Seasonal Pattern.

Associated Features and Disorders

Associated descriptive features and mental disorders. Completed suicide (usually during Major Depressive Episodes) is a significant risk, occurring in 10%–15% of persons with Bipolar II Disorder. School truancy, school failure, occupational failure, or divorce may be associated with Bipolar II Disorder. Associated mental disorders include Substance Abuse or Dependence, Anorexia Nervosa, Bulimia Nervosa, Attention-Deficit/Hyperactivity Disorder, Panic Disorder, Social Phobia, and Borderline Personality Disorder.

Associated laboratory findings. There appear to be no laboratory features that are diagnostic of Bipolar II Disorder or that distinguish Major Depressive Episodes found in Bipolar II Disorder from those in Major Depressive Disorder or Bipolar I Disorder.

Associated physical examination findings and general medical conditions. An age at onset for a first Hypomanic Episode after age 40 years should alert the clinician to the possibility that the symptoms may be due to a general medical condition or substance use. Current or past hypothyroidism or laboratory evidence of mild thyroid hypofunction may be associated with Rapid Cycling (see p. 427). In addition, hyperthyroidism may precipitate or worsen hypomanic symptoms in individuals with a preexisting Mood Disorder. However, hyperthyroidism in other individuals does not typically cause hypomanic symptoms.

Specific Gender Features

Bipolar II Disorder may be more common in women than in men. Gender appears to be related to the number and type of Hypomanic and Major Depressive Episodes. In men the number of Hypomanic Episodes equals or exceeds the number of Major Depressive Episodes, whereas in women Major Depressive Episodes predominate. In

addition, Rapid Cycling (see p. 427) is more common in women than in men. Some evidence suggests that mixed or depressive symptoms during Hypomanic Episodes may be more common in women as well, although not all studies are in agreement. Thus, women may be at particular risk for depressive or intermixed mood symptoms. Women with Bipolar II Disorder may be at increased risk of developing subsequent episodes in the immediate postpartum period.

Prevalence

Community studies suggest a lifetime prevalence of Bipolar II Disorder of approximately 0.5%.

Course

Roughly 60%–70% of the Hypomanic Episodes in Bipolar II Disorder occur immediately before or after a Major Depressive Episode. Hypomanic Episodes often precede or follow the Major Depressive Episodes in a characteristic pattern for a particular person. The number of lifetime episodes (both Hypomanic Episodes and Major Depressive Episodes) tends to be higher for Bipolar II Disorder compared with Major Depressive Disorder, Recurrent. The interval between episodes tends to decrease as the individual ages. Approximately 5%–15% of individuals with Bipolar II Disorder have multiple (four or more) mood episodes (Hypomanic or Major Depressive) that occur within a given year. If this pattern is present, it is noted by the specifier With Rapid Cycling (see p. 427). A rapid-cycling pattern is associated with a poorer prognosis.

Although the majority of individuals with Bipolar II Disorder return to a fully functional level between episodes, approximately 15% continue to display mood lability and interpersonal or occupational difficulties. Psychotic symptoms do not occur in Hypomanic Episodes, and they appear to be less frequent in the Major Depressive Episodes in Bipolar II Disorder than is the case for Bipolar I Disorder. Some evidence is consistent with the notion that marked changes in sleep-wake schedule such as occur during time zone changes or sleep deprivation may precipitate or exacerbate Hypomanic or Major Depressive Episodes. If a Manic or Mixed Episode develops in the course of Bipolar II Disorder, the diagnosis is changed to Bipolar I Disorder. Over 5 years, about 5%–15% of individuals with Bipolar II Disorder will develop a Manic Episode.

Familial Pattern

Some studies have indicated that first-degree biological relatives of individuals with Bipolar II Disorder have elevated rates of Bipolar II Disorder, Bipolar I Disorder, and Major Depressive Disorder compared with the general population.

Differential Diagnosis

Hypomanic and Major Depressive Episodes in Bipolar II Disorder must be distinguished from episodes of a **Mood Disorder Due to a General Medical Condition.**

The diagnosis is Mood Disorder Due to a General Medical Condition for episodes that are judged to be the direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, stroke, hypothyroidism) (see p. 401). This determination is based on the history, laboratory findings, or physical examination.

A **Substance-Induced Mood Disorder** is distinguished from Hypomanic or Major Depressive Episodes that occur in Bipolar II Disorder by the fact that a substance (e.g., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiologically related to the mood disturbance (see p. 405). Symptoms like those seen in a Hypomanic Episode may be part of an intoxication with or withdrawal from a drug of abuse and should be diagnosed as a Substance-Induced Mood Disorder (e.g., a major depressive–like episode occurring only in the context of withdrawal from cocaine would be diagnosed as Cocaine-Induced Mood Disorder, With Depressive Features, With Onset During Withdrawal). Symptoms like those seen in a Hypomanic Episode may also be precipitated by antidepressant treatment such as medication, electroconvulsive therapy, or light therapy. Such episodes may be diagnosed as a Substance-Induced Mood Disorder (e.g., Amitriptyline-Induced Mood Disorder, With Manic Features; Electroconvulsive Therapy–Induced Mood Disorder, With Manic Features) and would not count toward a diagnosis of Bipolar II Disorder. However, when the substance use or medication is judged not to fully account for the episode (e.g., the episode continues for a considerable period autonomously after the substance is discontinued), the episode would count toward a diagnosis of Bipolar II Disorder.

Bipolar II Disorder is distinguished from **Major Depressive Disorder** by the lifetime history of at least one Hypomanic Episode. Attention during the interview to whether there is a history of euphoric or dysphoric hypomania is important in making a differential diagnosis. Bipolar II Disorder is distinguished from **Bipolar I Disorder** by the presence of one or more Manic or Mixed Episodes in the latter. When an individual previously diagnosed with Bipolar II Disorder develops a Manic or Mixed Episode, the diagnosis is changed to Bipolar I disorder.

In **Cyclothymic Disorder,** there are numerous periods of hypomanic symptoms and numerous periods of depressive symptoms that do not meet symptom or duration criteria for a Major Depressive Episode. Bipolar II Disorder is distinguished from Cyclothymic Disorder by the presence of one or more Major Depressive Episodes. If a Major Depressive Episode occurs after the first 2 years of Cyclothymic Disorder, the additional diagnosis of Bipolar II Disorder is given.

Bipolar II Disorder must be distinguished from **Psychotic Disorders** (e.g., Schizoaffective Disorder, Schizophrenia, and Delusional Disorder). Schizophrenia, Schizoaffective Disorder, and Delusional Disorder are all characterized by periods of psychotic symptoms that occur in the absence of prominent mood symptoms. Other helpful considerations include the accompanying symptoms, previous course, and family history.

Diagnostic criteria for 296.89 Bipolar II Disorder

A. Presence (or history) of one or more Major Depressive Episodes (see p. 356).

B. Presence (or history) of at least one Hypomanic Episode (see p. 368).

C. There has never been a Manic Episode (see p. 362) or a Mixed Episode (see p. 365).

D. The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify current or most recent episode:

Hypomanic: if currently (or most recently) in a Hypomanic Episode (see p. 368)
Depressed: if currently (or most recently) in a Major Depressive Episode (see p. 356)

If the full criteria are currently met for a Major Depressive Episode, *specify* its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe With Psychotic Features (see p. 411) **Note:** Fifth-digit codes specified on p. 413 cannot be used here because the code for Bipolar II Disorder already uses the fifth digit.
Chronic (see p. 417)
With Catatonic Features (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)
With Postpartum Onset (see p. 422)

If the full criteria are not currently met for a Hypomanic or Major Depressive Episode, *specify* the clinical status of the Bipolar II Disorder and/or features of the most recent Major Depressive Episode (only if it is the most recent type of mood episode):

In Partial Remission, In Full Remission (see p. 411) **Note:** Fifth-digit codes specified on p. 413 cannot be used here because the code for Bipolar II Disorder already uses the fifth digit.
Chronic (see p. 417)
With Catatonic Features (see p. 417)
With Melancholic Features (see p. 419)
With Atypical Features (see p. 420)
With Postpartum Onset (see p. 422)

Specify:

Longitudinal Course Specifiers (With and Without Interepisode Recovery) (see p. 424)
With Seasonal Pattern (applies only to the pattern of Major Depressive Episodes) (see p. 425)
With Rapid Cycling (see p. 427)

Exhibit C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-019

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your supplemental new drug application (NDA) dated November 20, 2002, received November 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg. This supplemental NDA provides for the use of olanzapine in the long-term treatment of bipolar I disorder.

We also acknowledge receipt of your amendments dated November 4, 2003 and November 13, 2003. Your submission of November 13, 2003 constituted a complete response to our September 22, 2003 action letter.

Application approved. We have completed the review of this application as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text, per our discussions of January 13, 2004.

Final Printed Labeling. The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Please submit the FPL electronically, according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-592/S-019". Approval of this submission by FDA is not required before the labeling is used.

Waiver of Requirement for Pediatric Studies. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for the use of olanzapine in the long-term treatment of bipolar I disorder.

No Postmarketing Commitments Required. We note that there are no postmarketing commitments for this supplemental application.

Promotional Materials. In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communications (DDMAC), HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Healthcare Professional Letters. If you issue a letter communicating important information about this drug product (i.e., a "Dear Healthcare Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850, or via e-mail at batesd@cder.fda.gov.

Sincerely,

(See appended electronic signature page)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Agreed-Upon Labeling) [The electronic signature page will follow the labeling.]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
1/14/04 12:48:23 PM

Exhibit D

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

American Diabetes Association
American Psychiatric Association
American Association of Clinical Endocrinologists
North American Association for the Study of Obesity

Antipsychotic medications are an important component in the medical management of many psychotic conditions. With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol).

Because of the close associations between obesity, diabetes, and dyslipidemia and cardiovascular disease (CVD), there is heightened interest in the relationship between the SGAs and the development of these major CVD risk factors. To gain a better understanding of this relationship, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity convened a consensus development conference 19–21 November 2003 on the subject of antipsychotic drugs and diabetes. An eight-member panel heard presentations from 14 experts drawn from the areas of psychiatry, obesity, and diabetes. Presentations were also made by a representative from the U.S. Food and Drug Administration (FDA) and by representatives from the AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, and Pfizer pharmaceutical companies. In addition, before the conference, the consensus panel was given copies of most of the known peer-reviewed, English language clinical studies published in this area, as well as additional articles from animal studies; other papers and abstracts were reviewed at the conference.

With this information, the panel developed a consensus position on the following questions:

1. What is the current use of antipsychotic drugs?
2. What is the prevalence of obesity, prediabetes, and type 2 diabetes in the populations in which the SGAs are used?
3. What is the relationship between the use of these drugs and the incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipedemia, and diabetes, and how should they be treated if diabetes develops?
5. What research is needed to better understand the relationship between these drugs and significant weight gain, dyslipedemia, and diabetes?

1. WHAT IS THE CURRENT USE OF ANTIPSYCHOTIC DRUGS?

— Antipsychotic medications (Table 1) are the mainstay of treatment for psychotic illnesses and are also widely used in many other psychiatric conditions. Introduced ~50 years ago, these medications have helped millions of people manage their symptoms. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled.

The first-generation antipsychotics (FGAs) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma, and nonadherence.

The effort to find more effective medications with fewer and less-severe side effects led to the development of the SGAs, often referred to as the "atypical antipsychotics." SGAs have fewer or no extrapyramidal side effects at clinically effective doses. Many of these newer medications are also more effective than the older agents at treating the negative, cognitive, and affective symptoms of psychotic illnesses.

The six currently available SGAs vary in their efficacy, formulation, biochemistry, receptor binding, and side effect profiles. One of them, clozapine, is clearly the most effective antipsychotic. However, clozapine is only indicated after other medications have failed or in patients at high risk for suicidal behavior, largely because it can cause agranulocytosis.

In general, SGAs are better tolerated and more effective than the FGAs. Aside from clozapine, they have become the first-line agents for their indicated use and

From the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.
Address correspondence to Nathanial G. Clark, MD, American Diabetes Association, 1701 N. Beauregard St., Alexandria, VA 22311. E-mail: nclark@diabetes.org.

Abbreviations: CVD, cardiovascular disease; DKA, diabetic ketoacidosis; FDA, Food and Drug Administration; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics.

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Table 1—*Antipsychotic medications*

	Generic name	Trade name	Year approved
Commonly used FGAs	Chlorpromazine	Thorazine	—
	Perphenazine	Trilafon	—
	Trifluoperazine	Stelazine	—
	Thiothixene	Navane	—
	Haloperidol	Haldol	—
	Fluphenazine	Prolixin	—
SGAs	Clozapine	Clozaril	1989
	Risperidone	Risperdal	1993
	Olanzapine	Zyprexa	1996
	Quetiapine	Seroquel	1997
	Ziprasidone	Geodon	2001
	Aripiprazole	Abilify	2002

are increasingly being used off-label. In current practice, people who are likely to be treated with an SGA include those with schizophrenia spectrum disorders, bipolar disorder, dementia, psychotic depression, autism, and developmental disorders and, to a lesser extent, individuals with conditions such as delirium, aggressive behavior, personality disorders, and posttraumatic stress disorder. These psychiatric conditions are common and often require lifelong treatment. In the U.S., the prevalence of schizophrenia and related conditions is ~ 1%, the prevalence of bipolar disorders is ~ 2%, and the prevalence of major depression is ~ 8%. The SGAs are therefore widely used medications, and their use has important public health ramifications.

2. WHAT IS THE PREVALENCE OF OBESITY, PRE-DIABETES, AND TYPE 2 DIABETES IN THE POPULATIONS IN WHICH THE SGAs ARE USED?

— It is difficult to determine whether the prevalence of these metabolic disorders is increased in these psychiatric populations independent of drug treatment. Most of the available data are derived from studies of individuals with schizophrenia, and even in this condition, the evidence is very limited. Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is ~1.5–2.0 times higher than in the general population. Many characteristics of people with schizophrenia, such as sedentary behavior, may contribute to the apparently higher prevalence of metabolic abnormalities. However, none of these studies controlled for all of the major diabetes risk factors. For example, BMI and family history of diabetes were rarely determined, nor were the control populations appropriately matched for these and other variables. Thus, it is unclear whether psychiatric conditions per se, independent of other known diabetes risk factors, account for the increased prevalence.

There are limited data evaluating the metabolic profile and diabetes risk of drug-naïve subjects with schizophrenia. In a small cohort of adults with schizophrenia untreated with medications, visceral fat content (which is correlated with insulin resistance) was threefold higher than in age- and BMI-matched control subjects. In another study, the same investigators found that drug-naïve patients presenting with their first episode of schizophrenia had an increased prevalence of impaired fasting glucose, were more insulin resistant, and had higher plasma levels of glucose, insulin, and cortisol than did matched control subjects.

Overall, the limited amount of epidemiological data suggest an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness. Whether this is a function of the illness itself versus its treatment is unknown. Studies using the proper diagnoses of glucose intolerance and more complete risk factor characterization are necessary in order to resolve this issue.

3. WHAT IS THE RELATIONSHIP BETWEEN THE USE OF THESE DRUGS AND THE INCIDENCE OF OBESITY OR DIABETES?

— Recognition of an association between SGAs and diabetes was first derived from case reports of severe, sometimes fatal, acute diabetic decompensation, including DKA. Subsequent drug surveillance and retrospective database analyses suggest there is an association between specific SGAs and both diabetes and obesity. This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population. High rates of smoking and physical inactivity may also contribute to the excess mortality. Therefore, if SGA therapy further increases the risk for obesity and type 2 diabetes, this should be of major clinical concern.

Although there are significant shortcomings in many of the studies examining the relationships between the SGAs and obesity or diabetes, clear-cut trends can be identified.

Obesity

There is considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after 1 year of treatment. There is, however, considerable variability in weight gain among the various SGAs (Table 2). At 10 weeks of therapy, estimated average weight gain with drug treatment compared with placebo varies from ~0.5 to 5.0 kg. Limited data suggest that in humans, most of the weight gained

Table 2—*SGA's and metabolic abnormalities*

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

+ = increase effect; − = no effect; D = discrepant results. *Newer drugs with limited long-term data.

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is fat. Data derived from a canine model indicated that certain SGAs increase total visceral fat mass and intrahepatic lipid content.

The mechanism(s) responsible for weight gain associated with SGA therapy are unknown. Weight gain occurs when more energy is ingested than is expended. Therefore, weight gain is due to increased energy intake, decreased energy expenditure, or both. Even a small, chronic imbalance between energy intake and expenditure can lead to large changes in body weight over time. For example, ingestion of ~500 kcal/day more than is expended can account for the largest average weight gain reported with SGA therapy (4.5 kg at 10 weeks). This amount of daily increase in energy intake represents the calories in a normal-size candy bar plus a soda or in an ice cream dessert. Hunger and satiety may be altered in people taking SGAs because of the known binding affinities of these drugs to serotonin, norepinephrine, dopamine, and particularly histamine-H1 receptors. All of these receptors have been implicated in the control of body weight.

Weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., insulin resistance, pre-diabetes, diabetes, and dyslipidemia. A possible direct effect of SGAs on β-cell function and insulin action in liver and muscle tissue could also be involved, as discussed below.

Diabetes

Numerous case reports have documented the onset or exacerbation of diabetes, including the occurrence of hyperglycemic crises, following initiation of therapy with many of the SGAs.

Several of these events occurred within a few weeks of initiating drug treatment. In some, but not all cases, hyperglycemia promptly resolved after the medication was discontinued. Several reports documented recurrent hyperglycemia after another challenge with the same drug. Additional cases of diabetes or hyperglycemia have been reported through MedWatch into the FDA's Adverse Event Reporting System.

Large retrospective cohort studies have been reported that estimate the prevalence of diabetes in patients using SGAs. These reports relied on a variety of methods for determining the diagnosis of diabetes, such as ICD-9 codes and data on prescriptions for diabetes medications. In addition, several cross-sectional studies of patients taking different SGAs, "switch studies" of patients changed from one medication to another, and one prospective randomized controlled trial evaluating SGA therapy on parameters of insulin sensitivity and glycemic control have been conducted. Despite limitations in study design, the data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine compared with patients not receiving treatment with FGAs or with other SGAs. The risk in patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not. The two most recently approved SGAs, aripiprazole and ziprasidone, have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increased risk for diabetes (Table 2).

One possible mechanism for hyperglycemia is impairment of insulin action (i.e., insulin resistance). Drug-induced insulin resistance may occur because of weight gain or a change in body fat distribution or by a direct effect on insulin-sensitive target tissues. Patients treated with olanzapine and clozapine have higher fasting and postprandial insulin levels than patients treated with FGAs, even after adjusting for body weight. To date, studies in humans have not shown adverse effects of any antipsychotic medication on β-cell function, but this issue has not been adequately studied in individuals with psychiatric illnesses.

Dyslipidemia

An additional related consequence of SGA use is their effect on serum lipids. Although the data are limited, the available evidence suggests that changes in serum lipids are concordant with changes in body weight. Clozapine and olanzapine, which produce the greatest weight gain, are associated with the greatest increases in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol. Aripiprazole and ziprasidone, which are associated with the least amount of weight gain, do not seem to be associated with a worsening of serum lipids. Risperidone and quetiapine appear to have intermediate effects on lipids (Table 2).

Risk-benefit assessment

Despite the adverse effects cited above, a number of factors should be considered when choosing among the antipsychotic medications. These include the nature of the patient's psychiatric condition, specific target signs and symptoms, past history of drug response (both therapeutic and adverse), patient preference, history of treatment adherence, medication effectiveness, psychiatric and medical comorbidities, availability of appropriate formulations (e.g., fast-dissolving oral, short- or long-acting intramuscular), need for special monitoring, and cost of and access to medications. Nonetheless, the risks of obesity, diabetes, and dyslipidemia have considerable clinical implications in this patient population and should also influence drug choice.

Even for those medications associated with an increased risk of metabolic side effects, the benefit to specific patients could outweigh the potential risks. For example, clozapine has unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior. Since treatment response in many psychiatric conditions is heterogeneous and unpredictable, physicians and patients can benefit from the availability of a broad array of different therapeutic agents.

4. GIVEN THE ABOVE RISKS, HOW SHOULD PATIENTS BE MONITORED FOR THE DEVELOPMENT OF SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES, AND HOW SHOULD THEY BE TREATED IF DIABETES DEVELOPS? —

Given the serious health risks, patients taking SGAs should receive appropriate baseline screening and ongoing monitoring. Clinicians who prescribe SGAs for patients with psychiatric illnesses should have the capability of determining a patient's height and weight (BMI) and waist circumference. These values should be recorded and tracked for the duration of treatment. Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic

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Table 3—*Monitoring protocol for patients on SGAs**

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

complications for which these patients are at increased risk.

Baseline monitoring

The panel recommends that baseline screening measures be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication (Table 3). These include

- Personal and family history of obesity diabetes, dyslipidemia, hypertension, or cardiovascular disease
- Weight and height (so that BMI can be calculated)
- Waist circumference (at the level of the umbilicus)
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

These assessments can determine if the patient is overweight (BMI 25.0–29.9) or obese (BMI ≥30), has pre-diabetes (fasting plasma glucose 100–125 mg/dl) or diabetes (fasting plasma glucose ≥126 mg/dl), hypertension (blood pressure >140/90 mmHg), or dyslipidemia. If any of these conditions are identified, appropriate treatment should be initiated. Psychiatrists should not hesitate to refer the patient to the appropriate health care professional or specialist knowledgeable about these disorders.

The panel recommends that nutrition and physical activity counseling be provided for all patients who are overweight or obese, particularly if they are starting treatment with an SGA that is associated with significant weight gain. Referral to a health care professional or program with expertise in weight management may also be appropriate.

Health professionals, patients, family members, and caregivers should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes such as DKA (Table 4). The latter is a life-threatening condition and always requires immediate treatment. Patients, family members, and caregivers also need to know that treatment with some SGAs may be associated with significant weight gain and a heightened risk of developing diabetes and dyslipidemia. For patients with, or at higher risk for, diabetes and in those treated with other medications that may increase these risks (e.g., valproate, lithium, Depo-Provera), it may be preferable to initiate treatment with an SGA that appears to have a lower propensity for weight gain and glucose intolerance (Table 2). Potential for weight gain should also be considered in the choice of other psychiatric and nonpsychiatric medications.

Table 4—*DKA clinical presentation*

Rapid onset of:
- Polyuria, polydipsia
- Weight loss
- Nausea, vomiting
- Dehydration
- Rapid respiration
- Clouding of sensorium, even coma

Follow-up monitoring

The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy and quarterly thereafter at the time of routine visits (Table 3). If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching the SGA. In such a situation, the panel recommends cross-titration to be the safest approach; abrupt discontinuation of an antipsychotic drug should generally be avoided. When switching from one antipsychotic drug to another, it is preferable to discontinue the current medication in a gradual fashion. The profile of the subsequent drug will determine the initial dose and escalation strategy. Particular consideration should be given before discontinuing clozapine because of the potential for serious psychiatric sequelae.

Fasting plasma glucose, lipid levels, and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated.

Although limited data are available in children and adolescents regarding the risks of diabetes when SGAs are given, these patients should have their height, in addition to weight, measured at regular intervals and their BMI calculated. BMI percentile adjusted for age and sex should be used to determine if excessive weight gain has occurred, and if present, a change in therapy should be considered.

For people who develop worsening glycemia or dyslipidemia while on antipsychotic therapy, the panel recommends considering switching to an SGA that has not been associated with significant weight gain or diabetes (Table 2). All patients with diabetes should be referred to an American Diabetes Association–recognized diabetes self-management education program, if available. Referral to a clinician with experience treating people with diabetes is recommended. These patients should carry diabetes identification.

Immediate care or consultation is required for patients with symptomatic or severe hyperglycemia (glucose values ≥300 mg/dl), symptomatic hypoglycemia, or glucose levels ≤60 mg/dl, even in the absence of symptoms. The presence of

Zyprexa MDL Plaintiffs' Exhibit No.02368 ZY200

symptoms of DKA (Table 4), requires immediate evaluation and treatment.

Blood pressure, lipid, and glycemic goals of therapy for people with diabetes apply equally to those who also have psychiatric disorders. However, all goals need to be individualized. The benefits and risks of different therapeutic agents used in the treatment of diabetes and its comorbidities should be considered in the context of the patient's psychiatric condition and treatment.

In summary, the panel recommends the following:

- Consideration of metabolic risks when starting SGAs
- Patient, family, and care giver education
- Baseline screening
- Regular monitoring
- Referral to specialized services, when appropriate

5. WHAT RESEARCH IS NEEDED TO BETTER UNDERSTAND THE RELATIONSHIP BETWEEN THESE DRUGS AND SIGNIFICANT WEIGHT GAIN, DYSLIPIDEMIA, AND DIABETES?

— Evidence for weight gain and abnormalities of glucose and lipid metabolism in patients taking SGAs is in part derived from case-control studies, pharmacovigilance (e.g., through MedWatch), and database reviews. Many of these studies suffer from their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects. Comparison studies among SGAs are also limited by relatively short periods of study, by failure to control for a possible treatment sequence bias in "switchover" studies, and by not always using clinically equivalent dosages of the medications.

Trials with SGAs should be randomized and controlled, preferably using drug-naive subjects. Weight gain and measures of glucose and lipid metabolism should be thoroughly evaluated. Study subjects should be well-characterized in terms of their baseline risk factors for diabetes, obesity, and lipid disorders and their degree of baseline impairment in insulin sensitivity and β-cell function. The duration of exposure to the various SGAs should be carefully controlled. Future research studies should focus on the following:

- Baseline body composition in untreated patients with psychiatric disorders and changes that occur during treatment with SGAs need to be better characterized. This would include measures of fat versus fat-free mass and visceral and subcutaneous adipose stores, using valid methods to measure body fat (e.g., magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry).
- The contribution of altered neuroendocrine function (e.g., hypothalmic-pituitary-adrenal axis activation) to alterations in body composition and abnormalities in glucose and lipid metabolism needs further study to distinguish the acute effects of stress from the underlying disease process.
- Studies are needed that examine glucose and lipid metabolism as they relate to alterations in insulin sensitivity in peripheral and hepatic tissues (e.g., euglycemic-hyperinsulinemic clamp with labeled glucose infusions), alterations in β-cell function (hyperglycemic clamp or frequently sampled intravenous glucose tolerance test), and alterations in lipid metabolism (using tracer infusions).
- Large prospective studies should be conducted to identify baseline and early treatment factors that predict the later occurrence of abnormalities in body weight and composition and disorders of glucose and lipid metabolism during treatment with these drugs.
- Additional studies are needed to identify whether there are baseline characteristics that predict acute, life-threatening complications (e.g., DKA, pancreatitis).
- Additional data are needed to determine whether the risks of therapy are increased in certain ethnic groups (e.g., African Americans).
- Studies determining the effect of SGAs in various psychiatric disorders are needed to clarify the disease-related risk for the development of weight gain and metabolic disturbances.
- Alterations in energy intake and expenditure as contributors to weight gain in the psychiatric population and how these processes are altered by treatment with SGAs should be studied.
- Studies are needed to determine whether the disorders of body weight and glucose and lipid metabolism are due to central nervous system or peripheral tissue actions of the SGAs. Valuable information on the direct effects of SGAs on different body tissue compartments might be obtained from studies in appropriate animal models.
- Studies of the genetic markers that are associated with, and may be causally related to, the metabolic disturbances occurring in treated patients with psychiatric disorders (e.g., 5-HT_{2C}, histamine-H1 receptor alleles) are needed.

SUMMARY— The SGAs are of great benefit to a wide variety of people with psychiatric disorders. As with all drugs, SGAs are associated with undesirable side effects. One constellation of adverse effects is an increased risk for obesity, diabetes, and dyslipidemia. The etiology of the increased risk for metabolic abnormalities is uncertain, but their prevalence seems correlated to an increase in body weight often seen in patients taking an SGA. Direct drug effects on β-cell function and insulin action could also be involved, since there is insufficient information to rule out this possibility. In the general population, being overweight or obese also carries a much higher risk of diabetes and dyslipidemia.

These three adverse conditions are closely linked, and their prevalence appears to differ depending on the SGA used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprozole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents.

The choice of SGA for a specific patient depends on many factors. The likelihood of developing severe metabolic disease should also be an important consideration. When prescribing an SGA, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing CVD, diabetes, or other diabetes complications.

...MDL Plaintiffs' Exhibit No.02368 ZY2003

APPENDIX

Consensus panel

Eugene Barrett, MD, PhD, Chair; Lawrence Blonde, MD, Stephen Clement, MD, John Davis, MD, John Devlin, MD, John Kane, MD, Samuel Klein, MD, William Torrey, MD.

Support

This conference was supported in part by an educational grant from AstraZeneca, Bristol-Myers Squibb Co., Janssen Pharmaceutical Products, Eli Lilly and Co., and Pfizer, Inc.

Disclosure

These panel members have declared receiving research grant support, honoraria, or consulting fees from the following companies in the previous year: Eugene Barrett (BMS, Pfizer); Lawerence Blonde (BMS, Lilly, Novartis, Pfizer); Stephen Clement (Pfizer); John Kane (AstraZeneca, BMS, Janssen, Lilly, Novartis, Pfizer).

Presenters at the conference

David Allison, PhD, Richard Bergman, PhD, John Buse, MD, PhD, Patrizia Cavazzoni, MD, Fred Fiedorek, MD, Rohan Ganguli, MD, Andrew Greenspan, MD, David Kendall, MD, Ron Leonge, MD, Antony Loebel, MD, Patrick Lustman, PhD, Herbert Meltzer, MD, John Newcomer, MD, Judy Racoosin, MD, Bryan Roth, MD, Michael Sernyak, MD, Jogin Thakore, MB, Donna Wirshing, MD, William Wirshing, MD.

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/prexa MDL Plaintiffs' Exhibit No 02388

Exhibit E

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

vs.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

VOLUME 5

TRANSCRIPT OF PROCEEDINGS

March 7, 2008 - Pages 1 through 211

BEFORE THE HONORABLE MARK RINDNER
Superior Court Judge

Company on notice that there was an association between diabetes and Zyprexa?

A. Yes.

Q. In your opinion, was it inappropriate for Eli Lilly to be using these type of methods in dealing with physicians that were considering the use of Zyprexa?

A. Yes.

Q. Why, sir?

A. Well, simply stated, you shouldn't -- the rep is supposed to go to the physician and tell the physician the good sides of any drug and the good -- the bad sides of any of that drug.

Now, if you don't talk about the problems of Zyprexa proactively, then you're hoping that some of them will not raise the issue so you don't have to talk about it.

And if others raise the issue, then you have been given exactly what to say in order to reassure them.

Q. It says: Check for agreement and get back to Donna. Do you know what they're referring to here when they say check for agreement?

A. Well, if you have convinced with the

verbatim, the physician not to worry about Zyprexa and diabetes, then now is the time to talk about Donna, which is an off-label use, and try to convince the physician --

MR. BRENNER: Objection, Your Honor. We're going to need a sidebar on that one.

(Bench discussion.)

MR. BRENNER: Two objections, Your Honor. First, maybe it was inadvertent, but off-label -- the second is he's now really talking about marketing efforts, and I don't think this is what he's offered for and I don't think he's qualified for that --

THE COURT: No, I think he's talking about marketing efforts, but it's in the context of warnings and I'll alow it for that purpose. I did hear him say the term, it's an off-label use. The question is do you want an instruction or don't you want an instruction? But I have to tell the jury that off-label uses are not part of the issue in this case except as I would let them know that it relates to marketing as it relates to warning issues.

MR. BRENNER: I would request that instruction, Your Honor.

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

STATE OF ALASKA Plaintiff, v. ELI LILLY AND COMPANY Defendant	)	Case no. 3AN-06-5630CIV

JUDGES RULINGS 3/12/08 Made Part

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for Jack Jordan:

Start (Page:Line)	End (Page:Line)
238:7	238:19
238:22	239:2
244:9	244:11
244:14	244:20
248:8	248:20
332:8	332:17
342:16	343:1
343:9	343:24
344:5	344:10
344:13	344:15

No need to include with Plaintiffs - May use for cross

Start (Page:Line)	End (Page:Line)
369:12	369:24
375:8	375:21
376:2	376:13
393:15	395:1
421:14	422:11
422:14	422:15
462:11	462:14
462:23	463:7

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Jack Jordan.

Start (Page:Line)	End (Page:Line)	Objection
Start (Page:Line)	**End (Page:Line)**	**Objection**
137:24	138:6	Relevance; Probative value outweighed by danger of unfair prejudice; Foundation; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 701)
164:15	164:19	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in limine – profit/net worth/price (Alaska R. Evid. 401, 402, 403)
166:21	166:22	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)
167:1	167:2	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)

Start (Page:Line)	End (Page:Line)	Objection	
167:10	167:20	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)	sustained
168:14	168:17	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)	sustained
174:24	175:10	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)	sustained
175:24	176:14	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)	sustained
189:17	189:19	Compound; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 611)	sustain
189:20	190:2	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	sustained
209:15	209:20	Ambiguous; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 611)	sustain
223:13	223:17	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrul
223:22	223:24	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overru
236:4	236:7	Foundation; Misstates the evidence; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 611, 701)	overr
237:24	238:6	Foundation; Misstates the evidence; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 611, 701)	susta
243:24	244:8	Relevance; Probative value outweighed by danger of unfair prejudice; Summary Judgment – Off-label marketing (Alaska R.	Susta

Start (Page:Line)	End (Page:Line)	Objection	
		Evid. 401, 402, 403)	
246:9	246:18	Foundation; Misstates the evidence; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 611, 701)	sustai
246:19	247:4	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	Sustai
296:17	296:24	Foundation; Misstates the Evidence; Ambiguous; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 611, 701)	Sustai
297:18	297:20	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	Just han.. the w.. answ..
301:20	302:2	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	Overru
306:1	306:7	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	Over
308:18	309:4	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	Over
309:5	309:10	Foundation; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 601, 702)	Over
309:11	309:21	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	Over
318:15	318:23	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 611)	Su

Start (Page:Line)	End (Page:Line)	Objection	
339:6	339:11	Relevance; Probative value outweighed by danger of unfair prejudice; Argumentative; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 611)	sustain
342:8	342:9	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
342:11	342:15	Relevance; Probative value outweighed by danger of unfair prejudice; Argumentative; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 611)	overrule
343:2	343:8	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	sustain
344:16	345:9	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
347:12	348:4	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Other Lilly Drugs; Motion in limine – profit/net worth/prices (Alaska R. Evid. 401, 402, 403)	overrule
355:20	356:2	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)	overrule
362:20	363:3	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	sustain
363:16	364:18	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	sustain
366:19	366:23	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label; Motion in limine – profit/net worth/prices (Alaska R. Evid. 401, 402, 403)	sustain
368:5	368:14	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	sustain

Start (Page:Line)	End (Page:Line)	Objection	
369:2	369:11	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	sustain
373:22	375:7	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
388:7	388:23	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
389:6	389:20	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
396:7	397:8	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
413:6	413:8	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
421:05	421:13	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
422:16	423:6	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
436:14	436:22	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
437:20	438:7	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)	overrule
456:13	458:1	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in limine – profit/net worth/price; Motion in limine – Other Lilly drugs (Alaska R. Evid. 401, 402, 403)	overrule

Lilly also objects to Plaintiff's exhibits for use during the testimony of Jack Jordan

Plaintiff's Exhibit	**Objection(s)**
Zyprexa MDL Plaintiffs' Exhibit No. 3872 (Jordan Dep. Exh. 8)	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal planning document that discusses market positioning and strategy MIL regarding Profits and Price Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Zyprexa MDL Plaintiffs' Exhibit No. 8632 (Jordan Dep. Exh. 13)	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal document discussing sales representative interaction with physicians
Zyprexa MDL Plaintiffs' Exhibit No. 1301 (Jordan Dep. Exh. 23)	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: internal marketing plan Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) M.I.L. regarding Profits and Price

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

RECEIVED
Chambers of
Judge Rindner
MAR 10 RECD
State of Alaska Superior Court
Third Judicial District
in Anchorage

STATE OF ALASKA Plaintiff,	)	
v.	)	Case no. 3AN-06-5630CIV
ELI LILLY AND COMPANY Defendant	)	

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for Joey L. Eski (designated pages Exhibit A), all of which must be presented together with the State's affirmative designations to ensure proper context (Lilly will later be filing designations to be played in Lilly's own case):

Start (Page:Line)	End (Page:Line)
10:24	11:3
12:23	13:2
19:6	19:11
71:18	71:22
72:10	72:13
81:3	81:15
85:11	85:22
88:14	89:2
98:25	99:8

Start (Page:Line)	End (Page:Line)
151:8	152:4
264:24	265:12
267:15	267:18
267:20	268:4
271:23	271:24
272:1	272:3
340:22	341:4

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Joey L. Eski:

Start (Page:Line)	End (Page:Line)	Objection
12:18	12:22	Question without answer
25:10 27:02	25:17 27:18	Commentary of counsel; relevance (Alaska R. Evid. 401)
56:13	56:15	Commentary of counsel; relevance (Alaska R. Evid. 401)
57:13 59:02	57:24 59:07	Relevance (Alaska R. Evid. 401)
67:01 71:03	67:03 71:17	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
71:23	72:09	Relevance; foundation; lack of personal knowledge; assumes facts not in evidence (Alaska

Start (Page:Line)	End (Page:Line)	Objection
72:14	72:20	R. Evid. 401; 602)
75:04 75:11 76:06 77:05 81:6 82:13 83:05	75:07 75:17 76:08 77:19 81:18 83:02 83:17	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
84:02 85:01 85:23 86:16 88:06 89:08 90:16 92:14 93:05 93:11	84:18 85:10 86:11 86:18 88:13 89:11 90:24 92:23 93:06 93:15	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
97:21 99:09 103:19 104:10 104:14	98:24 99:14 104:07 104:10 104:16	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.

Start (Page:Line)	End (Page:Line)	Objection
104:19 107:04 107:14	104:20 107:11 107:23	
112:24 115:22 116:21 117:21 118:02	113:14 116:11 117:02 117:24 118:03	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
119:07 120:03	119:12 120:16	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
122:17 122:22 123:12 123:18	122:19 123:09 123:14 123:22	Vagueness; foundation (Alaska R. Evid. 602)
132:18 146:01 146:08	132:21 146:05 146:08	Vagueness; assumes facts not in evidence; foundation (Alaska R. Evid. 602)
166:06	166:10	Witness has not had an opportunity to review and sign transcript; improper hypothetical; assumes facts not in evidence; vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
168:04 168:11	168:08 168:14	Improper hypothetical; assumes facts not in evidence; vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).

Start (Page:Line)	End (Page:Line)	Objection
168:17	168:22	
168:23 169:15	169:11 169:24	Vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
187:17 189:13	188:06 189:23	Assumes facts not in evidence; vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602)
210:20 211:04 211:07 212:08	210:24 211:05 212:03 212:19	Foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 401; 602; 701).
218:06	219:04	Foundation; lack of personal knowledge (Alaska R. Evid 401; 602).
219:10	220:02	Foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
227:5	227:18	Vagueness; foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 602, 701)
226:07	226:11	Incomplete (no question designated); foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
243:17 243:24 244:07	243:22 244:05 244:07	Relevance; hearsay; improper hypothetical; foundation; lack of personal knowledge; assumes facts not in evidence (Alaska R. Evid. 401; 602; 802)
256:01	256:19	Relevance (Alaska R. Evid. 401)
258:12 259:07	259:04 259:07	Assumes facts not in evidence; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).

Start (Page:Line)	End (Page:Line)	Objection
259:12	259:19	
263:07	264:8	Relevance (Alaska R. Evid. 401).
266:14 266:17	266:15 267:14	Relevance; improper hypothetical; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
270:17 270:21 272:15 272:18	270:19 271:14 272:16 272:24	Relevance; foundation; lack of personal knowledge; vagueness (Alaska R. Evid. 401; 602).
284:12	284:22	Relevance (Alaska R. Evid. 401) (off-label issue).
285:15 287:08	285:25 287:12	Vagueness; relevance; foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 401; 602; 701).
288:04	288:09	Vagueness; relevance; foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 401; 602; 701).
301:13 301:25	301:22 301:25	Vagueness; relevance; foundation; lack of personal knowledge; lay opinion; asked and answered (Alaska R. Evid. 401; 602; 701).
304:06	304:22	Argumentative; foundation; lack of personal knowledge; assumes facts not in evidence (Alaska R. Evid. 602).
362:19	363:02	Relevance (Alaska R. Evid. 401).

Lilly also objects to Plaintiff's exhibits for use during the testimony of Joey L. Eski:

Plaintiff's Exhibit	Objection(s)

Plaintiff's Exhibit	Objection(s)
Zyprexa Plaintiff's Exhibit 10097	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal document concerning sales-representive interactions with physicians.
Zyprexa Plaintiff's Exhibit 10096	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit 10122	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit 10120	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Zyprexa Plaintiff's Exhibit 10121	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Eski Exhibit 6	(Provided without bates number; unable to match to previously identified plaintiff's exhibit) Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Eski Exhibit 7	(Unable to match to previously identified plaintiff's exhibit) Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

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Dated: March 10, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

FILED IN OPEN COURT
Date: 3-10-08
Clerk:

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CI

RESPONSE TO STATE'S MARCH 9, 2008, LETTER MOTION

The State has provided yet another letter (March 9), which re-treads three stale issues: (1) a redundant argument of its March 7 letter motion that has been fully briefed for the Court; (2) the mechanics of playing videotaped depositions that were already ruled on by the Court; and (3) deposition designations disputes already resolved by the Court. The only new issue that the State raises—superficially at best—is an objection to testimony that Lilly wishes to present to the jury, but the State does not identify the specific testimony to which it objects. Lilly urges the Court to deny the State's motion to set the trial back on track.

The only claims that remain in the State's case are the UTPCPA claims related to Zyprexa's labeling and the common law failure-to-warn claim. At the heart of these remaining claims is Zyprexa's labeling: Did Zyprexa's labeling convey the risks as required by federal law? Did Lilly adequately inform Alaska physicians about these risks? Allegations of off-label promotion are entirely irrelevant to these claims, but the State continues its full-court press to present evidence of this nature to the jury. In fact, without having considered Lilly's response to its March 7 letter motion on the issue, the State re-argues that Lilly "opened the door" during its

opening statement to evidence of off-label promotion. Lilly refers the Court to its March 8 response to this issue.[1]

Although the State's presentation of videotaped deposition is expected to last several days, the State asks the Court to allow *more* testimony—testimony that the Court already ruled out—to demonstrate bias and prejudice of witnesses.[2] It is no secret, however, that the witnesses whose deposition testimony the State will play are present or former Lilly employees, and that the entire scope of their deposition testimony relates to their roles as Lilly employees. The jury can make judgments about potential bias of the witnesses based on this fact.

Yesterday, the Court made rulings about which Lilly counter-designated deposition testimony could be played along with the State's affirmative designations to add necessary context to the State's presentation of evidence. The State's argument that Lilly "get[s] two bites at the same apple," although the procedure has been endorsed by the Court and accords with the Alaska Rules of Civil Procedure, is meritless.[3]

The State also asks the Court to exclude certain deposition testimony designated by Lilly because the State raised "nonresponsive" objections or because Lilly only designated answers, in some instances, without the question. The State has not identified this testimony

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[1] Lilly supplements its response to this issue with EL-2580, the April 2000 Zyprexa package insert, which notes, "ZYPREXA is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder. The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features." (Exh. A); *see also* EL-3798, Letter from FDA to Lilly, Mar. 17, 2000, which approves Zyprexa for "the treatment of manic or mixed episodes in bipolar disorder." (Exh. B)

[2] Judge's Rulings Re: Def. Eli Lilly and Co's Objs. to Pl. State of Alaska's Trial Dep. Designations, Mar. 5, 2007.

[3] Alaska Rule Civ. P. 32(a)(4) ("If only part of a deposition is offered in evidence by a party, an adverse party may require the offeror to introduce any other part which ought in fairness to be considered with the part introduced . . . .").

either to Lilly or to the Court. If the State timely identifies such testimony, Lilly will meet and confer with the State and/or address this issue with the Court.

For the foregoing reasons, Lilly requests that the Court enter an order denying the State's March 9 letter motion.

DATED this 10th day of March, 2008.

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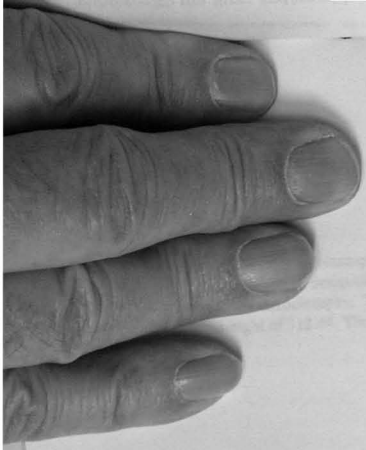


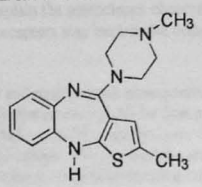
Exhibit A

ZYPREXA®
(Olanzapine) Tablets

ZYPREXA® ZYDIS®
(Olanzapine) Orally Disintegrating Tablets

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), or 15 mg (48 μmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths) and FD&C Blue No. 2 Aluminum Lake (15 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol) or 10 mg (32 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM),

ZY201316338

muscarinic $M_{1\text{-}5}$ (K_i=1.9-25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i > 10 μM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic $M_{1\text{-}5}$ receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics:

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination--Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Special Populations--

Renal Impairment--Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment--Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age--In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (*see* DOSAGE AND ADMINISTRATION).

Gender--Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status--Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race--No specific pharmacokinetic study was conducted to investigate the effects of race. A cross-study comparison between data obtained in Japan and data obtained in the US suggests that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a third pooled category including Asian and Hispanic patients. Dosage modifications for race are, therefore, not recommended.

Combined Effects--The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (*see* DOSAGE AND ADMINISTRATION).

Clinical Efficacy Data:

Schizophrenia

The efficacy of olanzapine in the management of the manifestations of psychotic disorders was established in 2 short-term (6-week) controlled trials of inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic

schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed but less well evaluated scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5.0±2.5 mg/day, 10.0±2.5 mg/day, and 15.0±2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

Bipolar Mania

The efficacy of olanzapine in the treatment of acute manic episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

INDICATIONS AND USAGE

Schizophrenia

ZYPREXA is indicated for the management of the manifestations of psychotic disorders.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (*see* CLINICAL PHARMACOLOGY).

The effectiveness of ZYPREXA in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Bipolar Mania

ZYPREXA is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (*see* CLINICAL PHARMACOLOGY).

The effectiveness of ZYPREXA for longer-term use, that is, for more than 4 weeks treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ZYPREXA for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)--A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia--A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to

rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension--Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures--During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia--As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is

contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations--In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. In the remaining two patients, one, seropositive for hepatitis C, had persistent enzyme elevation for four months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among all 2500 patients in clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Potential for Cognitive and Motor Impairment--Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Body Temperature Regulation--Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia--Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Two olanzapine-treated patients (2/407) in two studies in patients with Alzheimer's disease died from aspiration pneumonia during or within 30 days of the termination of the double-blind portion of their respective studies; there were no deaths in the placebo-treated patients. One of these patients had experienced dysphagia prior to the development of aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced

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Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide--The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness--Clinical experience with olanzapine in patients with certain concomitant systemic illnesses (*see* Renal Impairment and Hepatic Impairment *under* CLINICAL PHARMACOLOGY, Special Populations) is limited.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In a fixed-dose study of olanzapine (olanzapine at doses of 5, 10, and 15 mg/day) and placebo in nursing home patients (mean age: 83 years, range: 61-97; median Mini-Mental State Examination (MMSE): 5, range: 0-22) having various psychiatric symptoms in association with Alzheimer's disease, the following treatment-emergent adverse events were reported in all (each and every) olanzapine-treated groups at an incidence of either (1) two-fold or more in excess of the placebo-treated group, where at least 1 placebo-treated patient was reported to have experienced the event, or (2) at least 2 cases if no placebo-treated patient was reported to have experienced the event: somnolence, abnormal gait, fever, dehydration, and back pain. The rate of discontinuation in this study for olanzapine was 12% vs 4% with placebo. Discontinuations due to abnormal gait (1% for olanzapine vs 0% for placebo), accidental injury (1% for olanzapine vs 0% for placebo), and somnolence (3% for olanzapine vs 0% for placebo) were considered to be drug related. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia (*see* PRECAUTIONS).

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (*see* Orthostatic Hypotension).

Information for Patients--Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

Orthostatic Hypotension--Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see* Drug Interactions).

Interference with Cognitive and Motor Performance--Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Pregnancy--Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with olanzapine.

Nursing--Patients should be advised not to breast-feed an infant if they are taking olanzapine.

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Concomitant Medication--Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol--Patients should be advised to avoid alcohol while taking olanzapine.

Heat Exposure and Dehydration--Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics--ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34 and 0.45 mg per 5 and 10 mg tablet, respectively).

Laboratory Tests--Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Transaminase Elevations).

Drug Interactions--The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Olanzapine--Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (e.g., fluvoxamine) could potentially inhibit olanzapine elimination. Because olanzapine is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease olanzapine clearance.

Charcoal--The administration of activated charcoal (1 g) reduced the Cmax and AUC of olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids—Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine--Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Ethanol--Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine--Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Valproate--Studies in vitro using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Warfarin--Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.

Effect of Olanzapine on Other Drugs--In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and

CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, lithium, ethanol, or biperiden. However, the co-administration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility--

Carcinogenesis--Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily dose on a mg/m^2 basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily dose on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily dose on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily dose on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily dose on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at $\geq$2 mg/kg/day and in female rats dosed at $\geq$4 mg/kg/day (0.5 and 2 times the maximum recommended human daily dose on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (*see* Hyperprolactinemia *under* PRECAUTIONS, General).

Mutagenesis--No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility--In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily dose on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily dose on a mg/m^2 basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily dose on a mg/m^2 basis); therefore olanzapine may produce a delay in ovulation.

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Pregnancy--

Pregnancy Category C--In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily dose on a mg/m^2 basis, respectively) no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily dose on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily dose on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily dose on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery--Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Nursing Mothers--Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. It is recommended that women receiving olanzapine should not breast-feed.

Pediatric Use--Safety and effectiveness in pediatric patients have not been established.

Geriatric Use--Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in patients with various psychiatric symptoms in association with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 4189 patients with approximately 2665 patient-years of exposure. This database includes: (1) 2500 patients who participated in multiple-dose premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in a trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; and (4) 1316 patients from 43 additional clinical trials as of May 1, 1997.

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The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania. However, this information is also generally applicable to bipolar mania.

Adverse events during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms which were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Incidence of Adverse Events in Short-Term, Placebo-Controlled Trials--The following findings are based on the short-term, placebo-controlled premarketing trials for schizophrenia and bipolar mania and a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials--

Schizophrenia--Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for olanzapine vs 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug related (2% for olanzapine vs 0% for placebo) (*see* PRECAUTIONS).

Bipolar Mania--Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for olanzapine vs 2% for placebo).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials--The most commonly observed adverse events associated with the use of olanzapine (incidence of 5% or

greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 6-Week Trials - SCHIZOPHRENIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=248)	Placebo (N=118)
Postural hypotension	5	2
Constipation	9	3
Weight gain	6	1
Dizziness	11	4
Personality disorder[1]	8	4
Akathisia	5	1

[1] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Common Treatment-Emergent Adverse Events Associated with the Use of Olanzapine in 3-Week and 4-Week Trials– BIPOLAR MANIA		
Adverse Event	Percentage of Patients Reporting Event	
	Olanzapine (N=125)	Placebo (N=129)
Asthenia	15	6
Dry mouth	22	7
Constipation	11	5
Dyspepsia	11	5
Increased appetite	6	3
Somnolence	35	13
Dizziness	18	6
Tremor	6	3

Adverse Events Occurring at an Incidence of 2% or More Among Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials--

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with olanzapine (doses $\geq$ 2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

Table 1
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=532)**	**Placebo (N=294)**
Body as a Whole		
Accidental injury	12	8
Asthenia	10	9
Fever	6	2
Back pain	5	2
Chest pain	3	1
Cardiovascular System		
Postural hypotension	3	1
Tachycardia	3	1
Hypertension	2	1
Digestive System		
Dry mouth	9	5
Constipation	9	4
Dyspepsia	7	5
Vomiting	4	3
Increased appetite	3	2

Table 1 (cont.)
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=532)**	**Placebo (N=294)**
Hemic and Lymphatic System		
Ecchymosis	5	3
Metabolic and Nutritional Disorders		
Weight gain	5	3
Peripheral edema	3	1
Musculoskeletal System		
Extremity pain (other than joint)	5	3
Joint pain	5	3
Nervous System		
Somnolence	29	13
Insomnia	12	11
Dizziness	11	4
Abnormal gait	6	1
Tremor	4	3
Akathisia	3	2

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Table 1 (cont.)
Treatment-Emergent Adverse Events:
Incidence in Short-Term, Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Olanzapine (N=532)**	**Placebo (N=294)**
Nervous System (cont.)		
Hypertonia	3	2
Articulation impairment	2	1
Respiratory System		
Rhinitis	7	6
Cough increased	6	3
Pharyngitis	4	3
Special Senses		
Amblyopia	3	2
Urogenital System		
Urinary incontinence	2	1
Urinary tract infection	2	1

[1] Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea[2], hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder[3], rash, thinking abnormal, weight loss.
[2] Denominator used was for females only (olanzapine, N=201; placebo, N=114).
[3] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Additional Findings Observed in Clinical Trials--The following findings are based on clinical trials.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials--

Extrapyramidal Symptoms: The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY RATING SCALES INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL -- ACUTE PHASE*

	Percentage of Patients			
	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism[1]	15	14	12	14
Akathisia[2]	23	16	19	27

* No statistically significant differences.

[1] Percentage of patients with a Simpson-Angus Scale total score >3.

[2] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS ASSESSED BY ADVERSE EVENTS INCIDENCE IN A FIXED DOSAGE RANGE, PLACEBO-CONTROLLED CLINICAL TRIAL -- ACUTE PHASE

	Percentage of Patients Reporting Event			
	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Dystonic events[1]	1	3	2	3
Parkinsonism events[2]	10	8	14	20
Akathisia events[3]	1	5	11*	10*
Dyskinetic events[4]	4	0	2	1
Residual events[5]	1	2	5	1
Any extrapyramidal event	16	15	25	32*

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* Statistically significantly different from placebo.
[1] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[2] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[3] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
[4] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
[5] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events: The following table addresses dose relatedness for other adverse events using data from a schizophrenia trial involving fixed dosage ranges. It enumerates the percentage of patients with treatment-emergent adverse events for the three fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse events for which there was a statistically significant trend.

	Percentage of Patients Reporting Event			
Adverse Event	Placebo (N=68)	Olanzapine 5 ± 2.5 mg/day (N=65)	Olanzapine 10 ± 2.5 mg/day (N=64)	Olanzapine 15 ± 2.5 mg/day (N=69)
Asthenia	15	8	9	20
Dry mouth	4	3	5	13
Nausea	9	0	2	9
Somnolence	16	20	30	39
Tremor	3	0	5	7

Vital Sign Changes--Olanzapine is associated with orthostatic hypotension and tachycardia (*see* PRECAUTIONS).

Weight Gain--In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Laboratory Changes--An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (*see* PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

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Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

In the olanzapine clinical trial database, as of September 30, 1999, 4577 olanzapine-treated patients (representing approximately 2255 patient-years of exposure) and 445 placebo-treated patients who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Persistent random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 0.8% of olanzapine-treated patients (placebo 0.7%). Transient (i.e., resolved while the patients remained on treatment) random glucose levels ≥ 200 mg/dL were found in 0.3% of olanzapine-treated patients (placebo 0.2%). Persistent random glucose levels ≥ 160 mg/dL but < 200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 1.0% of olanzapine-treated patients (placebo 1.1%). Transient random glucose levels ≥ 160 mg/dL but < 200 mg/dL were found in 1.0% of olanzapine-treated patients (placebo 0.4%).

ECG Changes--Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (*see* PRECAUTIONS).

Other Adverse Events Observed During the Clinical Trial Evaluation of Olanzapine--Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with olanzapine (at multiple doses ≥ 1 mg/day) in clinical trials (4189 patients, 2665 patient-years of exposure). This listing does not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole--*Frequent:* dental pain, flu syndrome, intentional injury, and suicide attempt; *Infrequent:* abdomen enlarged, chills, chills and fever, face edema, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, and photosensitivity reaction; *Rare:* hangover effect and sudden death.

Cardiovascular System--*Frequent:* hypotension; *Infrequent:* bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, and ventricular extrasystoles; *Rare:* arteritis, atrial fibrillation, heart failure, and pulmonary embolus.

Digestive System--*Frequent:* increased salivation and thirst; *Infrequent:* dysphagia, eructation, fecal impaction, fecal incontinence, flatulence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal

ZY201316356

hemorrhage, stomatitis, tongue edema, and tooth caries; *Rare:* aphthous stomatitis, enteritis, esophageal ulcer, esophagitis, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

Endocrine System--*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis and goiter.

Hemic and Lymphatic System--*Frequent:* leukopenia; *Infrequent:* anemia, cyanosis, leukocytosis, lymphadenopathy, thrombocythemia, and thrombocytopenia; *Rare:* normocytic anemia.

Metabolic and Nutritional Disorders--*Infrequent*: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema, and water intoxication; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, and ketosis.

Musculoskeletal System--*Frequent:* joint stiffness and twitching; *Infrequent:* arthritis, arthrosis, bursitis, leg cramps, and myasthenia; *Rare:* bone pain, myopathy, osteoporosis, and rheumatoid arthritis.

Nervous System--*Frequent:* abnormal dreams, emotional lability, euphoria, libido decreased, paresthesia, and schizophrenic reaction; *Infrequent:* alcohol misuse, amnesia, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, coma, delirium, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, tobacco misuse, vertigo, and withdrawal syndrome; *Rare:* akinesia, circumoral paresthesia, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, and subarachnoid hemorrhage.

Respiratory System--*Frequent:* dyspnea; *Infrequent:* apnea, aspiration pneumonia, asthma, atelectasis, epistaxis, hemoptysis, hyperventilation, laryngitis, pneumonia, and voice alteration; *Rare:* hiccup, hypoventilation, hypoxia, lung edema, and stridor.

Skin and Appendages--*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin ulcer, and vesiculobullous rash; *Rare:* hirsutism, pustular rash, skin discoloration, and urticaria.

Special Senses--*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, corneal lesion, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; *Rare:* glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

Urogenital System--*Frequent:* amenorrhea*, hematuria, metrorrhagia*, and vaginitis*; *Infrequent:* abnormal ejaculation*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation, glycosuria, impotence*, increased menstruation*, menorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urination impaired, uterine fibroids enlarged*, and vaginal hemorrhage*; *Rare:* albuminuria, gynecomastia, mastitis, oliguria, and urinary urgency.

*Adjusted for gender.

Postintroduction Reports--Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: diabetic coma and priapism.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class--Olanzapine is not a controlled substance.

Physical and Psychological Dependence--In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily dose on a mg/m^2 basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience--In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

Overdosage Management--The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Dose--Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of

ZY201316358

15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations--The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥ 65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment--While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on olanzapine, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Mania

Usual Dose--Olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations--*See* Dosing in Special Populations *under* DOSAGE AND ADMINISTRATION, Schizophrenia.

Maintenance Treatment--There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with olanzapine. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of olanzapine in such longer-term treatment (i.e., beyond 3-4 weeks).

Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)--After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

HOW SUPPLIED

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The tablets are available as follows:

	2.5 mg	5 mg	7.5 mg	10 mg	15 mg
Tablet No.	4112	4115	4116	4117	4415
Identification	LILLY 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415
NDC Codes:					
Bottles 30	-----	-----	-----	-----	NDC-0002-4415-30
Bottles 60	NDC-0002-4112-60	NDC-0002-4115-60	NDC-0002-4116-60	NDC-0002-4117-60	----
Blisters - ID* 100	-----	NDC-0002-4115-33	NDC-0002-4116-33	NDC-0002-4117-33	NDC-0002-4415-33

*Identi-Dose® (unit dose medication, Lilly)

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

ZYPREXA ZYDIS Tablets*	TABLET STRENGTH 5 mg	10 mg
Tablet No.	4453	4454
Debossed	5	10
NDC Codes:		
Dose Pack 30	NDC-	NDC-
(Child-Resistant)	0002-	0002-
	4453-85	4454-85

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of R. P. Scherer Corporation.
* ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Scherer DDS Limited, United Kingdom, SN5 8RU.

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.
Protect from light and moisture.

ANIMAL TOXICOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily dose on a mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily dose on a mg/m^2 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily dose on a mg/m^2 basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily dose on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

Literature revised April 12, 2000

Eli Lilly and Company
Indianapolis, IN 46285, USA

Printed in USA

PV 3400 AMP

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ZY201316363

Date of Trial	Witness/ Examination	Trial Exhibit No.	Order of Appearance	Date of Exhibit	Description	Objected	Notes
3/6/2008	Brancati Direct				Direct Exam Slides		Used throughout direct; 6 slides shown not provided in copies (diabetic retinopathy, eye diagram, diabetic nephropathy 1, diabetic nephropathy 2, diabetic neuropathy, foot picture)
3/6/2008	Brancati Direct	Zyprexa Plaintiff's Exhibit 10133	1	9/22/2005	Lieberman JA, et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. N Engl J Med, September 22, 2005 (CATIE)	Hearsay (Alaska R. Evid. 801, 802)/Foundation (Alaska R. Evid. 901)	Discussed by Brancati; article not shown to jury
3/6/2008	Brancati Direct		2	11/00/1999	Allison, DB, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 156:1686-1696, November 1999		Discussed by Brancati; article not shown to jury; chart from the article is one of the slides
3/6/2008	Brancati Direct	Zyprexa MDL Plaintiffs' Exhibit No 02368	3	02/00/2004	ADA Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care, Volume 27(2), February 2004	Hearsay (Alaska R. Evid. 801, 802)/Foundation (Alaska R. Evid. 901)	
3/6/2008	Brancati Cross		1	5/00/1999	Brancati FL, et al. Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. Arch Internal Med, 1999.		
3/6/2008	Brancati Cross	EL-2001 **(Admitted)**	2	08/00/2004	Consensus development conference on antipsychotic drugs and obesity and diabetes: Response to consensus statement.		

Date of Trial	Witness/ Examination	Trial Exhibit No.	Order of Appearance	Date of Exhibit	Description	Objected	Notes
3/6/2008	Brancati Direct				Direct Exam Slides		Used throughout direct; 6 slides shown not provided in copies (diabetic retinopathy, eye diagram, diabetic nephropathy 1, diabetic nephropathy 2, diabetic neuropathy, foot picture)
3/6/2008	Brancati Direct	Zyprexa Plaintiff's Exhibit 10133	1	9/22/2005	Lieberman JA, et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. N Engl J Med, September 22, 2005 (CATIE)	Hearsay (Alaska R. Evid. 801, 802)/Foundation (Alaska R. Evid. 901)	Discussed by Brancati; article not shown to jury
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3/6/2008	Brancati Direct	Zyprexa MDL Plaintiffs' Exhibit No 02368	3	02/00/2004	ADA Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care, Volume 27(2), February 2004	Hearsay (Alaska R. Evid. 801, 802)/Foundation (Alaska R. Evid. 901)	
3/6/2008	Brancati Cross		1	5/00/1999	Brancati FL, et al. Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. Arch Internal Med, 1999.		
3/6/2008	Brancati Cross	EL-2001 **(Admitted)**	2	08/00/2004	Consensus development conference on antipsychotic drugs and obesity and diabetes: Response to consensus statement.		

Besa, Jennifer

From: Larris, Brian
Sent: Saturday, March 08, 2008 10:08 AM
To: Besa, Jennifer
Subject: FW: Court Box

From: Ronde, William A.
Sent: Saturday, March 08, 2008 9:04 AM
To: Ronde, William A.
Cc: Larris, Brian; Cameron, Eli
Subject: FW: Court Box

Our list is growing....

From: Ronde, William A.
Sent: Saturday, March 08, 2008 8:57 AM
To: Ronde, William A.
Subject: Court Box

NG Box
H2O/Snacks
Exhibit Lists
List of Admitted Exhibits
Cheat Sheet of Excluded Exhibits
Pleadings
Alaska Rules
FOR MONDAY ONLY: List of admitted exhibits for each party (we need to do a list for us and them) for the court clerk.

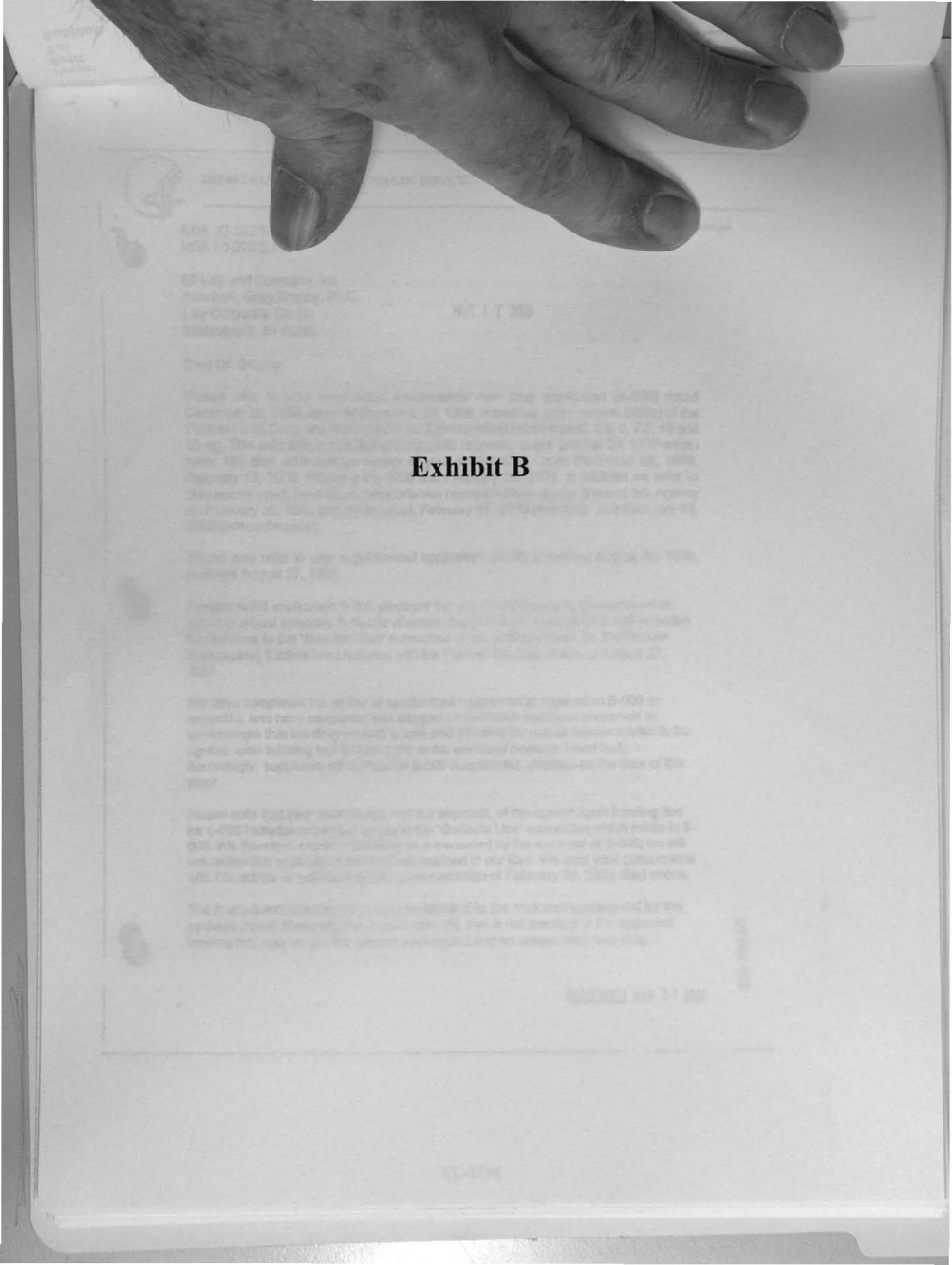

Exhibit B

DEPARTMENT OF HEALTH & HUMAN SERVIC

Food and Drug Administration
Rockville MD 20857

NDA 20-592/S-006
NDA 20-592/S-008

Eli Lilly and Company, Inc.
Attention: Greg Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

MAR 17 2000

Dear Dr. Brophy:

Please refer to your resubmitted supplemental new drug application (S-006) dated December 22, 1999, received December 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzepine) tablets, 2.5, 5, 7.5, 10 and 15 mg. This submission constituted a complete response to our October 28, 1999 action letter. We also acknowledge receipt of your submissions dated November 23, 1999, February 18, 2000, February 25, 2000 and February 29, 2000. In addition we refer to discussions which have taken place between representatives of your firm and this Agency on February 22, 2000 (teleconference), February 23, 2000 (meeting), and February 28, 2000 (teleconference).

Please also refer to your supplemental application S-008, submitted August 26, 1998, received August 27, 1998.

Supplemental application S-006 proposes the use of olanzapine in the treatment of manic or mixed episodes in bipolar disorder. Supplemental application S-008 provides for revisions to the "Geriatric Use" subsection of the package insert for ZYPREXA® (olanzapine) Tablets in compliance with the Federal Register Notice of August 27, 1997.

We have completed the review of resubmitted supplemental application S-006 as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (please refer to the enclosed package insert text). Accordingly, supplemental application S-006 is approved, effective on the date of this letter.

Please note that your acceptance, and our approval, of the agreed upon labeling text for S-006 includes labeling changes in the "Geriatric Use" subsection which relate to S-008. We therefore consider S-008 to be superseded by the approval of S-006; we will not review this application, but it will be retained in our files. We note your concurrence with this action as indicated by your communication of February 29, 2000 cited above.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

RECEIVED MAR 31 2000

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EL-3798

Please submit 20 copies of the FPL, as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved sNDA number 20-592/S-006". Approval of this submission by FDA is not required before the labeling is used.

Please also submit one market package of the drug product when it is available.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in the newly approved indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this supplemental NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

You have been advised that the Pediatric Final Rule (63 FR 66632) requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that your Proposed Pediatric Study Request was submitted to this supplemental NDA on February 25, 2000 and received February 28, 2000. A formal Written Request will be forwarded to you under separate cover.

Also, as you know, on February 2, 1999, the financial disclosure rule, published in the Federal Register of February 2, 1998, became effective. Although your supplemental NDA was submitted before this rule was in effect, for any covered clinical studies submitted after February 2, 1999 which relate to this supplement, the regulations require financial information on clinical investigators conducting those trials. Please note that this requirement also applies to pediatric studies conducted in accordance with the Pediatric Final Rule. For further information about this requirement, you may

ZYRTEC 37

contact Ms. Linda Carter, Associate Director, Regulatory Affairs, Office of Drug Evaluation I at 301.594.6758.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions concerning this supplemental NDA, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-5536.

Sincerely yours,

Russell Katz, MD
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and
Research

Attachment (agreed-upon package insert text)

ZY 968 138

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

FILED IN OPEN COURT
Date: 3-10-08
Clerk: MCS

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

PLAINTIFF'S OBJECTIONS AND COUNTER-DESIGNATIONS TO DEFENDANT'S DEPOSITION DESIGNATIONS AS OF MARCH 18, 2008

JOEY ESKI
FEBRUARY 29, 2008

In response to Defendant's designations, Plaintiff hereby objects to the following designations:

Page/Line Range	Objection
146:14-146:25	Non-responsive
177:07-177:14	Non-responsive

Plaintiff hereby offers the following counter-designations:

Start	Stop
353:15	353:18
353:23	356:11
356:15	357:9

GARY TOLLEFSON
NOVEMBER 6, 2006

Plaintiff hereby offers the following counter-designations:

Start	Stop
299:5	299:7
299:10	301:9
301:12	301:16
301:20	301:22
302:1	303:6
303:9	303:14
388:11	394:12

ROBIN WOJCIESZAK
DECEMBER 11, 2007

In response to Defendant's designations, Plaintiff hereby objects to the following designations:

Page/Line Range	Objection
171:1-171:5	Leading; lack of foundation
177:12-177:16	Leading
177:16-177:16	Leading

Plaintiff hereby offers the following counter-designations:

Start	Stop
51:05	52:14
54:06	54:08
54:11	54:14
54:22	54:22
54:24	55:05
62:18	63:11
63:16	64:15

CHARLES BEASLEY
JULY 26, 2006

In response to Defendant's designations, Plaintiff hereby objects to the following designations:

Page/Line Range	Objection
567:13 – 567:20	No preceding question; beyond scope of direct
572:22 – 573:12	Lack of foundation; improper expert testimony
573:13 – 575:12	Lack of foundation; improper expert testimony
575:13 – 578:01	Lack of foundation; improper expert testimony
578:05 – 578:05	Lack of foundation; improper expert testimony
578:18 – 580:21	Lack of foundation; improper expert testimony
583:04 – 583:16	Lack of foundation; improper expert testimony
722: 08 – 723:11	Relevance

Plaintiff hereby offers the following counter-designations:

Start	Stop
590:23	592:20
679:5	679:16
680:20	681:10
681:12	682:1
682:3	682:3
682:7	682:9
682:11	682:11

DATED this 18th day of March, 2008.

FELDMAN, ORLANKSY & SANDERS
Counsel for Plaintiff

By _____
Eric T. Sanders
AK Bar No. 7510085

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
Counsel for Plaintiff

RICHARDSON, PATRICK,
WESTBROOK & BRICKMAN, LLC
H. Blair Hahn
Christiaan A. Marcum
Counsel for Plaintiff

Certificate of Service

I hereby certify that a true and correct copy of **PLAINTIFF'S OBJECTIONS AND COUNTER-DESIGNATIONS TO DEFENDANT'S DEPOSITION DESIGNATIONS AS OF MARCH 18, 2008** was served via hand-delivery on:

George Lehner, Esq.
Pepper Hamilton LLP
Hotel Captain Cook, 19th Floor
Anchorage, Alaska 99501

By _____

Date 3-18-08

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

FILED IN OPEN COURT
Date: 3-10-08
Clerk:

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

DEFENDANT ELI LILLY AND COMPANY'S MOTION FOR RECONSIDERATION OF RULINGS ON OBJECTIONS TO AFFIRMATIVE DEPOSITION DESIGNATIONS OF JOHN LECHLEITER AND DENICE TORRES

Defendant Eli Lilly and Company ("Lilly") respectfully requests that the Court reconsider its rulings regarding the admissibility of the following excerpts from the depositions of John Lechleiter and Denice Torres. Each of these designations by the State reflect its allegations that Lilly engaged in off-label promotion—allegations which the Court has deemed irrelevant to, and beyond the scope of, any claim that State asserts. Consistent with the Court's rulings regarding other designated testimony in these same depositions, Lilly's objections set forth below should be sustained. Relevant pages of the transcripts are attached.

1. John Lechleiter, Ph.D. (TAB A)

The Court sustained Lilly's objection to testimony at 360:3 to 360:6, in which the State, as a prelude to discussing Exhibit 29 (Plaintiff's Exhibit 10041), asked, "Dr. Lechleiter, you went out to try to promote Zyprexa off label yourself, did you not?" and Dr. Lechleiter responded, "No, I did not." Despite sustaining Lilly's objection, the

Court overruled Lilly's later objections to specific testimony regarding Exhibit 29, the very testimony elicited by the State in support of its premise. These rulings are also contrary to those made on objections to testimony designated from the deposition of Ms. Torres. In those rulings, the Court *sustained* Lilly's objections to testimony concerning the very same document (identified as Plaintiff's Exhibit 10068). The following segments of testimony address Lechleiter Exhibit 29, which has no relevance to this case in light of the exclusion of the off-label issue:

Start (Page:Line)	**End (Page:Line)**	**Objection**
361:4	361:20	Relevance (testimony concerns off-label issue).
363:3	363:16	Relevance (testimony concerns off-label issue).
363:19	364:2	Relevance (testimony concerns off-label issue).
364:3	365:23	Relevance (testimony concerns off-label issue).
366:7	367:11	Relevance (testimony concerns off-label issue).

2. Denice Torres (TAB B)

The Court's sustained Lilly's objections to several of the State's designations of the testimony of Ms. Torres because they concern the off-label issue. Nevertheless, the Court overruled Lilly's objections to the following similar segments of testimony, each of which specifically concerns indications, and which have no probative value in a case from which off-label issues have been excised:

Start (Page:Line)	**End (Page:Line)**	**Objection**
150:8	150:11	Relevance (testimony concerns off-label issue).

Start (Page:Line)	End (Page:Line)	Objection
152:12	152:20	Relevance (testimony concerns off-label issue).
154:18	154:23	Relevance (testimony concerns off-label issue).
242:3	242:18	Relevance (testimony concerns off-label issue).
243:2	243:20	Relevance (testimony concerns off-label issue).
549:8	549:12	Relevance (testimony concerns off-label issue).

PEPPER HAMILTON LLP

Nina M. Gussack, admitted *pro hac* vice
George A. Lehner, admitted *pro hac* vice
John F. Brenner, admitted *pro hac vice*
3000 Two Logan Square
Philadelphia, PA 19103-2799
(215) 981-4618

LANE POWELL LLC

By: _____
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Attorneys for defendant Eli Lilly and Company

Dated: March 8, 2008

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of this document has been served via email upon counsel listed below, and by hand delivery and email upon Mary Beth Rivers, Room 532, Tower Two, Captain Cook Hotel.

_____
Brewster H. Jamieson

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1037 Chuck Dawley Boulevard, Building A
Mount Pleasant, SC 29464-4190

Date: March 8, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

STATE OF ALASKA	)	
Plaintiff,	)	
v.	)	Case no. 3AN-06-5630CIV
ELI LILLY AND COMPANY	)	
Defendant	)	

Judge Rindner
3/10/08
Mark Rindner

DEFENDANT ELI LILLY AND COMPANY'S SUPPLEMENTAL OBJECTION TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION

Defendant Eli Lilly and Company ("Lilly") objects to the following page and lines of Plaintiff State of Alaska's Trial Deposition Designations for Denice M. Torres:

Start (Page:Line)	End (Page:Line)	Objection
538:19	538:20	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)

overruled

Respectfully submitted,

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By:_____

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Attorneys for Defendant
Eli Lilly and Company

Date: March 9, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

RECEIVED
Chambers of
Judge Rindner
MAR 10 RECD
State of Alaska Superior Court
Third Judicial District
in Anchorage

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

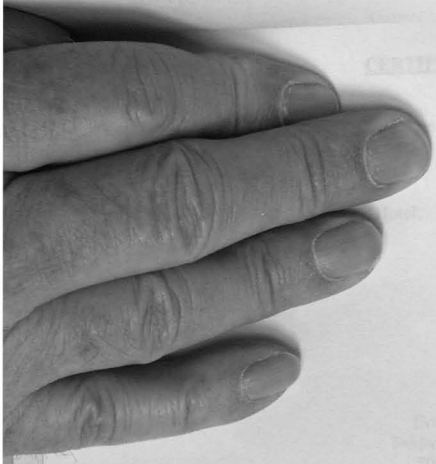
Judge's ruling
3/11/08 Mark Rindner

DEFENDANT ELI LILLY AND COMPANY'S MOTION FOR RECONSIDERATION OF RULINGS ON OBJECTIONS TO AFFIRMATIVE DEPOSITION DESIGNATIONS OF GARY TOLLEFSON, M.D.

Defendant Eli Lilly and Company ("Lilly") respectfully requests that the Court reconsider its rulings regarding the admissibility of the following excerpt from the deposition of Gary Tollefson, M.D. This designation by the State reflect its allegations that Lilly engaged in off-label promotion—allegations which the Court has deemed irrelevant to, and beyond the scope of, any claim that State asserts. Consistent with the Court's rulings regarding other similar designated testimony in other depositions, Lilly's objections set forth below should be sustained. Relevant pages of the transcripts are attached.

Start (Page:Line)	End (Page:Line)	Objection
124:5 124:21	124:9 125:21	Relevance, vague; foundation; personal knowledge; (Alaska R. Evid. 401, 402, 403, 602, 611). Subject to ruling on Motion for Summary Judgment: off label.

Sustained



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By: _____
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Attorneys for defendant Eli Lilly and Company

Dated: March 10, 2008

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of this document has been served via email upon counsel listed below, and by hand delivery and email upon Mary Beth Rivers, Room 532, Tower Two, Captain Cook Hotel.

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Mount Pleasant, SC 29464-4190

Date: March 10, 2008

Page 122

was spent on the drug; is that correct?
MR. LEHNER: Object to the form.
A. Probably reflecting both. But, specifically, the economics.
Q. Okay. And if I could direct your attention to Page 18, there's a chart on that page entitled, "Disease State Prioritization." Is that correct?
A. Correct.
Q. And at this point in time in 1997, Zyprexa was only indicated for the treatment of schizophrenia, correct?
MR. LEHNER: Object to the form.
A. That was the only currently or then approved indication. We were exploring additional ones at that time.
Q. The ones you were exploring, are those the ones listed in the box A on the left-hand side?
A. "A" would indicate ones that were candidates to be explored for a ... highest priority to be explored for a new

Page 123

indication.
Q. Okay. And those as listed, there were bipolar disorder, dementia with psychosis, depression with psychotic features, dysthymia, PD with treatment-associated psychosis, schizoaffective schizophrenia, and unipolar depression, correct?
A. Correct.
Q. What's dysthymia?
A. It's a chronic low-grade depression that's not of sufficient severity to be called a major depression. So it's a low-grade depression that tends to be chronic ... and what's PD?
A. This is Parkinson's disease.
Q. Okay. Did you become aware of efforts to promote Zyprexa to physicians for dementia and depression?
MR. LEHNER: Object to the form.
A. If you're referring to the disease state prioritization table here --

Page 124

Q. No, I'm not.
A. -- these are clinical candidates.
Q. No, I'm not referring to that at all. Did you become aware of efforts by the sales force to promote Zyprexa for treatment of depression and dementia associated with -- pardon me -- dementia with psychosis?
MR. LEHNER: Object to the form.
A. No, I wasn't aware of that because those were not approved indications. There would be no reason to do that.
Q. If, in fact, Zyprexa was promoted for depression and dementia, or any other diseases that were not approved indications, that would be wrong, correct?
MR. LEHNER: Object to the form.
A. I think within the confines of the Washington Legal Foundation opinion that said if a company was pursuing an indication and a physician were to inquire of

Page 125

have interest, that there could ... peer-reviewed materials could be shared, and in that context I believe it was acceptable. Outside of the WLF boundaries it would be ...
Q. So if a salesman approached a physician and tried to promote the use of Zyprexa without first being asked questions about the disease, if a salesman went and actively promoted Zyprexa for the treatment of diseases other than ...

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

RECEIVED
Chambers of
Judge Rindner
MAR 1
State of Alaska Superior Ct
Third Judicial District
In Anchorage

STATE OF ALASKA, Plaintiff,

v.

ELI LILLY AND COMPANY, Defendant

Case no. 3AN-06-5630CIV

Judge's Rulings
3/11/08 Mark Rindner

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for Joey L. Eski (designated pages Exhibit A), all of which must be presented together with the State's affirmative designations to ensure proper context (Lilly will later be filing designations to be played in Lilly's own case):

Start (Page:Line)	End (Page:Line)	
10:24	11:3	include
12:23	13:2	include
19:6	19:11	NO
71:18	71:22	include
72:10	72:13	include
81:3	81:15	include if I allow ## design.
85:11	85:22	include if I allow
88:14	89:2	NO
98:25	99:8	include if I allow

Start (Page:Line)	End (Page:Line)
151:8	152:4
264:24	265:12
267:15	267:18
267:20	268:4
271:23	271:24
272:1	272:3
340:22	341:4

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Joey L. Eski:

O = Overrule

S = Sustain

Start (Page:Line)	End (Page:Line)	Objection	
12:18	12:22	Question without answer Overruled - answer	starts at 13:03 - 13:08
25:10 27:02	25:17 27:18	Commentary of counsel; relevance (Alaska R. Evid. 401)	Sustained
56:13	56:15	Commentary of counsel; relevance (Alaska R. Evid. 401)	O
57:13 59:02	57:24 59:07	Relevance (Alaska R. Evid. 401)	O
67:01 71:03	67:03 71:17	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.	Need to discuss
71:23	72:09	Relevance; foundation; lack of personal knowledge; assumes facts not in evidence (Alaska	Need to Discuss

Start (Page:Line)	End (Page:Line)	Objection	
72:14	72:20	R. Evid. 401; 602)	Need to Discuss
75:04 75:11 76:06 77:05 81:6 82:13 83:05	75:07 75:17 76:08 77:19 81:18 83:02 83:17	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.	Need to Discuss
84:02 85:01 85:23 86:16 88:06 89:08 90:16 92:14 93:05 93:11	84:18 85:10 86:11 86:18 88:13 89:11 90:24 92:23 93:06 93:15	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.	Need to Discuss
97:21 99:09 103:19 104:10 104:14	98:24 99:14 104:07 104:10 104:16	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.	Need to Discuss

Start (Page:Line)	End (Page:Line)	Objection
104:19 107:04 107:14	104:20 107:11 107:23	
112:24 115:22 116:21 117:21 118:02	113:14 116:11 117:02 117:24 118:03	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
119:07 120:03	119:12 120:16	Relevance; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403). Subject to Motion to Exclude Evidence Regarding Speech Protected by the *Noerr-Pennington* Doctrine and Common Law Privilege, filed March 6, 2008.
122:17 122:22 123:12 123:18	122:19 123:09 123:14 123:22	Vagueness; foundation (Alaska R. Evid. 602)
132:18 146:01 146:08	132:21 146:05 146:08	Vagueness; assumes facts not in evidence; foundation (Alaska R. Evid. 602)
166:06	166:10	Witness has not had an opportunity to review and sign transcript; improper hypothetical; assumes facts not in evidence; vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
168:04 168:11	168:08 168:14	Improper hypothetical; assumes facts not in evidence; vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).

P ?
safety issue

Need to Discuss

Start (Page:Line)	End (Page:Line)	Objection
168:17	168:22	
168:23 169:15	169:11 169:24	Vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
187:17 189:13	188:06 189:23	Assumes facts not in evidence; vagueness; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602)
210:20 211:04 211:07 212:08	210:24 211:05 212:03 212:19	Foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 401; 602; 701).
218:06	219:04	Foundation; lack of personal knowledge (Alaska R. Evid 401; 602).
219:10	220:02	Foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
227:5	227:18	Vagueness; foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 602, 701)
226:07	226:11	Incomplete (no question designated); foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
243:17 243:24 244:07	243:22 244:05 244:07	Relevance; hearsay; improper hypothetical; foundation; lack of personal knowledge; assumes facts not in evidence (Alaska R. Evid. 401; 602; 802)
256:01	256:19	Relevance (Alaska R. Evid. 401)
258:12 259:07	259:04 259:07	Assumes facts not in evidence; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).

Start (Page:Line)	End (Page:Line)	Objection
259:12	259:19	
263:07	264:8	Relevance (Alaska R. Evid. 401).
266:14 266:17	266:15 267:14	Relevance; improper hypothetical; foundation; lack of personal knowledge (Alaska R. Evid. 401; 602).
270:17 270:21 272:15 272:18	270:19 271:14 272:16 272:24	Relevance; foundation; lack of personal knowledge; vagueness (Alaska R. Evid. 401; 602).
284:12	284:22	Relevance (Alaska R. Evid. 401) (off-label issue).
285:15 287:08	285:25 287:12	Vagueness; relevance; foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 401; 602; 701).
288:04	288:09	Vagueness; relevance; foundation; lack of personal knowledge; lay opinion (Alaska R. Evid. 401; 602; 701).
301:13 301:25	301:22 301:25	Vagueness; relevance; foundation; lack of personal knowledge; lay opinion; asked and answered (Alaska R. Evid. 401; 602; 701).
304:06	304:22	Argumentative; foundation; lack of personal knowledge; assumes facts not in evidence (Alaska R. Evid. 602).
362:19	363:02	Relevance (Alaska R. Evid. 401).

Lilly also objects to Plaintiff's exhibits for use during the testimony of Joey L. Eski:

Plaintiff's Exhibit	Objection(s)

Plaintiff's Exhibit	Objection(s)
Zyprexa Plaintiff's Exhibit 10097	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal document concerning sales-representive interactions with physicians.
Zyprexa Plaintiff's Exhibit 10096	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit 10122	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)
Zyprexa Plaintiff's Exhibit 10120	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Zyprexa Plaintiff's Exhibit 10121	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Eski Exhibit 6	(Provided without bates number; unable to match to previously identified plaintiff's exhibit) Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Eski Exhibit 7	(Unable to match to previously identified plaintiff's exhibit) Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

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Attorneys for Defendant
Eli Lilly and Company

Dated: March 10, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

STATE OF ALASKA	)	FILED IN OPEN COURT
Plaintiff,	)	Date: 3-10-08
	)	
v.	)	**Case no: 3AN-06-5630CIV**
	)	Clerk:
ELI LILLY AND COMPANY	)	
Defendant	)	

DEFENDANT ELI LILLY AND COMPANY'S SUPPLEMENTAL OBJECTION TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION

Defendant Eli Lilly and Company ("Lilly") objects to the following page and lines of Plaintiff State of Alaska's Trial Deposition Designations for Denice M. Torres:

Start (Page:Line)	End (Page:Line)	Objection
538:19	538:20	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)

Respectfully submitted,

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Attorneys for Defendant
Eli Lilly and Company

Date: March 9, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

FILED IN OPEN COURT
Clerk:
Date: 3-10-08

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-5630 CIV

DEFENDANT ELI LILLY AND COMPANY'S *CORRECTED* IDENTIFICATION OF COUNTER-DESIGNATIONS THAT MUST BE PRESENTED CONTEMPORANEOUSLY WITH THE STATE OF ALASKA'S AFFIRMATIVE DESIGNATIONS

Pursuant to the Court's March 6, 2008 oral order regarding the procedure for presenting videotaped deposition designations to the jury, defendant Eli Lilly and Company ("Lilly") identifies the following counter-designation excerpts from the that must be presented together with the State's affirmative designations to ensure proper context.

1. John Lechleiter

Start (Page:Line)	End (Page:Line)
149:3	149:12
267:12	268:11
277:9	277:17
367:12	368:2

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Attorneys for Defendant
Eli Lilly and Company

Dated: March 9, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

FILED IN OPEN COURT
Date: 3-10-08
Clerk: MH
Case no. 3AN-06-5630CIV

STATE OF ALASKA)
Plaintiff,)
)
v.)
)
ELI LILLY AND COMPANY)
Defendant)

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for **Gary Tollefson, M.D.** The highlighted excerpts are those that must be presented together with the State's affirmative designations to ensure proper context.

Start (Page:Line)	End (Page:Line)
82:6	82:15
96:23	97:13
97:16	97:23
98:2	98:13
109:4	109:18
124:12	124:18
126:10	127:11
142:15	143:9
203:13	203:15
203:18	204:3

208:10	208:23

Lilly objects to the following pages and lines of plaintiff State of Alaska's Trial Deposition Designations for Gary Tollefson, M.D.:

Start (Page:Line)	End (Page:Line)	Objection
51:22 52:3	51:24 52:14	Vague; assumes fact not in evidence (Alaska R. Evid. 403, 611)
91:24 92:7	92:4 92:14	Foundation (Alaska R. Evid. 401)
102:4 102:13	102:6 102:15	Speculation; personal knowledge (Alaska R. Evid. 602)
103:11 103:17	103:14 103:19	Vague; foundation (Alaska R. Evid. 401, 402, 403, 611)
108:22 109:16	109:1	Assumes facts not in evidence; unfair prejudice (Alaska R. Evid. 403, 611, 802)
124:5 124:21	124:9 125:21	Relevance, vague; foundation; personal knowledge; (Alaska R. Evid. 401, 402, 403, 602, 611). Subject to ruling on Motion for Summary Judgment: off label.
134:20 135:1	134:22 135:16	Relevance, vague; foundation; personal knowledge (Alaska R. Evid. 401, 402, 403, 602, 611). Subject to Motion in Limine: price.
205:16 206:4	206:1 206:18	Vague; foundation; speculation; argumentative (Alaska R. Evid. 401, 402, 403, 611)
206:19	208:9	Foundation; misstates evidence; personal knowledge (Alaska R. Evid. 401, 402, 602; 611)

Start (Page:Line)	End (Page:Line)	Objection
209:19	209:22	Vague, misstates evidence; question re-phrased (Alaska R. Evid. 403, 602; 611)

Lilly also objects to Plaintiff's exhibits for use during the testimony of Gary Tollefson, M.D.:

Plaintiff's Exhibit	Objection(s)
Zyprexa MDL Plaintiff's Exhibit No. 6100	Relevance; probative value is outweighed by prejudice, delay and confusion; foundation (Alaska R. Evid. 401, 402, 403, 901). Subject to Motion in Limine: profits and price.

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

Dated: March 9, 2008

LANE POWELL, PC

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Attorneys for Defendant Eli Lilly and Company

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

FILED IN OPEN COURT
Date: 7-10-08
Clerk: MZ4

STATE OF ALASKA, Plaintiff,

v.

ELI LILLY AND COMPANY, Defendant

Case no. 3AN-06-5630CIV

DEFENDANT ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for **Bruce Kinon, M.D**. The highlighted excerpts are those that must be presented together with the State's affirmative designations to ensure proper context.

Start (Page:Line)	End (Page:Line)
52:9	52:16
65:20	66:7
72:16	72:17
73:17	73:18
80:7	80:15
82:4	82:18
92:10	92:15
93:7	93:17
140:15	141:7
236:8	236:20
237:17	237:24

Start (Page:Line)	End (Page:Line)
241:2	241:21
247:10	247:12
263:18	263:22
264:1	264:11
412:14	412:23

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Bruce Kinon:

Start (Page:Line)	End (Page:Line)	Objection
51:11	52:8	Foundation; lack of personal knowledge; authentication. (Alaska R. Evid. 401; 602, 901).
53:3	53:24	Foundation; lack of personal knowledge; authentication. (Alaska R. Evid. 401; 602, 901).
84:9	84:18	Foundation; lack of personal knowledge; authentication. (Alaska R. Evid. 401; 602, 901).
139:4	139:23	Lay opinion as to what was "generally accepted" in the field. (Alaska R. Evid. 701).
235:13	235:24	Vague; foundation (Alaska R. Evid. 401; 602; 901).
244:16	244:22	Probative value is outweighed by the danger of unfair prejudice; calls for a legal conclusion as to "liability"; probative value is outweighed by the danger of unfair prejudice; lay opinion testimony, calls for expert opinion (Alaska R. Evid. 403; 701).
245:6	251:8	Foundation; lack of personal knowledge; authentication. (Alaska R. Evid. 401; 602, 901).
261:12	261:18	Foundation; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403).

Start (Page:Line)	End (Page:Line)	Objection
262:14	266:6	Foundation; probative value is outweighed by the danger of unfair prejudice (Alaska R. Evid. 401; 403).
265:9	265:10	Argumentative.

Lilly also objects to Plaintiff's exhibits for use during the testimony of Bruce Kinon:

Plaintiff's Exhibit	Objection(s)
Zyprexa MDL Plaintiffs' Exhibit No. 1213	Not Relevant (Alaska R. Evid. 401, 402) Hearsay (Alaska R. Evid. 801, 802)
Zyprexa MDL Plaintiffs' Exhibit No. 4517	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901)
Zyprexa MDL Plaintiffs' Exhibit No. 8905	Not Relevant (Alaska R. Evid. 401, 402).
Zyprexa MDL Plaintiffs' Exhibit No. 4532	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: draft, incomplete marketing planning document Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901) Not Authenticated (Alaska R. Evid. 901, 902)
Zyprexa MDL Plaintiffs' Exhibit No. 7668	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Subsequent Remedial Measures (Alaska R. Evid. 407)
Zyprexa MDL Plaintiffs' Exhibit No. 5522	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: market research/marketing planning document Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Hearsay (Alaska R. Evid. 801, 802)

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

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By: _____

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Dated: March 9, 2008

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

FILED IN OPEN COURT
3-10-08
CLERK

STATE OF ALASKA, Plaintiff,

v.

ELI LILLY AND COMPANY, Defendant

Case no. 3AN-06-5630CIV

ELI LILLY AND COMPANY'S DEPOSITION COUNTER-DESIGNATIONS FOR TRIAL AND OBJECTIONS TO PLAINTIFF STATE OF ALASKA'S TRIAL DEPOSITION AND EXHIBIT DESIGNATIONS

Defendant Eli Lilly and Company ("Lilly") counter-designates for trial the following deposition transcript excerpts in response to Plaintiff State of Alaska's Trial Deposition Designations for Michael Bandick:

Start (Page:Line)	End (Page:Line)
165:17	166:3
169:8	169:19
170:6	170:20
202:15	202:19
389:16	389:22
390:1	390:6
400:11	400:18
400:21	401:7
403:21	403:24
404:24	405:7
419:23	420:9

Start (Page:Line)	End (Page:Line)
420:14	420:21
445:24	446:8
446:12	446:13
446:17	446:24
448:21	449:4
449:16	449:24
450:1	450:7
453:18	454:6
504:13	504:15
504:18	504:21
514:22	515:1
515:6	515:12
522:14	523:2

Lilly objects to the following pages and lines of Plaintiff State of Alaska's Trial Deposition Designations for Michael Bandick:

Start (Page:Line)	End (Page:Line)	Objection
130:18	131:6	Vague (Alaska R. Evid. 611)
164:20	165:8	Relevance; Probative value outweighed by danger of unfair prejudice; Compound; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)
169:1	169:7	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)

Start (Page:Line)	End (Page:Line)	Objection
201:24 202:14	202:11 202:14	Foundation; Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403, 602, 701)
373:7	374:4	Hearsay – Admit for Notice (Alaska R. Evid. 802)
376:23	377:9	Hearsay – Admit for Notice (Alaska R. Evid. 802)
378:4	378:19	Hearsay – Admit for Notice (Alaska R. Evid. 802)
379:14	380:5	Hearsay – Admit for Notice (Alaska R. Evid. 802)
398:16	399:5	Hearsay – Admit for Notice (Alaska R. Evid. 802)
408:8	409:3	Hearsay – Admit for Notice (Alaska R. Evid. 802)
411:8	412:2	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions; (Alaska R. Evid. 401, 402, 403)
415:14	416:13	Hearsay – Admit for Notice; Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403, 802)
418:21	419:17	Hearsay – Admit for Notice; Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions; (Alaska R. Evid. 401, 402, 403, 802)
419:18	419:22	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403)
421:17	422:1	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403)
435:2	435:4	Relevance; Probative value outweighed by danger of unfair prejudice; Foundation; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403, 602, 701)

Start (Page:Line)	End (Page:Line)	Objection
435:10	435:10	Relevance; Probative value outweighed by danger of unfair prejudice; Foundation; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403, 602, 701)
435:15	435:16	Commentary by Counsel; Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403, 611)
435:17	435:18	Relevance; Probative value outweighed by unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
436:15	435:17	Relevance; Probative value outweighed by unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
438:23	439:5	Relevance; Probative value outweighed by unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
443:12	444:4	Relevance; Probative value outweighed by unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
450:22	451:4	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403)
451:7	451:10	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403)
451:13	451:15	Relevance; Probative value outweighed by danger of unfair prejudice; Motion in Limine – Foreign Regulatory Actions (Alaska R. Evid. 401, 402, 403)
452:21	452:22	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
452:23	453:8	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
453:9	453:14	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)

Start (Page:Line)	End (Page:Line)	Objection
457:24	458:7	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
461:17	462:1	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
462:3	462:19	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
462:20	462:23	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
463:12	463:16	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
464:6	464:16	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
470:10	471:16	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
472:10	472:23	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
476:5	476:15	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)
478:8	478:19	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)
479:2	479:5	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)

Start (Page:Line)	End (Page:Line)	Objection
479:24	480:6	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing; Motion in Limine – profit/net worth/price (Alaska R. Evid. 401, 402, 403)
480:9	481:1	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing; Motion in Limine – profit/net worth/price (Alaska R. Evid. 401, 402, 403)
489:3	489:14	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
491:10	491:19	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
491:24	492:11	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
493:3	493:12	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)
496:9	497:3	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
499:14	499:18	Foundation; Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 701)
504:6	504:12	Foundation; Hearsay – Admit for Notice (Alaska R. Evid. 602, 701, 802)
506:1	506:12	Relevance; Probative value outweighed by danger of unfair prejudice (Alaska R. Evid. 401, 402, 403)
510:11	510:18	Relevance; Probative value outweighed by danger of unfair prejudice; Misstates Evidence (Alaska R. Evid. 401, 402, 403, 611)

Start (Page:Line)	End (Page:Line)	Objection
511:3	511:11	Relevance; Probative value outweighed by danger of unfair prejudice; Assumes facts not in evidence (Alaska R. Evid. 401, 402, 403, 611)
516:2	516:	Relevance; Probative value outweighed by danger of unfair prejudice; Foundation; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403, 602, 611, 701)
516:6	516:9	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label marketing (Alaska R. Evid. 401, 402, 403)
516:24	517:13	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)
519:17	519:19	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)
521:13	521:15	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)
521:21	522:9	Relevance; Probative value outweighed by danger of unfair prejudice; Motion for Summary Judgment – Off-label (Alaska R. Evid. 401, 402, 403)

Lilly also objects to Plaintiff's exhibits for use during the testimony of Michael Bandick:

Plaintiff's Exhibit	Objection(s)
Zyprexa MDL Plaintiffs' Exhibit No 01926 (Bandick Exh. 17)	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Foundation (Alaska R. Evid. 901)

Plaintiff's Exhibit	Objection(s)
Zyprexa MDL Plaintiffs' Exhibit No 09807 (Bandick Exh. 18)	Not Relevant (Alaska R. Evid. 401, 402) to Labeling Claims: Internal document discussing upcoming programs related to Zyprexa's efficacy Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403) Not a Complete Document
Zyprexa MDL Plaintiffs' Exhibit No 04104 (Bandick Exh. 19)	Not Relevant (Alaska R. Evid. 401, 402) Prejudicial, Confusing, Waste of Time (Alaska R. Evid. 403)

Lilly reserves the right to object to these exhibits, and any others that may be introduced by Plaintiff, under the Alaska Rules of Evidence or any other applicable rule of law, based on this Court's rulings or the purposes for which Plaintiff seeks to use the exhibits at trial.

Respectfully submitted,

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Dated: March 8, 2008