EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE:

SEROQUEL PRODUCTS LIABILTY LITIGATION

CASE NO. 6:06-MD-01769-ACC-DAB

MDL DOCKET NO. 1769

May 28, 2008

Confidential Videotaped Oral Deposition of MARTIN BRECHER, M.D., D.M.Sc., MBA, held in the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, Philadelphia, Pennsylvania beginning at approximately 9:00 a.m., before Ann V. Kaufmann, a Registered Professional Reporter, Certified Realtime Reporter, Approved Reporter of the U.S. District Court, and a Notary Public.

GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
Philadelphia, Pennsylvania 19103
877.370.3377

Page 206

merged entity for six to eight months when I joined.
Q. And you mentioned that Wayne Geller came over from Janssen a little bit after you; correct?
A. That's right.
Q. Was there any connection between you going to AstraZeneca and Dr. Geller going to AstraZeneca or was it coincidence?
A. I had given Wayne Geller's name to the director of safety as someone who was a good worker.
Q. Okay. So was he recruited to work at AstraZeneca because of your recommendation?
A. Possibly. I remember a conversation with Vikram Dev. I don't -- and I don't think I would have offered. I think, my best recollection, he would have asked, do you know. So it would have been along the lines, do you know any good safety people.
And assuming that was the

Page 207

question, I would have said, Yeah, Wayne Geller.
Q. Okay. You trusted his judgment?
A. Yes, I did.
Q. He wasn't fired from Janssen, was he?
A. No.
Q. When you started in December of 1999, did you take some period of time to educate yourself about Seroquel and what had happened previously?
A. I tried.
Q. Did you take a look at what studies were out there that had been done that were successful studies?
A. I remember reviewing the submissions to the FDA and the European countries.
Q. Okay. Did you review the studies that were failed studies?
A. I was aware of them.
Q. Okay. Did you review any

Page 208

cursed studies?
A. Sorry? Any?
Q. Cursed studies.
MR. McCONNELL: Objection to form.
A. I don't know any cursed studies.
Q. Okay. Do you know any studies that you reviewed where smoke and mirrors were used to present them?
MR. McCONNELL: Objection to form.
A. I don't -- I heard that expression in one context, I don't remember which, but that -- but certainly in my review of the documents when I joined the company, it did not include a reference to smoke and mirrors.
Q. Do you know about study 15?
A. Pardon?
Q. Do you know about study 15?
A. Yes.
Q. What was study 15?

Page 209

A. Study 15 was a long-term study comparing three doses of Seroquel to haloperidol for the prevention of relapse in schizophrenia.
Q. Okay. And when did you first become familiar with study 15?
A. I must have read about it in reviewing the submission documents to the FDA and the EEU because it was in the package.
Q. Okay. Did you ever review the weight gain data from study 15?
A. I can't say. I don't believe the weight gain -- I don't think there was a lot of weight gain data from study 15 because, as I understand now, only 28 patients actually completed a year of treatment.
Q. I'm going to show you what was previously marked as Schwartz Exhibit No. 41 and now is marked as Brecher Exhibit 3.
(Below-described document marked Brecher Exhibit 3.)

Page 210

BY MR. BLIZZARD:
Q. Do you see that this is an e-mail or an internal memorandum that's dated February 12, 1997?
MR. McCONNELL: Objection, foundation.
A. I'm sorry, your question again, please?
Q. Do you see this is an e-mail dated February 12, 1997? Actually, strike that.
Do you see this as an internal memorandum dated February 12, 1997?
A. Yes.
Q. It says here that it is from Richard Lawrence. Do you know who Richard Lawrence is?
A. I never met him, and his name has come up, but he was way before my time.
Q. Okay. Well, this looks like it's about almost three years before your time.

Page 211

A. That's right.
Q. It's regarding a U.S./Canada investigator meeting and study 15. Do you know anything about the U.S./Canada investigator meeting?
A. No.
Q. Did you review any of the that material when you came on board at AstraZeneca?
A. I don't recall ever seeing material specifically relating to the U.S./Canada investigator meeting.
Q. Do you see that this distribution of this e-mail went to Don Stribling?
A. Yes.
Q. Do you know who Don Stribling is?
A. I knew him when he worked in Japan. He once came to a meeting that we had with our Japanese collaborators. And he subsequently was the head of regulatory affairs.
Q. So he was pretty high up

Page 212

the corporate totem pole, wasn't he?
MR. McCONNELL: Objection to form.
A. I don't know what position he had in 1997.
Q. Well, when you knew him, he was fairly high up the corporate totem pole, wasn't he?
A. Yes.
MR. McCONNELL: Objection to form.
A. Yes. He was the --
Q. Let me try corporate ladder.
A. In his role as the head of regulatory affairs for the company, that's a responsible and senior position within the clinical development organization.
Q. Okay. Now, do you see in this -- first of all, that this was CC'd to a Lisa Arvanitis?
A. Yes.
Q. Do you see that? Do you

Page 213

know who Lisa Arvanitis is?
A. Lisa Arvanitis was the medical leader for Seroquel probably at the time of the writing of this e-mail. She had been gone from the company for some time when I arrived.
Q. So was she in your job as of the time of this e-mail?
A. To the extent -- I think she was the medical leader for Seroquel at the time. I think that's a fair guess on my part. Obviously I wasn't there, but I was aware that Lisa Arvanitis was leading the quetiapine effort, and so I think that she had a job roughly analogous to mine.
Q. Okay. Do you see where it says in the e-mail here that: "I am not 100% comfortable with this data being made publicly available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke and mirrors' job!" Do you see that?

Page 330

Q. Okay. So he wasn't happy, was he?
MR. McCONNELL: Objection to form.
A. Well, I think his e-mail speaks for itself. I think he was -- expressed concern, I would say. As he said he questioned the rationale for distributing it to the marketing people for, quote, informal review.
Q. And your response is to say I don't see a problem with marketing knowing where we're going; correct?
A. Yes.
Q. Were you trying to lobby the marketing people to support you in the decision to keep "limited" in the core data sheet?
A. I don't think that's where that e-mail is going at all. I think all I'm saying there is I didn't see a problem with marketing knowing what our position was. And that's what I said before, before you showed me this

Page 331

document, I said I didn't see a problem with the marketing people seeing the discussion documents prior to the meeting.
Q. Well, do you see a problem with soliciting their comments to the discussion document?
A. I think that this -- it would be inappropriate if a drug safety person would ask for marketing comments, and I don't think that ever happened. This --
Q. Well, you were -- I'm sorry. Go ahead.
A. This discussion document, as I said, immediately after you showed it to me, is unusual in that it's being produced by a member of the Seroquel team. And I have offered a possible explanation why. And clearly the writer wanted to get marketing's view on the content.
Q. Well, did you -- you were on the e-mail that was sent by Emma

Page 332

Witch soliciting comments of the marketing folks and others; correct?
A. Yes.
Q. Okay. Did you say "Whoa, Emma, don't go submitting this for comment to the marketing people"?
A. I did not.
Q. Did you tell her in any way that she should hold off sending this to marketing for comment because it was inappropriate?
A. I did not.
Q. Now, the discussion -- the SERM meeting that occurred in June of 2000, did you attend that in person?
A. The June 2000 SERM, yes.
Q. Where did it occur?
A. It must have occurred in Wilmington.
Q. Okay. But you specifically have a memory of being there for the meeting?
A. Not a strong one. You know, it's clear from the earlier

Page 333

document that you showed me that I was there. And I don't have a vivid recollection of the meeting, but I do have a recollection of being there.
(Below-described document marked Brecher Exhibit 18.)
BY MR. BLIZZARD:
Q. I have handed you Exhibit No. 18, and it has a number of handwritten notes on it. Are those -- is that your handwriting?
A. Yes.
(Below-described document marked Brecher Exhibit 19.)
BY MR. BLIZZARD:
Q. Before I get to what that says, let me mark as Exhibit 19 to your deposition -- are these draft minutes of a meeting in July of 2000?
A. This is -- are you talking about 19?
Q. Yes.
A. They are draft minutes.
Q. Okay. Is that a -- are the

Page 334

minutes prepared by Emma Witch?
A. Yes.
Q. And is Emma Witch shown as an attendee at this meeting?
A. Yes.
Q. Are these other people involved in this meeting, SERM members?
A. Wayne is a SERM member. I don't know whether or not Paul Duffy would have participated in SERM. He was a -- he is a toxicologist and was involved in the preclinical work with Seroquel.
Q. Okay. So these meeting minutes do not reflect the minutes of SERM, do they?
A. No.
Q. Okay. This is a separate meeting that relates to the preparation of the FDA response to the -- on the diabetes issue?
A. Response to the FDA, right.
Q. Okay. Well, we will get to that in a minute then.

Page 335

Take a look at the discussion document for Seroquel. These handwritten notes that were made on this document, Exhibit 18, were -- when were those made?
A. You know, I'm not sure what document this is. I can guess, but perhaps you could tell me.
Q. Well, as the title says, "Diabetes Mellitis, Diabetic Ketoacidosis, Non-Ketotic Hyperosmolar Coma, and Hyperglycaemia." And it is a discussion document regarding Seroquel; correct?
A. Yes.
Q. And it's prepared by Wayne Geller; correct?
A. Yes.
Q. I believe that this document was prepared in advance of the SERM meeting and was discussed at the SERM meeting. That's my belief. Do you recall that?
A. Are you referring to the

Page 336

June 2000 SERM meeting?
Q. Yes.
A. That's what I think as well. I just don't see a date on this document. But looking at the cover and just quickly glancing through the interior, I think this is the discussion document or a draft of it prepared for this -- as a discussion document for the June 2000 SERM.
Q. Okay. What I would like for you to do for me is to read your handwriting. Sometimes I can read it; sometimes I can't. And I want to make sure we have an accurate rendition of your handwritten notes from this meeting.
First, on the first page at the top, what does that say?
A. Where it says 1)?
Q. Yes.
A. That's angioedema.
Q. What have you crossed through at 2)?

Page 337

A. I think it's -- "limited" is crossed out.
Q. Okay. What's No. 3)?
A. It looks like "hyperglycemia" and "diabetes."
Q. Okay. Do you know why "limited" is crossed out in No. 2)?
A. I can't recall.
Q. Is it possible it relates to the weight gain issue?
A. I have no recollection what I was thinking when I wrote these notes.
Q. Okay. So all you can do at this point is read them to me; correct?
A. That's right.
Q. Okay. What does the note on the right-hand margin say that says "OS"?
A. I think that's "US."
Q. Okay.
A. That makes more sense to me. And I think to the right of that it says "involuntary movements."
Q. Okay. And then it says

Page 338

"CDS"?
A. "Discussion."
Q. What does "CDS" stand for?
A. Core data sheet.
Q. Okay. Then on the first page out on the left-hand side under the heading "All Findings Presented in This Document Are to Be Subject to Further Consideration at SERM," does it say "6 cases"?
A. Yes.
Q. What does it say beneath that?
A. Below that?
Q. Yes.
A. I can't make out the first word. And then it says "time to onset new diabetes 0.5 months." Oh, "Median." "Median time to new onset diabetes 0.5 months."
Q. Okay. And then in the middle of that, just to the right of that note, what does that say? It says "Wayne" at the top and that is

Page 339

underlined?
A. Yeah. "Page 8, 2240 base rates." And then it says something that doesn't make sense to me, gdv or gov. I don't know what that means --
Q. Okay.
A. -- with a question mark.
Q. And then over on the right-hand margin, what does that say?
A. "Emma, MJ - dose response." MJ would be Martin Jones. And then below that --
Q. Is Emma Emma Witch?
A. Probably. I think that we also had an Emma Westhead, but -- so I don't know which Emma this is referring to.
Q. Okay.
A. And then "Geert - 6 cases, conclusions."
Q. So what does "Geert" refer to?
A. Geert would refer to Geert deVriese, who was the global product

Page 340

director.
Q. Okay. Do you know what the "6 cases" references?
A. You know, I don't know if it's the same six cases referred to on the left.
Q. Okay. And what does it say beneath that? There's an arrow pointing down.
A. I can't quite read the first word. And then the second word is "CDS in line with US PI?" Oh, "bring." I think it says "Bring CDS in line with US PI?"
Q. Okay. So there was some question about whether -- or somebody was raising the question of whether the CDS should be brought in line with the U.S. package insert; correct?
A. I don't know if that was my question or someone else's question.
Q. Okay. And then underneath that what does it say?
A. "Conclusion: Keep issue

Page 341

under review."
Q. And then under -- on the bottom of the page what does it say?
A. "Of 10 cases from clinical trials," arrow "each source?"
Q. Second page up at the top?
A. "RIS labelled for diabetes, DKA."
Q. And that's diabetic ketoacidosis?
A. That's what the DKA would stand for.
Q. Okay. Under -- right next to the "Introduction" section, what does that say?
A. "Criteria used in this assessment." It looks like "FBS," which would be fasting blood sugar, "greater than 126 2 hour post, 75 grams greater than 200."
Q. Okay. Can you interpret that note?
A. Yeah. I think that -- what I think it means, without confirming it

Page 342

from the text, is that the criteria used in the assessment was either a fasting blood sugar greater than 126 or a two-hour glucose value following 75 grams of glucose -- in other words, a glucose tolerance test -- with a value greater than 200.

Q. Okay. If you go turn the page to the next note that we have. It looks like it's over on Page 6.

Okay. What does that say?

A. On the top?

Q. Yes.

A. "No attribution." And then to the right of that it says "16, SPONT," probably referring to -- standing for spontaneous; "10 clinical" -- "10 CLIN trials," referring to ten clinical trials; and "2 lit reports." So what this is referring to is 16 spontaneous reported adverse events, ten clinical trial reports, and two reports in the literature, and they are pointing to no attribution.

Page 343

Q. Okay. Under "CLINTRACE Database (In House Safety Data)," there's a note that says "9 cases"?

A. "9 cases new onset, 4 DKA, 2 new onset, 2 worsening." And then below that is "NKHOC-0." And NKHOC would stand for nonketotic hyperosmolar coma.

Q. And then you've got a star next to this particular description of this event of a 43-year-old male with a history of mental illness who developed new onset diabetes. Do you see that?

A. Yes.

Q. Do you know why it was starred?

A. No. And I'm just curious whether I starred other cases.

Q. I think you did. Look over at the next page. Do you see that?

A. Yes.

Q. And this particular case is a diabetes case with weight gain; correct?

Page 344

A. Yes.

Q. And you starred that?

A. Yes.

Q. And do you know why you starred it?

A. No.

Q. I assume that you starred things that were important to you; is that correct?

A. Presumably. I certainly don't -- I'd have to pore over this document to see what were the common features of the starred cases. I don't recall that now.

Q. Okay. Look over at the next page. Do you see that there's a starred event on this page as well?

A. Yes.

Q. And the next page, "Loss of Diabetic Control, Tooth Pain, Insomnia"?

A. Yes.

Q. Do you see that that event is starred?

A. Yes.

Page 345

Q. If you look over at Page 11 --

A. Yes.

Q. -- do you see a star there?

A. Yes.

Q. Do you know anything about why that star is there?

A. I don't recall the principle leading to the starring of cases.

Q. Okay. If you look over on Page 15, there's a star next to another case of hyperglycemia?

A. Yes.

Q. Okay. On Page 16 --

A. Yes.

Q. -- could you read that handwriting for us?

A. It says "Median?" Below that "time to onset." There's text that reads "The former patient reportedly lost 30 pounds," and then there's a line from that going to a handwritten note saying "Type 1 - pattern."

Page 346

Below that it says "2 cases of DKA - weight gain associated." And then below that there's a -- it says "criteria greater than 110" -- it looks like greater than 110 pounds, but I'm not sure what that means.

Q. This relates to reports of hyperglycemia.

A. Oh, I'm sorry. I can -- this one on Page 16 on the bottom that the arrow says "criteria greater than 110 fbs," it's for fasting blood sugar.

Q. Okay. And the last page, Page 17, what does the note at the top say?

A. "Note, Wayne impressed by 2 physicians noting diabetes onset with dose increase."

Q. Okay. So does that note reflect that Dr. Geller was impressed with the dose-response?

A. I don't think that represents a dose-response so much as exactly what it says, that two

Page 347

physicians noted diabetes onset following a dose increase. I don't think that indicates a dose-response.

Q. It indicates that the diabetes onset occurred after the dose was increased; right?

A. That's right. It is different from a dose-response.

Q. Okay. The next item in the middle of the page says what?

A. "Usually no baseline blood glucose. 7 taking drugs associated with diabetes. Some reports - scant information" -- "scant inf" meaning scant information -- "no positive de," which means no positive dechallenge or rechallenge.

Q. What's the next note say?

A. "Seroquel may cause impaired glucose regulation in some individuals. No signal of Type 1 ie no negative impact on insulin production."

Q. Okay.

A. Well, that -- "Discussion:

Page 348

No positive re,de challenge. No baseline CHO," referring to no baseline glucose. "Low number of cases for a common condition."

That's actually an important point because diabetes is very common. And my comment here, I think, reflects the view that this is a small number of cases for an illness as common as diabetes, given the exposure that we had by 2000.

"No mechanism of effect."

On the right it says "For my part only 4 cases of DKA speaks to absence of diabetogenic effect."

Below that: "Other patients: 1., will get long term data from olanz trial. 2., will" --

Q. What's "olanz trial"?

A. That would refer to olanzapine, but I'm not -- I don't know what olanzapine trial I was referring to, unless -- probably given that it was 2000, it could either have referred to

Page 349

the long-term trials that Lilly conducted or to the long-term trial that Janssen conducted.

And then below that, "will" --

Q. "Know more?"

A. "Will" --

Q. -- "know more after response to FDA concludes."

A. I think so.

Q. I may have stared at it longer than you, so whatever you need to do to confirm it.

A. Yeah, I think that's right.

Q. Okay. So in looking at this, you made the -- when you started talking about this discussion down here below the line, you may have said, well, here are a couple of important points.

And then there's these comments above the line that you read without making a comment about it.

Is it your memory, from looking at this now, that the points

Page 374

metabolism disorders. Dear Wayne, thank you for yoy fax" -- I guess that is supposed to be "your fax" -- "which I sent to the local authorities."
A. Yes.
Q. And when he actually faxed it to her, if you look at the -- Geller's communication on Page 2, do you see where he says: "Hi, Dorothee. The document is 11 pages. I can fax a signed copy to you or mail one. If you prefer the latter, please send me your address and I will send it out at once." Do you see that?
A. Yes.
Q. And then she sends back and says thanks for the fax; correct?
A. Yes.
Q. Okay. So, again, Dr. Geller is offering to sign this document before faxing it; right?
MR. McCONNELL: Objection to form.
BY MR. BLIZZARD:

Page 375

Q. Let me rephrase that. Dr. Geller is offering to sign the document that was attached; right?
MR. McCONNELL: Same objection.
A. Wayne is offering to sign the document.
Q. Right. and would that indicate to you, as a reasonable person who conducts business in the way that people typically conduct business, that that is not a draft?
MR. McCONNELL: Objection to form.
A. I was not involved with this correspondence between the Dutch and Wayne. And if Wayne was mistaken about his document, I don't think it matters whether or not he signed it or not. I don't know whether he knew it was a draft or not. And I can't comment. I just don't know his procedures well enough to comment on what's the implication of signing the

Page 376

document.
Q. What is the implication when you sign a document?
MR. McCONNELL: Objection to form.
A. When I sign a document, I usually -- it means that I wrote this document.
Q. It means you are taking responsibility for what's in the document; right?
A. Usually.
Q. And that's what it would mean here, wouldn't it, that he was taking responsibility as a global drug safety physician for the statements made in the document?
A. I want to say --
MR. McCONNELL: Excuse me. Objection to form.
A. I want to say two things: I don't know what Wayne -- was going through Wayne's mind and I don't want to comment on what it meant that he signed

Page 377

this document.
Moreover, if we get back to the document, I just don't feel that the arguments and the data that are in the document, particularly in the executive summary, are supporting the conclusions. So -- but, regardless, I don't think that -- I just can't comment -- I don't know whether this was the document that was mistakenly sent and I don't know --
Q. How do you --
A. I can't comment on the interaction between Wayne and the Dutch authorities because I was not involved in that transaction.
Q. Well, the e-mail that we just reviewed clearly indicates that the Dutch authorities were asking for an analysis of glucose metabolism and Seroquel; correct?
MR. McCONNELL: Objection to form.
A. The Dutch wanted a review

Page 378

of cases or an analysis of cases of diabetes and glucose metabolism that may or may not have been related to Seroquel.

Q. Right. And people within the marketing company over in the Netherlands asked Wayne Geller to submit a paper, and he offered to sign and faxed this safety position paper to them; correct?

MR. McCONNELL: Objection to form.

A. Wayne attempted to be responsive to a request and offered to sign a document.

Q. Now, the Dutch authorities weren't just acting as a single country in Europe at the time with respect to Seroquel, were they?

A. The Dutch was a reference member state.

Q. And the reference member state takes the lead for the entire European Union with respect to a

Page 379

particular drug that they are the reference member state for; right?

A. Right, for those states participating in the process.

Q. Okay. Do you know how many states in the European Union were participating in the process at the time in 2000 when this paper was sent to the Dutch authorities?

A. Well, account -- you know, there were new countries that joined the European Union over time, so I don't recall how many were there in 2000.

What I do know is that France was not a part of it and we had a separate registration procedure in England and Italy. So that the reference member state would have -- or that role as reference member state would have applied to the other Western European countries.

Q. Okay. Now, this document that we just read the conclusion of that was submitted to the Dutch, assuming it

Page 380

was the one that was submitted to the Dutch, that contained markedly different conclusions than the one that was given to the FDA, didn't it?

A. Well, I don't think I've looked at the FDA position paper today. And I think the position stated here is at variance with the FDA position paper.

Q. Okay. Well, we can look at the FDA position paper, and we will probably do that tomorrow. But I mean, without reading it, you know that the company did not write a paper to the FDA saying that there's reasonable evidence to -- that Seroquel can cause diabetes or hyperglycemia in certain individuals?

A. That's right.

Q. Right. In fact, you never sent this safety position paper of Dr. Geller to the FDA, did you?

MR. McCONNELL: Objection to form.

A. I don't think this safety position paper was sent to the FDA.

Page 381

Q. Right. Even today FDA doesn't have this safety position paper, does it?

A. And I don't think that this represents the view of AstraZeneca or the drug safety department at that time or, for that matter, now.

MR. BLIZZARD: Objection, nonresponsive.

BY MR. BLIZZARD:

Q. Now, let me ask you something that's really on a different subject now, and I think with that I'd like to maybe conclude for the day and we will save some additional time for tomorrow.

After the SERM meeting in 2007 there was a discussion document that was actually presented at the SERM meeting. And I have a copy of it. I'm not going to attach it today, but I think it's about 500 pages long. Do you recall that document?

A. It was a long discussion

Page 943

Q. Do marketing and commercial people at AstraZeneca have any role whatsoever in the SERM process?
A. They do not.
Q. Doctor, as part of the preparation for SERM, is safety data review and analyzed?
A. Yes.
Q. Could you explain to the jury what type of data is reviewed and analyzed as part of the SERM process?
A. The SERM reviews should include, and typically do include, the data from clinical trials, postmarketing surveillance and literature reviews, and sometimes the preclinical data as well.
Q. Is material from the global drug safety database reviewed as part of the SERM process?
A. Yes.
Q. Doctor, did AstraZeneca create the SERM process specifically to examine the glucose issue relating to Seroquel?

Page 944

A. Yes.
Q. They did that in the spring of 2000?
A. The SERM meeting for glucose was in June of 2000.
Q. Okay. Does AstraZeneca also use the SERM process at times for other drugs involving other issues?
A. The SERM process is used for all drugs, all marketed drugs at AstraZeneca.
Q. Does AstraZeneca convene SERMs only to respond to FDA requests?
A. No.
Q. In your experience, is the SERM process an effective tool to monitor the safety of the drug?
A. Yes.
Q. Why?
A. The SERM -- a SERM meeting is called whenever a question or an issue is raised around the safety of marketed medicine. So that could happen whether concerns are raised from within the

Page 945

company or in response to a request from a regulatory agency.
Q. Does the SERM process play a role in determining whether the core data sheet should be changed?
A. Yes.
Q. What is the core data sheet?
A. The core data sheet is the best description of the safety profile of the drug and represents the core items that have to be included in every product label. So it's that -- those facts about the safety of the drug that must be included in every label around the world.
Q. When AstraZeneca does convene a SERM, does the SERM always conclude that the core data sheet should be changed?
A. No, it doesn't.
Q. Does the SERM always conclude that the core data sheet should not be changed?
A. No, it doesn't.
Q. What explains the difference

Page 946

in those different kinds of decisions?
A. The critical point is whether the label accurately reflects the safety profile of the drug as we understand it.
Q. Does the SERM decision as to whether or not to change the core data sheet depend in any way upon the available data?
A. The SERM decision to change the core data sheet depends entirely on the data.
Q. Is the SERM process the only way that AstraZeneca monitors the safety of Seroquel?
A. No.
Q. What other procedures are in place at AstraZeneca to monitor the safety of Seroquel?
A. The drug safety department is monitoring safety on a continuous basis. And so are the clinical trials people. Clinical trials people are monitoring safety as the clinical trials

Page 947

are ongoing.
Q. Does anyone or any department at AstraZeneca monitor adverse events?
A. Primarily drug safety and also the clinical group.
Q. Does AstraZeneca submit periodic safety updates to the FDA?
A. Yes.
Q. In your experience, did AstraZeneca closely monitor the safety of Seroquel?
A. Yes.
Q. Now, you've discussed the SERM process generally. Are there documents that are associated with the SERM process?
A. Yes. Prior to a SERM meeting there's a discussion document. Following the SERM meeting there is either a position paper or justification document that's prepared.
Q. What's the purpose of a discussion document for SERM?

Page 948

A. A discussion document is written so as to inform the discussions at SERM of all the relevant facts.
Q. What's the purpose of a SERM position paper?
A. A SERM position paper is that -- is a paper that is written after a SERM meeting when the core data sheet is not changed on a particular issue. And it reflects the reasoning as to why the core data sheet is not changed on that point.
Q. Now, we talked about the FDA request in May of 2000 regarding glucose data. Did you participate in a SERM in 2000 regarding glucose issues?
A. Yes.
Q. Was there, in fact, a discussion at AstraZeneca at the SERM regarding glucose data?
A. Yes.
Q. What did that SERM conclude regarding whether there was reasonable evidence of an association between

Page 949

Seroquel and hyperglycemia or diabetes?
A. SERM decided to keep those issues under review, but not to change the core data sheet.
Q. What did SERM conclude as to whether there was a causal link between Seroquel and hyperglycemia or diabetes?
A. SERM did not conclude that there was a causal link between Seroquel and hyperglycemia or diabetes.
Q. What did SERM conclude in 2000 as to whether the data demonstrated reasonable evidence of an association between Seroquel and hyperglycemia or diabetes?
A. SERM concluded that the data did not show a reasonable evidence of an association.
Q. I want you to take a look at a document that the plaintiffs' lawyers put in front of you. It's Exhibit 18. Could we get a look at that?
Doctor, first of all, do you remember taking a look at Exhibit 18, I

Page 950

don't know if it was yesterday or the day -- I think it was the day before yesterday?
A. Yes, I remember.
Q. Could you turn to the last page, please?
A. Yes.
Q. Do you see handwritten notes on that page?
A. Yes.
Q. And that's your handwriting. Is that right?
A. Yes.
Q. I want to direct your attention to the handwritten notes that are underneath the typed section of the page. Do you see what I'm talking about?
A. Yes.
Q. All right. Do you recall testifying on Wednesday that those notes were your reflections on reading the document?
A. Yes.
Q. I want to get you to focus

Page 1015

questions now about another trial, it's one that you've been asked some questions about. I want to give you an opportunity to describe it to the jury. That's trial 125. Were you involved with trial 125?

A. Yes.

Q. Could you explain to the jury what trial 125 is?

A. Trial 125 was an effort by AstraZeneca to understand the effects of Seroquel on glucose metabolism. And to do that we used a more sensitive assay even -- than even the fasting glucose. We used the glucose tolerance test. That's very important because the glucose tolerance test becomes abnormal earlier in the course of diabetes than the fasting blood sugar so it was a sensitive test for the emergence of diabetes. We --

Q. Would it be -- I'm sorry, keep going.

A. We measured the area under the curve for the two hours of the

Page 1016

glucose tolerance test, and that, too, is a sensitive measure of whether there's an effect of a drug on glucose regulation. That was -- that's one important point.

The second important point was that we hospitalize the patients overnight both at baseline at week 12 and at week 24. And, therefore, we could be sure or as sure as one could reasonable want that the patients had not eaten prior to the exam both at baseline and at week 24.

Third, we were able to find patients who had not been previously exposed to atypical antipsychotics, so we were measuring -- we were studying relatively naive patients, and so we were able to look at results independent of what the patients had been on before. And lastly, the study was a long study, it was 24 weeks, and so we were able to have a good assessment of what the prolonged effect of treatment was on patients' glucose metabolism.

Page 1017

Q. Would it be absolutely accurate to describe trial 125 as a diabetes study?

A. No, it was not a diabetes study. It was an attempt to look at the effects of Seroquel on glucose metabolism measured by the two-hour glucose tolerance test.

Q. I just asked you about whether you can call 125 a diabetes study. Are there any ethical constraints to conducting a study that a scientist would actually be able to call a diabetes study?

A. I think it will depend on the design. There are a lot of different design possibilities, and one -- it would depend -- you know, ethical issues in the study would depend on what was actually being done. One point about this study was that every patient received active medication. We could not use a placebo in this trial because it would have been unethical to deprive patients of

Page 1018

medication for 24 weeks.

Q. Did the FDA or any other government body require AstraZeneca to conduct trial 125?

A. This was done on our initiative.

Q. When did AstraZeneca decide to start designing and planning trial 125?

A. The decision to conduct that trial was made in November 2002.

Q. Why then?

A. That was shortly after we had received a strong label change in Japan and -- requiring us to provide warnings and I believe a contraindication for the use of Seroquel in patients with diabetes. And we recognized that we did not have sufficient data to address concerns that other regulatory agencies might have, and, therefore, we wanted to collect data that could establish, as best we could, the fact that Seroquel did not cause diabetes or it is not

Page 1019

associated with glucose metabolism. And conversely, if Seroquel was associated with disorders of glucose metabolism, we wanted to know and we wanted to have the data in which to -- to be sure that that was the case so we could write the label accordingly.

Q. Why did AstraZeneca include Risperdal in trial 125?

A. We wanted to compare Seroquel to the two other comparators -- to two competitors on the market. We wanted to make sure that everybody got medication. The study was, therefore, able to compare all three drugs for their effects on glucose metabolism. And the study was able to look at the effects on each drug relative to the others as well as the change in each drug compared to baseline.

Q. Why didn't AstraZeneca start planning trial 125 prior to the year 2002?

A. We -- prior to the Japanese

Page 1020

action, we thought that our -- that the data that we had gathered, particularly the summary prepared for the FDA in August of 2000, had established that Seroquel was not associated with diabetes or abnormalities in glucose metabolism.

The Japanese regulatory action made it clear that our data was not persuasive, at least to them, and so we wanted to do two things as I just said, gather data that would allow us to persuade another regulatory agency that might have had a concern; or conversely, if there was than effect of Seroquel on glucose metabolism, we wanted to show and demonstrate it to ourselves.

Q. Prior to the planning of trial 125, in your mind, had the preclinical and clinical studies that supported the FDA initial approval of Seroquel revealed any evidence that Seroquel could cause glucose dysregulation?

A. The evidence that we had at

Page 1021

that time did not show -- did not provide any evidence that Seroquel caused diabetes or abnormalities in glucose regulation.

Q. Prior to the planning of trial 125, did the postmarketing surveillance data reveal evidence of a causal link between Seroquel and diabetes or hyperglycemia?

MR. PIRTLE: Leading.

THE WITNESS: The postmarketing data did not provide data showing a causal link between Seroquel and diabetes.

BY MR. McCONNELL:

Q. At the time that you started planning trial 125 in the fall of 2002, were you aware of any trial like it that any company had ever done?

A. I was not aware of any such trial. I thought this was innovative on our part.

Q. And in terms of numbers of patients, was trial 125 a large clinical

Page 1022

trial?

A. Yes. We enrolled 500 patients, a little over 500 patients, and that's a moderate to large size trial, especially for one that's going for 24 weeks.

Q. Did AstraZeneca consult with outside experts on the design of trial 125?

A. I believe so.

Q. Who did you consult with?

A. I'm not sure. I don't recall precisely who we consulted with. Probably -- I think we consulted with Woolf and Goldstein. I don't recall for sure. Possibly consulted with John Newcomer. Again, I don't recall for sure.

Q. Does it take a long time to get a trial --

A. Let me finish.

Q. I'm sorry, go ahead.

A. We probably also consulted with endocrinologists within the company.

Page 1031

A. That result is an important one. The primary result of the trial as stated in the protocol was the area under the curve from zero to two hours of the glucose -- of the glucose values following the ingestion of 75 grams of glucose. And what you can see in Table S4 is that the change from baseline for Seroquel was not statistically significant at week 24 compared to baseline, while the change from baseline from both olanzapine and risperidone was statistically significant.

So in terms of the area under the curve of the glucose tolerance test, both olanzapine and risperidone showed a statistically significant worsening, whereas quetiapine did not.

Also in Table S5 when you compare the change from baseline in the area under the curve, the difference between quetiapine and olanzapine was statistically significant, obviously olanzapine was worse, and the

Page 1032

olanzapine-quetiapine difference was statistically significant in favor of quetiapine. The difference between quetiapine and risperidone was not statistically significant.

Q. At week 24, can you tell if there was a -- what sort of increase, if any, there was from baseline and fasting glucose for people who were using quetiapine?

A. We have to go -- it's not here. That -- the answer to that question I don't think is in the summary. I'm going to have to go into the body of the document to find that.

MR. McCONNELL: Go off the record for a second.

VIDEOGRAPHER: Off the record at 2:41.

- - -

(A recess was taken from 2:41 p.m. to 2:52 p.m.)

- - -

VIDEOGRAPHER: The beginning

Page 1033

of tape number four. We're back on the record at 2:52.

BY MR. McCONNELL:

Q. Doctor, did you manage to find the fasting glucose results for Seroquel?

A. Yes.

Q. What were the results?

A. The change from base --

MR. PIRTLE: Could you point me to the page? It's a big document.

THE WITNESS: Page 156. The change at week 24 in the quetiapine group was .177 millimeters per liter.

BY MR. McCONNELL:

Q. In the context of all the results of trial 125, did you find the results reassuring or not in terms of whether there was a connection between Seroquel and glucose dysregulation?

A. We found it very reassuring.

Q. Why is that?

Page 1034

A. Because the change in the area under the curve, which is the primary assessment, was not -- did not change significantly between baseline in week 24, and also because there was no change at all in the two-hour value, that is the blood glucose value two hours after glucose challenge showed no change. That value typically begins to go up as diabetes emerges. And the fact that there was no change in that value after 24 weeks on Seroquel was also reassuring.

Q. Doctor, I want to direct your attention to other studies now, studies 126 and 127. My first question to you is, did AstraZeneca collect fasting glucose samples in trials 126 and 127?

A. We attempted to and we also -- and we collected the time since the last meal, which will enable us to ascertain whether -- reasonably ascertain whether the sample was fasted or not.

Q. Can you explain to the jury

Page 1035

what it was that was studied in trials 126 and 127?
A. Trials 126 and 127 were designed to show that Seroquel could prevent relapse in patients with bipolar disorder. It was a complicated trial insofar as we studied patients who either -- had recently had or were having either a manic episode or an episode of depression and who had recovered on Seroquel and the mood stabilizer. And then we randomly assigned patients to continue on the combination or on the mood stabilizer alone. It was a -- it took a long time to recruit the number of patients. And it was a long time to accumulate the number of relapses. And we conducted that study twice in order to be sure of the result.
Q. What was the primary endpoint of 126 and 127?
A. The primary endpoint was relapse of -- having a relapse of either a manic episode or a depressed episode.

Page 1036

Q. Were trials 126 and 127 designed to determine if Seroquel can cause hyperglycemia?
A. No.
Q. Nevertheless, did AstraZeneca collect fasting glucose samples from the patients to monitor the glucose issues?
A. Yes.
Q. What were the efficacy results of trials 126 and 127?
A. Both 126 and 127 were robustly positive showing the decrease in relapse rates to both manic events and depressive events.
Q. Has AstraZeneca submitted the results of trials 126 and 127 to the FDA?
A. We submitted to the FDA and the indication was approved about two weeks ago.
Q. Prior to the submission of the results of 126 and 127 to the FDA, did there come a time when you analyzed

Page 1037

the glucose results from those studies?
A. Yes.
Q. Did you, in fact, do an extensive reanalysis of the results?
A. We did extensive additional analyses of the results of the glucose parameters.
Q. And why did you do that extensive reanalysis?
A. What we found in the pooled safety results was changes in blood glucose of similar magnitude that we had observed before. We also saw similar changes in hemoglobin A1c of the magnitude we had seen before. But in this trial, there were seven reports, seven adverse event reports of diabetes, six of which occurred in the Seroquel patients and only one occurred in the placebo patients. And that could have been a matter of chance, but we wanted to investigate whether or not there was a relationship between Seroquel and the emergence of diabetes. And we undertook

Page 1038

an extensive analysis of all of the data in that trial.
Q. Did that extensive reanalysis involve endocrinologists employed by AstraZeneca?
A. Yes.
Q. Did that reanalysis involve an endocrinologist who is not employed by AstraZeneca?
A. After extensive review and discussion internally, we presented the results to an external endocrinologist.
Q. And after an external discussion and after getting the results from the endocrinologist, was there a consensus among the SERM team about what the data revealed?
A. There was consensus among the clinical team that we took to SERM and we -- the data showed that there was an increase in the -- of about twofold in the rate of emergent hyperglycemia in patients who took Seroquel and a mood stabilizer compared to those that took a