IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

WENDY B. DOLIN, Individually and as Independent Executor of the Estate of STEWART DOLIN, deceased,	)	
Plaintiffs,	)	
vs.	)	No. 12 CV 6403
SMITHKLINE BEECHAM CORPORATION, d/b/a GLAXOSMITHKLINE, a Pennsylvania Corporation,	)	Chicago, Illinois
Defendant.	)	April 6, 2017 1:30 p.m.

VOLUME 15-B

TRANSCRIPT OF PROCEEDINGS - Trial

BEFORE THE HONORABLE WILLIAM T. HART, and a Jury

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(Proceedings heard in open court. Jury out.)

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(Proceedings heard in open court. Jury in.)

THE COURT: Thank you very much, ladies and gentlemen. Please be seated. We will resume.

You may proceed.

MR. BAYMAN: Thank you, your Honor.

JOHN KRAUS, M.D., DEFENDANT'S WITNESS, PREVIOUSLY SWORN

DIRECT EXAMINATION (Resumed)

BY MR. BAYMAN:
Q. Dr. Kraus, I'd like to talk to you about adverse events in clinical trials. What -- in the context of a clinical trial, what is an adverse event?
A. So it is -- in general, an adverse event is any event that occurs in any portion of the clinical trial that is uncomfortable or a discomfort or painful or different for the patient under study.
Q. Does it matter about the severity of what it may be?
A. No. You're typically supposed to collect everything.
Q. And were --the investigators in the paroxetine clinical trials, were they required to record adverse events and report those to the FDA?
A. Yes.
MR. WISNER: Objection, lacks foundation. All of these clinical trials were completed before he arrived at GSK.
THE COURT: Overruled.
MR. BAYMAN: Thank you, your Honor.
BY MR. BAYMAN:
Q. You can answer.
A. Yes, they require the investigators to record and report the adverse events.
Q. And were the investigators in the paroxetine or Paxil clinical trials directed to report occurrences of suicidal thoughts and behavior?

A. Yes, as that would be considered an adverse event.
Q. Now, so that we're clear, were -- the investigators in the Paxil clinical trial, were they employees of GSK?
A. No.
Q. Who were they?
A. Investigators in clinical trials are typically affiliated with academic institutions of psychiatry and are researchers and clinicians who work to be the investigator and execute the protocols or study designs for the trial.
Q. Were GSK's investigators required to state whether they believed adverse events were related to the medication that the patient was taking or not?
A. Yes. In the clinical trials, it's required that the investigator make what's called an attribution. So if an adverse event happens, they have to write down whether they think it may or may not have been related to the treatment that the patient is taking.
Q. Did they make those attributions for placebo as well as active control if applicable?
A. Yes, because they're blinded. They don't know what the patient is taking. Usually in the placebo controlled portion, so they make that assessment for both compounds, placebo, drug.
Q. And based on your review of the clinical trial data, did you find occasions where clinical investigators attributed

certain adverse events to placebo?
A. Yes, that happens.
Q. Did GSK ever do an analysis of the relatedness assessments that the clinical investigators made for suicide-related adverse events in paroxetine or Paxil trials?
A. Yes. GSK did an analysis looking at that.
Q. And just tell us about that.
A. In the analysis of the clinical trials looking at possibly suicidality-related adverse events, when they compared the investigator attribution for paroxetine-related events versus placebo, more often did they relate the event as occurring as related to placebo treatment than paroxetine treatment.
Q. And explain the significance of that.
A. I mean, the significance of this is, why do we collect investigator attribution. It's really to see if over time, more investigators than not think that a certain adverse event or side effect might be related to treatment. That can give you a signal that could be something you need to look at down the line.

In this case because there -- actually, for placebo, there was more attribution to suicidality than Paxil, there didn't appear to be a signal with drug treatment that required further follow-up.
Q. You're familiar with the opinions of the plaintiff's experts, notably, most notably Dr. Healy from your work in

this case?
A. Yes.
Q. You have reviewed his report?
A. I have in the past.
Q. And you're aware that Dr. Healy and, in fact, Dr. Healy testified companies generally tend to emphasize when the investigator thinks a person has got better and that this is related to the drug, they'll emphasize that?
MR. WISNER: Objection.
MR. BAYMAN: I'm quoting him as you told me to do, your Honor.
THE COURT: Well --
MR. WISNER: Page, line number?
MR. BAYMAN: It's the trial transcript Page 584.
MR. WISNER: What was the quote?
I'm sorry, your Honor. I should talk to the Court. Your Honor, I have no context to what he's referring to. I can't verify this. I don't know what's going on here.
MR. BAYMAN: I can ask it a different way.
THE COURT: Well, you'd better give him the page numbers if you're going to do that.
MR. BAYMAN: That's fine. It's Page --
THE COURT: That is the way to do it. We don't know -- I'm sure you're giving us a fair summary, but counsel may disagree, so we have to give them the reference.

Anyway, you can answer the last question. Let's move in the direction of being very specific --

MR. BAYMAN: Yes, sir.

THE COURT: We are dealing in terms of rebutting.

MR. BAYMAN: Well --

THE COURT: Read it back. Let's hear it again.

(Record read as follows: "Question: And you're aware that Dr. Healy and, in fact, Dr. Healy testified companies generally tend to emphasize when the investigator thinks a person has got better and that this is related to the drug, they'll emphasize that?")

BY THE WITNESS:

A. I did hear that, but that's not how the trials are conducted. Attribution, the investigator's relatedness is given for adverse events, not for the efficacy ratings.

BY MR. BAYMAN:

Q. And has it been your experience that GSK, when it comes to an adverse event from a clinical trial, GSK will say, well, the investigators didn't think this was related and ignore that -- ignore what the investigator's attributions were?

A. No.

Q. When did -- I want to talk to you just about the approvals of Paxil. When did Paxil first get approved for sale in the United States?

A. I believe it was in 1992 for major depressive disorder.

MR. WISNER: At this time, your Honor, I'm going to object to the question regarding Dr. Healy's testimony. I have now read it, and it is actually misleading and out of context.

THE COURT: You can take that up on redirect --

MR. WISNER: Yes, your Honor.

THE COURT: -- or cross. Excuse me, cross-examination.

BY MR. BAYMAN:

Q. Turn, if you would, in your book to Tab 1, defense Exhibit 306.

A. There's not enough room up here for this stuff. Okay.

Q. Are you familiar with this document?

A. Yes.

Q. What is it?

A. This is a note from the FDA from Bob Temple who is the director of the office of drug evaluation and center for drug evaluation and research giving the approve -- approvable, FDA's approval of the paroxetine for the treatment of major depressive disorder.

Q. That was the initial new drug application?

A. Yes.

Q. Does this record set out the FDA's official position?

A. Yes, it does.

Q. Do you and your colleagues at GSK rely on information in FDA approval letters as a statement of the agency's position?

A. Yes, we do.
Q. Do you maintain -- does GSK maintain records such as this in the ordinary course of business?
A. Yes, we do.
Q. Did you, as part of -- when you got job responsibilities of being responsible for Paxil, did you go back and review this letter as part of your work?
A. Yes, I did, and for other indications as well.

MR. BAYMAN: Your Honor, at this point, I move for permission to publish defense Exhibit 306.

MR. WISNER: Objection, your Honor. Hearsay and 403. If we can have a sidebar on this, I can walk you through the legal issue.

THE COURT: All right. Go to sidebar.

(Proceedings heard at sidebar:)

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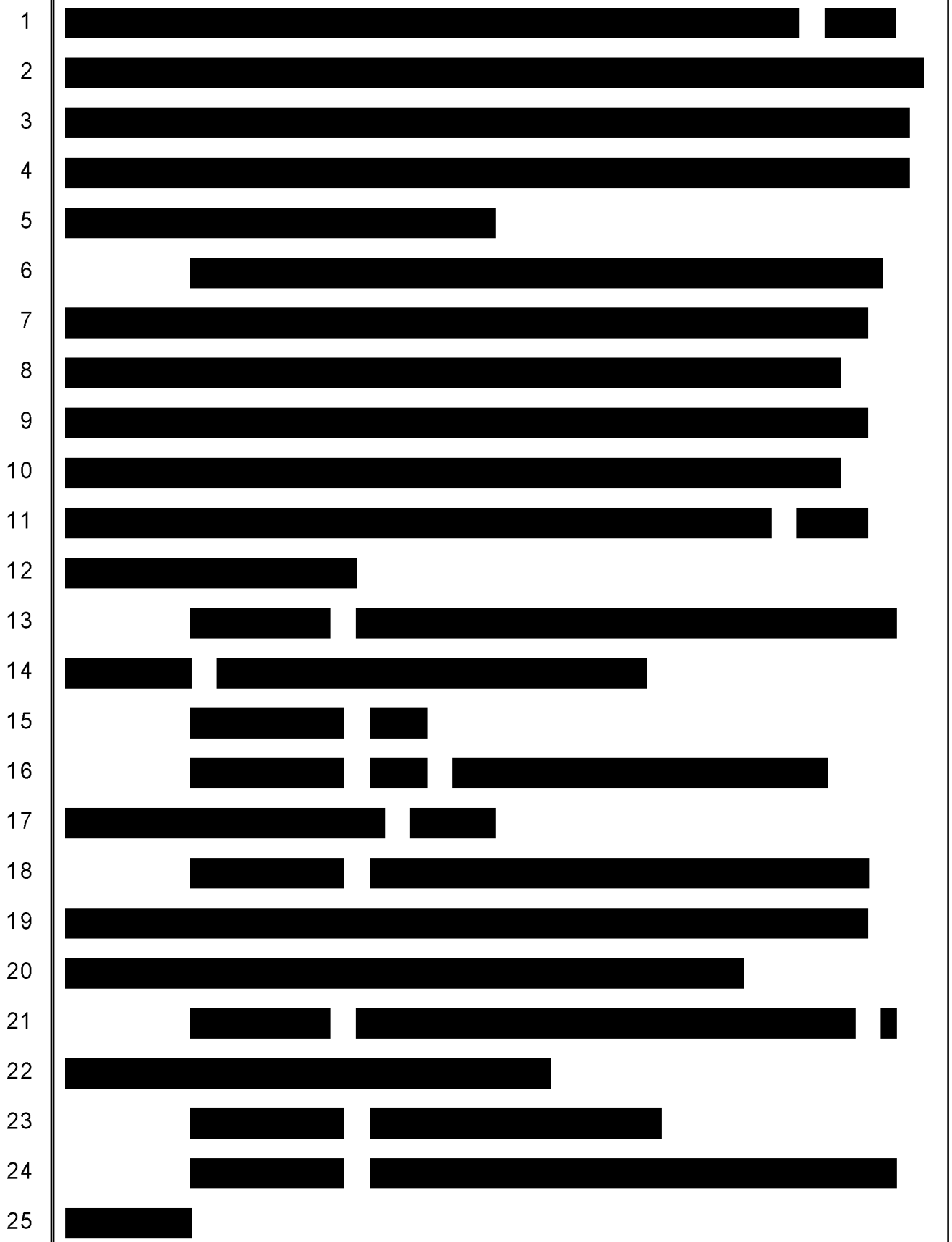

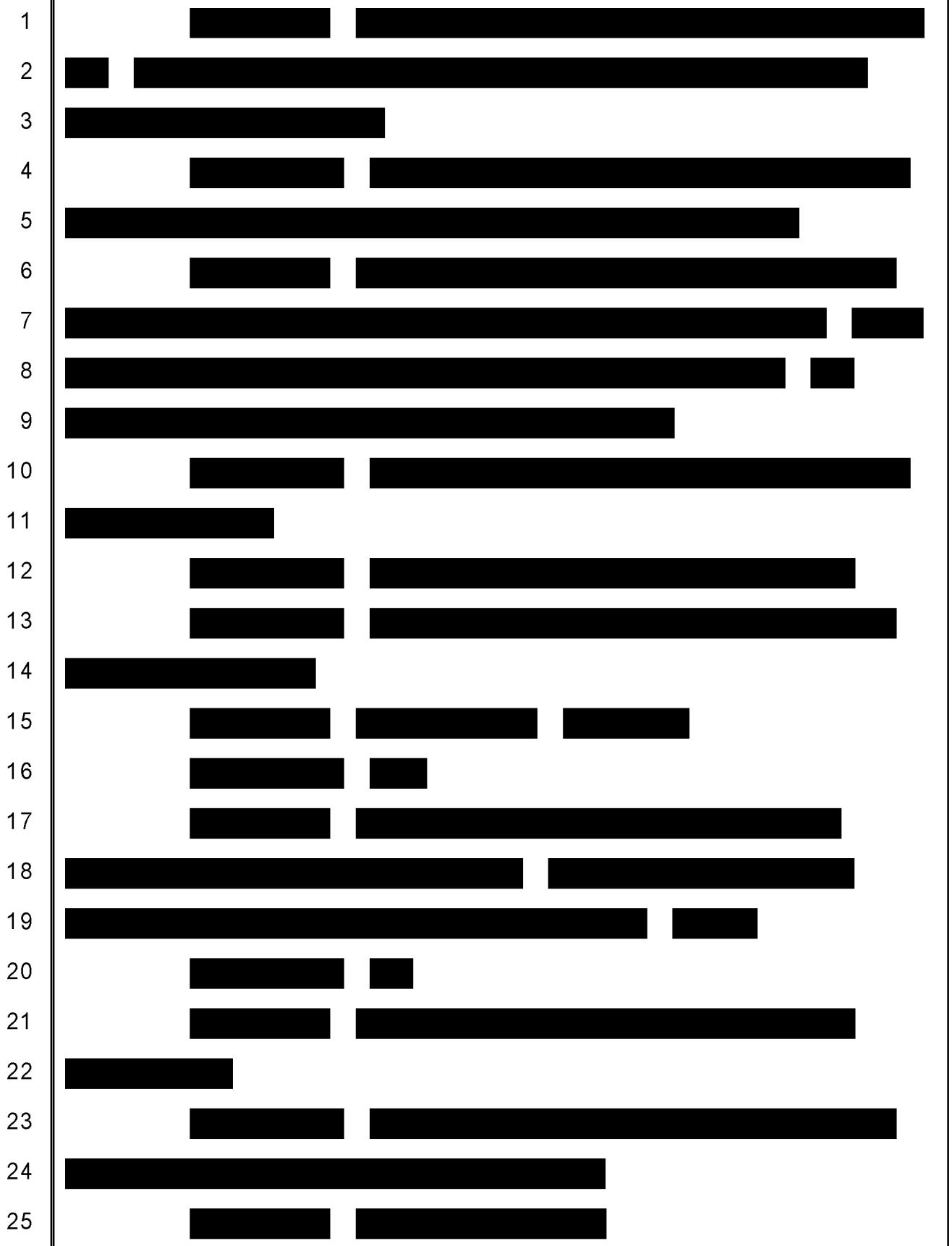

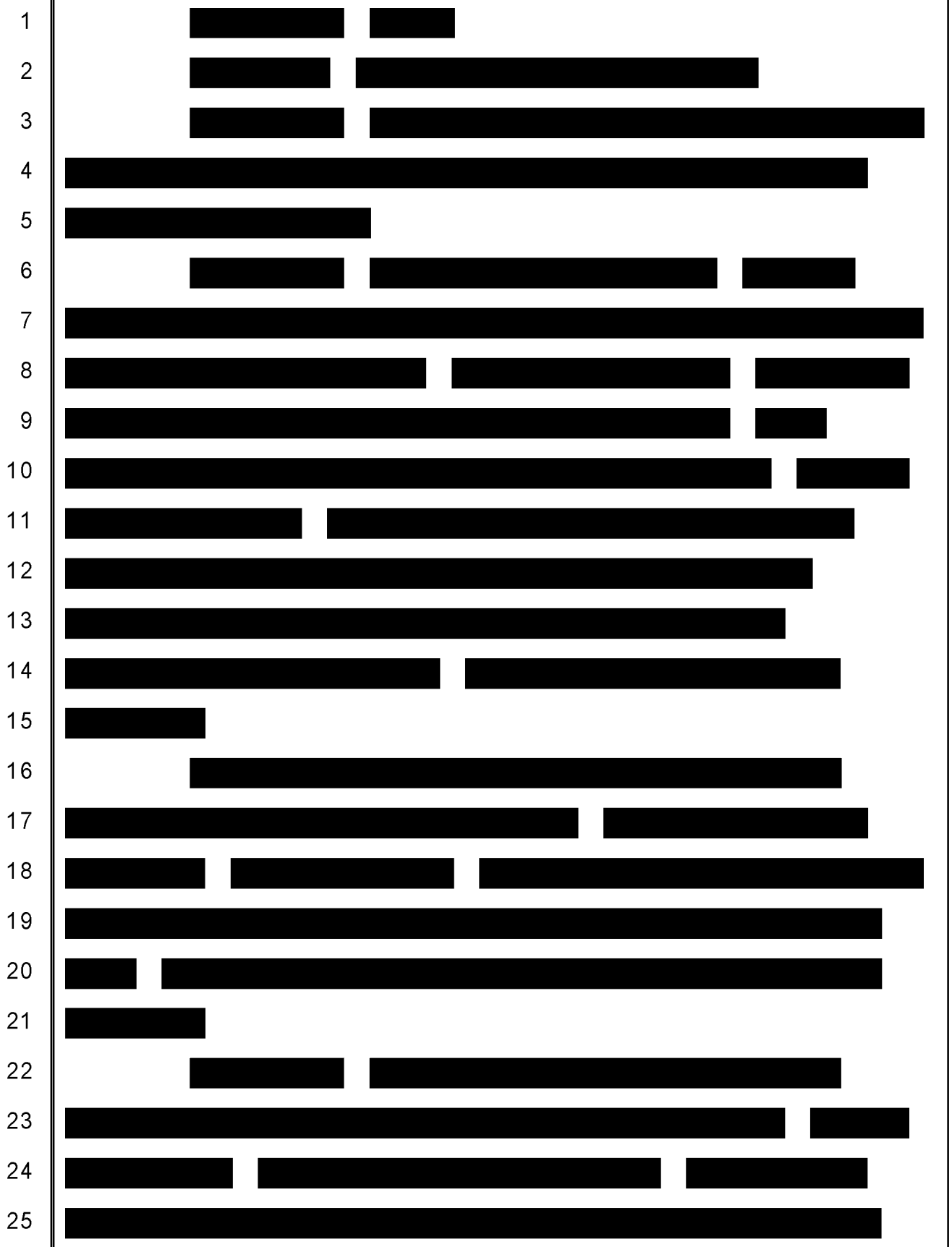

[redacted]

(Proceedings heard in open court:)

BY MR. BAYMAN:

Q. Dr. Kraus, did -- in 1992, did the FDA approve Paxil for sale in the United States?

A. Yes.

Q. And did it approve it as safe and effective for use as recommended in the labeling?

A. Yes, it did.

Q. Did the label in 1992, the Paxil label, include any language about suicide?

A. About suicidality, yes.

Q. And what did the -- what did the language say with respect to suicidality? You'll probably have to look at the document.

A. Within the precautions section, it has a heading:

"Suicide. The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose."

Q. Did GSK have any choice about whether or not to use this

labeling?

MR. WISNER: Objection, speculation, misstates the law.

THE COURT: You can ask him his opinion about that, and I'll let that in as his opinion, but I will not let it in as a statement of the law. Do you understand?

MR. BAYMAN: Understood, your Honor.

THE COURT: Okay.

BY MR. BAYMAN:

Q. In your opinion, did GSK have any choice about whether or not to use this language in the label?

A. The answer is no.

Q. Are you familiar with the term "disease management"?

A. Sure, yes.

Q. How would -- how would you describe this suicide language in the 1992 label?

A. In the context of what was known about paroxetine at the time, and this is really advising about the general risk in depression itself ensuring that physicians are aware and maintain vigilance even when starting drug therapy.

Q. Is that --

A. So it's -- it's primarily disease management, in my opinion, at this stage.

Q. Did that change over time?

A. Yes, it did.

Q. Explain that, please.
A. Over time, as more information evolved on antidepressants and suicidality, the warnings and precautions actually highlighted information around starting medicine, changing dose, and then ultimately having findings about association in young adults and pediatric subjects.
Q. In your opinion, were those subsequent warnings and precautions disease management?
A. No. They're related to analyses conducted based on data, clinical trials, things of that nature.
Q. Now, following the FDA's first approval of Paxil, did FDA then approve Paxil as safe and effective for additional indications?
A. Yes, FDA did.
Q. Okay. I'm -- we're not going to go through them all, but if you'll turn to Page -- Tabs 2 through 12 in your notebook.
A. Yes.
Q. What other indications did the FDA approve Paxil as being safe and effective when used in accordance with the labeling?
A. In addition to major depressive disorder, there are a number of anxiety disorders that were also approved including generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder.

There was approval for different formulations, an oral suspension which is like a liquid. There was approval

for a sustained-release tablet or controlled-release tablet, CR, for depression and some anxiety disorders as well. And there were indication of PMDD as well. I think I've covered them all. Maybe not, though.

Q. And when -- were those called supplemental NDAs?

A. They are called supplemental NDAs because they add on to the first drug approval which was for major depressive disorder.

Q. So did GSK provide safety information or other data to the FDA in connection with obtaining these supplemental approvals for these other disorders?

A. Right. Each of the supplemental approvals have to have within them an integrated safety summary. So all the updated safety information goes with these submissions.

Q. For each subsequent approval, supplemental approval, did FDA have to make a determination that Paxil was safe and effective when used in accordance with the labeling?

A. Yes, it did.

Q. And did it do so?

A. Yes. These indications were approved.

Q. Did you assist in preparing a graphic that lists those indications that you described?

A. Yes.

Q. Would that assist you in explaining your testimony to the jury?

A. Yes. It would show all the indications for which the

approvals occurred.

MR. BAYMAN: Your Honor, just permission to publish 7036-14.

MR. WISNER: Objection, argument. It's the same graphic that was not permitted earlier.

THE COURT: I don't remember this graphic before.

MR. BAYMAN: I didn't use it earlier.

MR. WISNER: Instead of having the check boxes, it said "approved," but it's the same graphic.

THE COURT: Well, this one is -- all right. You may show it.

MR. BAYMAN: Thank you.

Put it up there.

THE WITNESS: Right. This is a summary of the different diseases that I summarized as well as the formulations and the dates when those approvals occurred.

BY MR. BAYMAN:

Q. Now, in connection with those approvals, subsequent approvals, was FDA required to make a new determination about whether the medicine was safe and effective when used in -- with the prescribing information based on your experience and expertise?

A. Yes.

MR. WISNER: Objection, your Honor. This witness is not an FDA expert, and he's testifying about what the FDA does

and does not do, and he's never worked there. I move to strike.

THE COURT: He can testify as to what they did.

THE WITNESS: The answer is yes.

THE COURT: The answer is yes as to what?

BY MR. BAYMAN:

Q. That they had to -- when a new supplemental drug application is submitted, does FDA and did they make a determination each time after studying that new information that the medicine was safe and effective for the indication?

A. Yes, they did.

MR. WISNER: Your Honor, again, I object to relevance. There's no dispute that Paxil has been approved by the FDA. The question is whether or not it causes suicide --

MR. BAYMAN: And I'm going to get to that, your Honor.

MR. WISNER: -- and there's nothing about that on this page. This is highly prejudicial and, quite frankly, contrary to binding Supreme Court precedent. We think this is highly prejudicial.

THE COURT: Proceed.

BY MR. BAYMAN:

Q. In connection with each of these approvals through January 2004 that we looked at, did FDA ever request the inclusion of any new or different language in the Paxil label concerning

the risk of suicidality?
A. It contained the same language I read earlier from the very first approval. As some of these anxiety disorders were approved, it also added language that because anxiety disorders can coexist with major depression, there should also be observation in these patients for the risk of suicide attempt. I could look up the exact language if that's helpful in one of the labels, but that's a paraphrase.
Q. Did FDA ever say to GSK that it -- during this time period that it believed the data on Paxil showed reasonable evidence of an association between Paxil and suicide attempts, suicide, or suicidal thinking?
A. No.
Q. Did FDA ever say to GSK that the labeling should include information that there was an increased risk of suicide attempts, suicide, or suicidal thinking for adult patients who took Paxil during this time period?
A. No, they did not.
Q. Did FDA ever say to GSK there was a scientific or other basis for changing the Paxil label and warnings to suggest that there was an increased risk of suicide attempt, suicide, or suicidal thinking from Paxil in adult patients during this time period?
MR. WISNER: Objection --
THE WITNESS: No --

MR. WISNER: -- hypothetical, hearsay.
THE COURT: Sustained.
MR. BAYMAN: Okay. You can take that down.
BY MR. BAYMAN:
Q. I need to shift gears with you, Doctor, and I'm going to try to do this as quickly as I can. Are you familiar in your work in this case by having reviewed the expert reports that the plaintiff's issues have raised -- plaintiff's experts have raised as an issue about certain suicides and suicide attempts in the early Paxil trials having occurred during the placebo run-in?
A. Yes, I'm aware of that issue.
Q. Do patients, based on your experience and your review of the clinical trial data, do they sometimes attempt or commit suicide or experience suicidal thinking during the placebo run-in period?
A. Yes, that has occurred.
Q. Does that surprise you?
A. No, because again, the diseases under study, major depressive disorder, one of the key symptoms for diagnosis includes suicidal thinking, suicidal behavior. It's part of the disease. For this to occur in trials is not unexpected just like in studies of statins for high cholesterol, you might see heart attacks, things like that. It's not unusual.
Q. Are companies required to record and report to FDA adverse

events that occur during the placebo run-in period to FDA?
A. Yes. After a patient signs informed consent saying they'll go into a study, every adverse event that occurs, no matter what part of the study, has to be reported.
Q. In your opinion, did GSK correctly disclose the fact that certain suicide and suicide attempts in the early paroxetine clinical trials occurred during the run-in phase?
A. Yes, that has been disclosed.
Q. You agree that --
A. Yes, I agree, that has been disclosed.
MR. BAYMAN: Your Honor, at this point, I'd move for permission to publish Plaintiff's Exhibit 82 which is already in evidence. It's the 1991 suicide report.
MR. WISNER: No objection. It's in evidence.
THE COURT: Proceed.
MR. BAYMAN: Put it up, please.
THE WITNESS: Which tab is this?
BY MR. BAYMAN:
Q. This is Tab 13.
A. It's going to be -- okay.
Q. Got it?
A. Yeah.
Q. This is -- this has already been -- this document is in evidence and shown to the jury. And I'm going to try to shortcut this as much as we can to get through this. What is

this -- essentially, what is this document?
A. This is a submission to FDA from SmithKline Beecham -- that's an old company that later became part of GSK -- providing a report to the FDA on suicide, suicide attempts that occurred in the clinical trials that supported the approval for major depressive disorder. This report happened while the drug was under review, so before its approval.
Q. So did -- does the report look at suicide and suicide attempts that occurred in all Paxil clinical trials?
A. It does, that were available at that time.
Q. So that would be placebo control, open label, active control?
A. That's correct.
Q. What proportion of the patients involved in the trials that are the subject of this report were in placebo-controlled trials as compared to patients enrolled in non-placebo-controlled trials?
A. I'd have to look at the numbers, but I think it's approximately, the placebo controlled, a little more than half.
Q. There were more patients in this -- in the studies that are the subject of this report, were more patients in non-placebo controlled than in placebo-controlled trials?
A. Yes.
Q. What is the significance to you in terms of whether it's valid to make comparisons between the entire paroxetine

patient population versus placebo patients?
A. Can you ask that again, Mr. Bayman?
Q. Yes. What's the significance to you of comparing the entire paroxetine patients from all the different trials versus just placebo patients, making a comparison between the two?
A. Oh, okay. So for the purposes of a comparison, it goes back to what we talked about before. The important part is trying to assess at the same time, side by side, drug and placebo, whether or not there might be a difference in effect. So if you're actually looking at a comparison of drug/placebo to address the question of emergent suicidality, that is the position to look at.

In the uncontrolled phase or the open-label phases of Paxil where patients are only getting Paxil and there's no comparison and as the time can go on, up to 52 weeks in some cases, without a comparator group, as we've said, the disease itself has as a part of its diagnostic features and symptoms is suicidality. So that can occur. And not knowing what that kind of rate would have been in a placebo group, you can't use that for comparison.

So in answer to your question, the placebo controlled portions versus the Paxil in those parts of the study are informative, but this report, as you know, was looking at all parts of the studies.

Q. Was GSK's analysis of suicidality in that report limited only to looking at the numbers of suicides and attempted suicides between Paxil and placebo and active control?
A. It looked throughout all of the study, at each portion of the study.
Q. Right. But this analysis, was it just a comparison of numbers, or was there other analysis done?
A. Oh, there were other analyses in this manuscript as well that controlled for the exposure. So remember, we talked about how the patients could be followed a long period of time, that an adverse event that's part of the disease can occur during that time. So the longer you observe someone, the more likely you may able to see that adverse event. So this patient exposure years kind of controls for how long a patient has been observed.

There were also analyses in this report of rating scale measures of suicidal thinking and behavior. So the depression measures, those rating scales we talked about earlier, the depression measures have a specific item asking about suicidal thinking. It goes all the way from none to mild, like wishes to be dead to a suicide attempt. And those rating scales were also analyzed. And what was seen in this report is a reduction in suicidality by rating scale in patients treated with paroxetine compared to placebo.
Q. Before we look at those, I want to ask you a question.

Based on your experience as a psychiatrist and someone who's conducted clinical trials, was it expected or unexpected that during the development of an antidepressant like paroxetine or Paxil, patients in the clinical trials would from time to time report that they experienced suicidal thinking or behavior?

MR. WISNER: Objection, speculation, vague, lacks foundation.

THE COURT: Well, he's a psychiatrist, and he's looked into it. I'll let him testify.

MR. WISNER: Just to be clear, your Honor, at the time that we're talking about, he was not a psychiatrist. This is 1985.

THE COURT: No, but he's taken over the responsibility for the examination of the drug for the company. On that basis, I'll let him testify.

MR. BAYMAN: Thank you, your Honor.

BY THE WITNESS:

A. It's not unexpected. As suicidality and suicidal thinking are part of the disease itself, obviously we're studying that disease, this would occur. It's like if you're studying a blood pressure medicine, you may expect to see stroke in those studies, things of that nature.

BY MR. BAYMAN:

Q. Turn, if you would, to Page 5 of the report which is Page 11 of Exhibit -- can we pull that up?

A. Okay.
Q. And do you see Table 5 there?
A. Yes, I do.
Q. What does this table show?
A. This shows the baseline score, meaning when patients come into the study before they get randomized to any treatment, an assessment is made of how they're doing at that time. That's the baseline. And then you can compare that to each subsequent analysis to see if they're getting better or changing.

So at baseline before they received treatment, this is the kind of rating score on the Hamilton depression suicide item, which is Item 3. And as I said earlier, zero is no suicidality. 4 is all the way up to a suicide attempt before enrollment.

Q. So what does this tell you about where the patients were with respect to suicidality prior to being given either Paxil or placebo or active control?
A. Right. So this indicates that most patients in the study had a score above zero, so they had some thoughts of at least wanting to die and above. Only about 25 percent or so had no thoughts of suicidality. And as I said, that's not unexpected in a study of depression because suicidal thinking can be part of the disease.

What you also see here is the paroxetine patients may

have had some higher severity as if you look at the 3 and 4 items of the Hamilton rating scale which are more severe suicidality, the paroxetine patients as compared to the placebo patients were at the higher score at baseline.

Q. And what's the significance of all this to you?

A. So suicidal thinking, suicidal behavior is a risk factor for later suicidal attempts or suicides. So those patients could be at increased risk of those behaviors in the studies.

Q. Does it tell you anything about whether it's appropriate to compare all the paroxetine patients from all the various trials against just placebo-controlled patients?

A. No. The other thing to point out is, if you look at the active comparator on the end which is also active drug, they also have evidence of a more severe baseline. So in some of these studies, we had Paxil versus another medicine. There's no placebo.

In those studies, the investigator, although not knowing exactly whether they'll get Paxil or the comparator medicine, know they're going to get a medicine, so there may be more severe patients that go into those types of studies. And I think that's why you see the higher amount of suicidality in Paxil and active comparator with low in placebo because in a placebo study, if an investigator knows that their patient may not get an active medicine, they may not enroll a more severe patient.

Q. An active medicine, is that a medicine that would -- to treat the disease?
A. Yes. It's a medicine to treat the disease.
Q. Now, in your practice and experience, have you administered Hamilton depression rating scales to patients?
A. Yes, I have.
Q. Just tell the jury how that -- briefly how that works and what kinds of things people are asked.
A. So the Hamilton Depression Rating Scale goes through a number of the symptoms that are associated with major depressive disorder including, an important one, depressed mood, including items around sleep, including items around agitation, anxiety and, of course, items around suicidality.

And each item has the same sort of zero through 4 -- or actually, not all of them are through 4, but they give a number that anchors it to a specific level of severity. And usually in these scales, the lower number is absent symptom. The higher number is the most severe.

Q. What does 4 mean?
A. 4 for the Hamilton item means suicide attempt.
Q. Attempt?
A. Yeah.
Q. And tell the jury, as a practical matter, how is it -- how is -- the Hamilton-D, how is it given and what kinds of questions, how are the questions phrased?

A. Typically, the investigator would have the rating scale in front of them, and you would go through the order. So for example, when describing depressed mood or asking about that, you might ask the patient, "Can you tell me a bit about your mood? How have you been doing?"

Elicit that information from them. And then you anchor it. For suicidal thinking, you may say, "In the past two weeks" or whenever the time was you last saw them, "have you had any thoughts of wanting to die, any thoughts of wanting to harm yourself" and investigate that.

So for each one, you specifically elicit the information and then record the number based on their response.

Q. And are they asked over like a certain time period like, "In the past two weeks, have you ever" --

A. Yes. It's related to a time period such that it's usually the last study visit, for example.

Q. And are they asked specific questions, "Have you thought about killing yourself?"

A. Yes.

Q. "Have you thought about not waking up?" They're asked questions like that?

A. Yes. You have to ask specific questions to fill this out.

Q. Let's look at then completed suicides, if you would turn to Page 1 of the report which is actually Page 7 of the exhibit. Can we pull that up?

A. Okay.
Q. What is this -- this is the information about the number of suicides in the trials?
A. Yes, it is.
Q. And what does it say with respect to how many completed suicides occurred on patients who were randomized to paroxetine?
A. It speaks to ten suicides were committed by patients who participated in the worldwide paroxetine clinical trials. Five suicides were committed by patients who were randomized to paroxetine. Two were committed by patients who were randomized to placebo. And three were committed by patients randomized to other active control regimens.
Q. Let's go down to the bottom of the page, Table 1. The jury has seen this previously, but one thing I want you to, if you would, explain, there's a shorthand there called PEY. What does that mean?
A. I touched on that a little earlier. That is patient exposure year. So as I described, patients in these studies were more likely to be on paroxetine for a longer period of time. And again, for a disease like depression where suicidal thoughts and behaviors are part of the disease, over time, these may occur in the course of depression.
So part of trying to kind of normalize for that is to look at the total patient years of exposure. So that's adding

up all the weeks the patients have been exposed or treated with the medicine and taking that and dividing the total number of cases. So it kind of gives you a rate over time that would occur. And in this instance, we see the rate over time for paroxetine was .005 as composed -- compared to .028 for placebo and .014.

And what you can also see is there's really a low number of exposure years for placebo compared to paroxetine. And that makes sense because the placebo part of these trials was typically limited to the acute phase, eight weeks, for example, whereas some of the Paxil exposure parts of the trials could be up to 52 weeks as we described.

Q. And then read the phrase underneath the table.

A. The phrase underneath the table, "There were no substantive differences in the number or incidence of suicides among treatment groups."

Q. What does that mean?

A. That when looking at the percentages as well as normalized for exposure time, there did not appear to be differences among these groups.

Q. Does it show whether -- when you look at it using the patient exposure years, does it show whether patients taking Paxil were more likely to commit suicide than patients taking placebo?

A. No, it does not.

Q. And what about Paxil with respect to active control, the other antidepressants that were in the trials?
A. There was no increase in paroxetine compared to the active controls. It was smaller.
Q. Why does the duration of exposure to Paxil versus placebo have such importance when analyzing the data?
A. Again, the longer you observe a condition over time, you begin to see symptoms of that condition. So the longer you watch, again, for depression where suicidality is part of the disease, the more likely you may see it. So it helps to control over time what that natural rate may be.
Q. I went to law school because I wasn't good at math, but that difference in number is about 14 times greater, right?
A. For which ones?
Q. Between the duration of exposure on Paxil --
A. Oh, for the exposure.
Q. -- versus placebo.
A. Yes.
Q. Have you -- based on your work in this case and your review of the opinions of the plaintiff's experts, you're familiar with Dr. Healy's opinion that it's inappropriate to analyze data for suicide events using patient exposure years because the risk is at the start of therapy and when the medication is discontinued?
A. I've heard that, yes.

Q. Okay. What's your reaction to that?
A. My reaction is, I disagree with that given that the disorder is major depressive disorder where suicidality is a part of the disease. It would be similar to ignoring in long-term cancer studies the development of tumors or ignoring in long-term statin studies heart attacks if you don't normalize over time because those things happen naturally as the age. So I disagree.
Q. Let's look at, again, quickly, Paragraph 3 on the same page.
A. Okay.
Q. And let's highlight that, please. What is that -- what is that telling us?
A. This is essentially providing where in the study this occurred for the placebo suicides and that they -- two suicides committed by the patients on placebo occurred during that run-in phase.
Q. And what's the significance of the minus 2, minus 7?
A. That's how many days before they would have been randomized to Paxil or placebo.
Q. So did GSK disclose the fact that two suicides in placebo patients occurred during the run-in?
A. Yes.
Q. When GSK makes submissions, regulatory submissions to FDA, does the company expect and assume that the FDA reads the reports it submits?

A. Yes.
Q. Now, why were placebo run-in events even included in this analysis?
A. For the same reason that all the Paxil extension suicides were included in the analysis. It was capturing all the events that occurred across all phases of the studies. And it actually says that in the methodology, that all data from worldwide studies irrespective of time on therapy were considered for the analysis of safety and the reporting of adverse experiences.
Q. Did any of the five suicides that occurred in the paroxetine patients happen in placebo-controlled trials?
A. They did not occur during placebo-controlled phases, no.
Q. Did including suicides committed by patients taking paroxetine outside of placebo-controlled trials have any effect on the analysis?
A. Yes, because it increased the number of Paxil suicides, yes.
Q. Then why did GSK do that?
A. Because the methodology was --
MR. WISNER: Objection, lacks foundation. He wasn't there.
THE WITNESS: It's written in the report.
THE COURT: Well --
THE WITNESS: I'm sorry.

THE COURT: You're running into argument now. Yes, sustained.

BY MR. BAYMAN:

Q. What did the FDA ask the companies to do who submitted these reports at the time? What did they ask to be included?

A. To provide all adverse events of suicidality throughout the trials.

Q. And is a run-in period included part of the trial?

A. Yes, because the patient has provided informed consent, so those adverse events are recorded.

Q. Now, based on your work reviewing the data when you took responsibility for Paxil, do you have an opinion as to if you took the two placebo suicides that occurred during the run-in and took them out of this analysis but left the five placebo suicides from the non-placebo controlled studies in, would there be a statistically significant difference between Paxil and placebo with regard to completed suicides?

A. No, but I don't think that's a valid analysis unless you remove the paroxetine uncontrolled portions as well.

Q. Why not?

A. For the reason we said earlier. If you're trying to understand the difference between treatment versus what might happen naturally over time, you have to look at the drug and the placebo side by side concomitantly. At the time of this submission, the placebo suicides occurred before that

randomization. And the paroxetine suicides either occurred in the extension phase without any placebo or with just an active comparator where you couldn't describe it.

So to take out just the run-ins but to leave all the Paxil data doesn't make any sense and is inappropriate analysis, but if you did it, it wouldn't be statistically significant.

THE COURT: It wouldn't what, sir?

THE WITNESS: It wouldn't be statistically significant. So if you chose to run that analysis again, which I don't agree with, but...

BY MR. BAYMAN:

Q. All right. Let's take a look at the category of suicide attempts. Would you turn to -- it's Page 2 of the report, Page 8 of the exhibit. It's Table 2.

A. Okay.

Q. How many Paxil patients made a suicide attempt in the clinical trials that were part of the report?

A. 40 patients in the paroxetine group.

Q. And what was included broadly in the definition of a suicide attempt in this analysis, what kinds of things?

A. It was any evidence of self-harm so, you know, something as minor as, you know, slapping oneself all the way to actually a serious attempt.

Q. And then how many placebo attempts were reported here?

A. 6.
Q. And then how many for the active comparator?
A. 12.
Q. If the number of suicide attempts reported in 1989 to the FDA by GSK was 42 but in 1991, GSK reported 40, what's the explanation for that?
A. The explanation is that the 42 was likely two subject numbers counted twice. So if you look at all the subject numbers with a suicide attempt, that actually lines up to 40, although two of those subjects may have had two attempts.
Q. So -- and based on your work in getting up to speed to take responsibility of Paxil and the documents you reviewed and the people you talked to, was there an attempt made to reconcile the database between 1989 and 1991?
A. Yes, yes, there was, to ensure that that was an accurate representation of the subject numbers.
Q. Did GSK inform the FDA that some of the suicide attempts for placebo patients occurred during the run-in?
A. We did inform FDA of that.
MR. BAYMAN: Let's pull up Plaintiff's Exhibit 75, which is admitted into evidence, your Honor. That's the 1989 integrated safety summary.
THE COURT: You may proceed.
BY MR. BAYMAN:
Q. Let's just go quickly. What is this document, Doctor?

It's Tab 14.
A. So this is what's called the integrated safety summary which is part of the new drug application that contains all of the safety information from all the studies in kind of a combined manner, integrated.
Q. Let's go to 206, Table XXI.21. Are you familiar with this table?
A. Yes.
Q. And let's just -- does this table include any information on whether any of the placebo suicide attempts during the run-in period happened during the run-in period?
A. Yes. There's an asterisk indicating that two of the overdoses occurred during the run-in period.
Q. All right. Turn, if you would, then, Tab 16.
MR. BAYMAN: You can take that down.
THE WITNESS: Okay.
MR. BAYMAN: That's defense Exhibit 305, your Honor.
BY MR. BAYMAN:
Q. What is this document?
A. This is the clinical review of the new drug application by Martin Brecher of FDA.
Q. Who is Dr. Brecher?
A. He was the FDA-assigned clinical reviewer to make a judgment about the safety and efficacy of the application submitted.

Q. Did this report reflect the FDA's analysis of Paxil safety based on the data in the new drug application?
A. Yes, it did.
Q. Does this report reflect the FDA's official activities?
A. Yes, absolutely.
Q. And is this a document that the company relied on in making decisions regarding paroxetine or Paxil?
A. Yes.
Q. And is this a document that you reviewed and relied on based on your work in getting up to speed in Paxil and in getting -- for giving opinions in this case?
A. Yes.
MR. BAYMAN: Your Honor, at this point, I move to publish this. It was shown during Dr. Ross's testimony.
MR. WISNER: No objection.
THE COURT: You may proceed.
BY MR. BAYMAN:
Q. Let's turn quickly, since it's been shown before, to -- bring up 305.28. Page 23, Doctor.
A. Okay.
Q. Does this -- is what we're bringing up up on the screen say anything about whether FDA was aware that GSK's 1991 suicidality report included patients who committed suicide during the placebo run-in?
A. Yes. It shows he was aware. He listed it.

Q. Okay. And could you look at the very bottom of the page?
A. Yes.
Q. Does this give information about the patients who committed suicide during the placebo run-in?
A. Right. It gives a brief summary, their subject number, and the time it occurred in the placebo run-in.
Q. Did FDA or Dr. Brecher in this report include those suicides that occurred during the placebo run-in in his analysis of the data?
A. Yes, he did.
Q. Okay. Does that have any significance to you when considering the argument advanced by the plaintiff's expert that it was improper for GSK to have included placebo run-in events in the 1991 report, in your opinion?
MR. WISNER: Objection, argument.
THE COURT: Yes, that's argument.
BY MR. BAYMAN:
Q. Did the FDA include suicide events during the run-in when it did its analysis?
A. Yes.
MR. WISNER: Objection, asked and answered.
THE COURT: You may answer.
THE WITNESS: Yes, they included them.
BY MR. BAYMAN:
Q. Turn, if you would, to Page 25. It's Page 30 of the

exhibit, the middle of the page. What did Dr. Brecher conclude when he did his review and analysis of the Paxil, paroxetine, suicidality?

MR. WISNER: Your Honor, I think for completeness, the table that he's talking about should be displayed as well.

THE COURT: Well, you can do that on cross-examination.

MR. BAYMAN: Yes. I just wanted his conclusion.

MR. WISNER: Okay. We don't have to look at the table?

MR. BAYMAN: He said you can do it on cross.

MR. WISNER: Okay.

BY MR. BAYMAN:

Q. Go ahead.

A. The conclusion is that there is no signal in this large database that paroxetine exposes a subset of depressed patients to additional risk for suicide, suicide attempts, or suicidal ideation.

Q. Now, in reaching his conclusion in the report, did Dr. Brecher discuss only the differences in numbers between suicides and suicide attempts, or did he look at other measures and data points?

A. He also reviewed the patient exposure years, as we've discussed earlier, and also reviewed the rating scale, emergent suicidality as well.

Q. Now, you're -- are you aware -- you can take that down.

Are you aware from your work in this case that Dr. Ross and Dr. Glenmullen have attempted to correct the numbers that GSK submitted to FDA in the NDA on the number of suicides and suicide attempts for paroxetine to remove the placebo run-in events?

A. I have seen that, yes.

MR. BAYMAN: At this point, your Honor, we'd move for permission to publish Slide 7036-16, which is Table 3 from Dr. Ross's report that's been previously shown to the jury.

MR. WISNER: No objection beyond the fact that this is argument.

THE COURT: You may show it.

MR. BAYMAN: Thank you.

Can you blow that up? And then -- thanks.

BY MR. BAYMAN:

Q. Have you seen this chart before?

A. Yes.

Q. Okay. In your opinion, is this a proper way to analyze the data?

A. No.

Q. Why not?

A. As I described before, what this does is takes one part of the uncontrolled study and removes it, so the placebo run-in, and yet still keeps the other uncontrolled part of the study,

so the longer-term Paxil extension.

If you are going to assess whether or not the drug may contribute to a signal or a risk of suicidality, you need that placebo comparison group. So what you would have to do here is actually remove the non-controlled paroxetine suicides or suicide attempts if you wanted to make this comparison.

Q. To your knowledge, has F -- based on your experience, has FDA ever utilized this methodology employed by the plaintiff's experts for assessing suicidality risk with any SSRI, antidepressant, or psychiatric medication since 1999?

A. No.

MR. WISNER: Your Honor, at this time, we would move Plaintiff's Exhibit 258 into evidence. They've used a portion of it here which is Dr. Ross's report, and for the rule of completeness, the jury should have the benefit of the entire document.

THE COURT: Well, you can deal with that on cross-examination.

MR. BAYMAN: Thank you, your Honor.

Take that down, Mr. Holtzen, please.

BY MR. BAYMAN:

Q. Did GSK go back at some point and reanalyze the data on suicide and suicide attempts from the new drug application submission looking at only events that occurred in the controlled portions of randomized double-blind

placebo-controlled trials?
A. Yes, we did.
MR. BAYMAN: At this point, your Honor, I move to display Plaintiff's Exhibit 124, which is admitted into evidence.
THE COURT: You may.
THE WITNESS: Which tab are we on?
BY MR. BAYMAN:
Q. I'm sorry. Tab 18. Are you familiar with this document?
A. Yes, I am.
Q. Is this something that you reviewed when you were getting up to speed for your responsibilities with respect to Paxil and paroxetine?
A. Yes, it was.
Q. What is this document?
A. This document is a communication memo from a conversation with GSK regulatory with FDA, Tom Laughren. And it details our intention to evaluate the suicides and suicide attempts in the new drug application looking at the placebo-controlled portions of the trial.
Q. What was Dr. Wheadon's responsibility at the time?
A. He was senior vice president of U.S. regulatory affairs.
Q. And did he have responsibility for -- one of the people for interacting with the FDA?
A. Yes.

Q. Let's pull up the first paragraph. It says:

"I spoke to Dr. Tom Laughren of the FDA neuropsychopharmacology division last Wednesday, April 10, concerning the updated Paxil analyses on suicide attempts. I explained to Dr. Laughren that subsequent to ongoing defense of Paxil cases, the issue of attempts in patients on placebo during placebo run-in had been debated and a decision had been made to reanalyze the original NDA data on suicide attempts, doing the apples to apples comparison."

What does "apples to apples" mean in this context?

A. So that's the like to like, so that placebo-controlled phase where both the placebo arm and the drug arm are being observed at the same time, treated the same way under the same conditions.

Q. And then he describes the analysis that the company was doing?

A. Yes, those three bullets there.

Q. And then as part of your work in getting up to speed to take over your responsibilities with respect to paroxetine, did you talk to the statistician that was involved in preparing this report?

A. Yes. I've worked with -- John Davies is the statistician who did this report. I've worked with him for years.

Q. And Mr. Davies testified by video in this case previously.

Based on what you've learned in your work and in reviewing of the Paxil file, do you have an understanding of the reference to "ongoing defense of Paxil cases"?
A. Yes, I do.
Q. What is that understanding?
A. It's related to, I guess, some of the issues that we're discussing today in terms of the placebo run-in. There had been litigation issues in the past related to this issue. They had come up as they are now, and they led to our trying to use some of that new information to do the scientifically appropriate assessment of the NDA based on this concept of like to like, apples to apples.
Q. Did Dr. Wheadon -- does Dr. Wheadon's memo indicate that GSK disclosed to the FDA that it had previously included run-in events in the placebo category?
A. Yes.
Q. And did it -- and, in fact, did GSK go ahead and do that reanalysis?
A. Yes, we did.
MR. BAYMAN: Turn, if you would, to Tab 19.
You can take that down, Mr. Holtzen.
This is Plaintiff's Exhibit 129, which is already admitted into evidence, your Honor. Permission to publish to the jury.
MR. WISNER: No objection.

THE COURT: You may proceed.

MR. BAYMAN: You're -- can you please blow that up?

BY MR. BAYMAN:

Q. This is Dr. -- or Mr. Davies who you mentioned a minute ago?

A. Yes.

Q. You're familiar with this document?

A. Yes, I am.

Q. What is it?

A. This is the report from the analysis that we described that we would do to the FDA. This one in particular is about the data on suicides.

Q. I want to ask you about one particular study that's been mentioned in this trial, and that is Study 004. Can you turn to -- bring up Page 2, the first paragraph?

What does this document say about Study 04, excuse me, not 004?

A. Study PAR-04 was excluded from the analysis because of its design. It was an extension study of PAR-03 including an element of crossover between treatments of the two studies.

Q. Are you -- have you gone back and looked at Study 04?

A. Yes.

Q. Okay. Why -- what was the design or what was it about the design of Study 04 that led it to be excluded from this analysis?

A. So the study looked at three different groups treated with

active comparator, paroxetine, and placebo over time. Then there was an extension phase at the end where non-responders could then switch to an active treatment or stay on their original treatment. So essentially, you have randomization, and then at the point of the extension phase, you kind of have an enriched responder group. So the group populations were a bit different in this study.

Q. Why doesn't the fact that there was a placebo group in Study 03 make Study 04 a placebo-controlled study?

A. Because at the time of that extension, the placebo, the patients who stayed on would have been considered responders, so it wasn't an appropriate randomization. And also, some of those placebo groups that started switched on to Paxil, so the numbers also changed.

Q. Was Study 03 included in the analysis?

A. Yes.

Q. Now, the fact that Study 04 was excluded from this analysis, does that mean that GSK ignored that study?

A. No. Indeed, we wrote why we didn't include it in this note.

Q. And did GSK report the suicide in Study 04?

A. Yes.

Q. And did they report on it, in fact, in a different section of this report?

A. Yes.

Q. Did GSK provide information to FDA about the suicide in

Study 04 even though it was not part of the calculation in the 2002 analysis?
A. Yes, of course.
Q. Was -- as part of your work in your job responsibilities, were you familiar with the clinical trials, GSK Paxil clinical trials that were submitted to FDA when it did its analysis in 2006?
A. Yes.
Q. Was Study 04 included -- well, first of all, was it included in the analysis that GSK did of its own data, adult data, in 2006?
A. No, it was not.
Q. Why not?
A. For the same reasons. It's not the acute part of the placebo-controlled study.
Q. Was it submitted, requested and submitted to the FDA as part of its analysis in 2006?
A. No. This, it was not a study that FDA requested for the same reasons I just described.
MR. BAYMAN: Let's pull up at the bottom of the page the results.
BY MR. BAYMAN:
Q. Just summarize the results, if you would, Doctor.
A. And again, this is for suicide. So in the placebo-controlled portions of the trials, there were no completed

suicides in either the paroxetine group or the placebo group for those sets of studies that supported the original approval for major depressive disorder.

Q. And does it indicate whether the placebo suicides that occurred during the run-in, does it indicate whether those were included or excluded?

A. It indicates that they're excluded, but it does highlight them in the last bullet or statement below.

Q. Were those the same two placebo run-in suicides that were reflected in the earlier reports that we looked at?

A. Yes, they're the same ones.

MR. BAYMAN: Turn, if you would, to Tab 15.

Your Honor, this is Plaintiff's Exhibit 122, which is also admitted into evidence. Permission to publish.

THE COURT: Proceed.

BY MR. BAYMAN:

Q. What is this analysis?

A. This is the analysis around suicide attempts from the original clinical data set that contributed to the approval for major depressive disorder.

Q. Let's look at Page 2 in the chart at the bottom. With respect to suicide attempts from the randomized double-blind placebo-controlled trials, what were the results of this reanalysis?

A. So this analysis of again the like-to-like, the placebo-

controlled portions of the study found 5 out of 921 attempts on paroxetine versus 1 out of 544 out of placebo. That was not statistically significant, and it was also controlled for the patient exposure years. Again, we have -- even in the placebo-controlled portion, there are longer exposures for paroxetine than for placebo and they -- we do highlight again that five patients with attempted suicide have been excluded from the figures above for the placebo group because they occurred during the placebo run-in, and we list those subject numbers.

Q. Did this analysis reflect an increased risk for suicide attempts for patients who were taking Paxil?

A. No, it didn't.

Q. Put the statistics aside, Doctor. As a clinician who's treated hundreds of patients, you said earlier, at risk for possible suicide, do these numbers give you any pause?

A. Well, I've treated thousands, but they don't give me --

Q. Okay.

A. -- pause in terms of the frequency. These are both very low frequency.

Q. Do the number of suicide or suicide attempts on paroxetine, or Paxil, is that surprising to you?

A. It's only surprising that it's low because in the major depressive group, you may expect more when looking at 1,000 patients. However, in clinical trials, as we said before, we

want to ensure the safety if a patient may go on to placebo. So these patients may have been at lower risk.

Q. Based on your experience, would it surprise you if there were no suicides on Paxil, or paroxetine, in the clinical trials?

A. It is surprising given the nature of the disease, but as I said before, in clinical trials, you're typically trying to not include patients that might be at acute risk of suicide for the reasons we discussed before. The safety of the patient in the trials is very important.

Q. So did the two analyses we've just looked at, in your opinion, say anything to you based on your experience about whether it mattered one way or another whether GSK did or did not count the placebo run-in events back in 1991?

A. The conclusions are the same in both analyses. There's no evidence of an increased risk with paroxetine compared to placebo.

Q. Do you feel one analysis is better than the other?

A. When you are trying to understand whether an adverse event might be related to drug treatment versus no drug treatment, the placebo-controlled analysis that we're looking at now is the analysis to perform. And again, that's what FDA asked us to perform in 2006 as we got there.

MR. BAYMAN: You can take that down, please.

BY MR. BAYMAN:

Q. Let's be clear. From the time of first approval of Paxil in 1992, did FDA continue to evaluate Paxil's safety both generally and specifically with respect to suicidality?

MR. WISNER: Objection, lacks foundation.

BY MR. BAYMAN:

Q. Do you know that from your review of the file --

A. The answer is clearly yes given all these analyses we've looked at.

Q. And after FDA -- based on your review of the Paxil file in order to perform your job responsibilities and including your conversations with others who were there at the time, after FDA received the re-analyses that we've just looked at, those two submissions, did FDA take any action indicating that it would not have approved Paxil had it received more information about the Paxil run-in events?

A. No.

MR. WISNER: Objection, speculation. Move to strike.

THE COURT: Sustained.

BY MR. BAYMAN:

Q. After FDA received the re-analyses that we just looked at, did FDA ask GSK to make any changes to the Paxil label concerning suicidality?

A. No.

MR. WISNER: Objection. Move to strike.

THE COURT: Now, wait. What time are we talking

about, what timeframe?

MR. BAYMAN: 2002-2003 when they received the analysis.

THE COURT: He wasn't there then.

MR. BAYMAN: But he's reviewed the file. He's reviewed the regulatory --

THE COURT: Based on the file?

MR. BAYMAN: Yes, sir.

THE COURT: Okay. With the understanding it's based on the file --

MR. BAYMAN: Correct.

THE COURT: -- he may answer.

MR. BAYMAN: His review of the file, right.

BY THE WITNESS:

A. Right. The answer is no.

BY MR. BAYMAN:

Q. Turn, if you would, to Tab 20 in your notebook. What is this document?

A. This is what's called an -- excuse me -- FDA talk paper. It's posted by FDA to provide information on an issue that is of interest to them.

Q. Does this talk paper communicate FDA's official activities and views?

A. Yes, it does.

Q. Do you and your colleagues at GSK regularly review FDA talk papers?

A. Yes, we do.
Q. Do you and your colleagues at GSK rely on FDA talk papers to understand the FDA's view of a particular subject?
A. Yes, in addition to direct correspondence with the company, but yes.
Q. And does this talk paper relate to paroxetine and suicidality?
A. Yes, it does.
THE COURT: What exhibit number is this? You said Tab 20.
MR. BAYMAN: I'm sorry. It's Exhibit, defense Exhibit 414, your Honor.
BY MR. BAYMAN:
Q. Does -- you said FDA posts these talk papers. Where do they post them?
A. They have a website where these are posted.
Q. Does this document provide context for GSK's decision regarding paroxetine and suicide based on your review of the Paxil file for purposes of getting up to speed to perform your job responsibilities?
A. Yes.
MR. BAYMAN: Your Honor, I would at this point move for admission under Rule 803(8) and for permission to publish the talk paper.
MR. WISNER: Your Honor, pretrial, they moved to

exclude any reference to pediatrics, objected numerous times during our case in chief. The title of this is regarding antidepressant Paxil for pediatric population. So goose and gander here. If they're going to strike all that stuff from our case, they can't suddenly bring it in after we've closed.

MR. BAYMAN: Judge, the pediatric story has been touched. I'm not going into pediatrics. There's some statement about adults in here that I want to use. I'm not opening the pediatric story up. There's been plenty brought up by the plaintiffs about pediatrics.

THE COURT: What part of this are you interested in?

MR. BAYMAN: I was going --

THE COURT: Just without reading it --

MR. BAYMAN: The second paragraph, second sentence, your Honor.

THE COURT: Of the second -- of the first page?

MR. BAYMAN: Yes, sir.

THE COURT: Let me look at it.

MR. WISNER: To the extent they're offering that sentence, I'd object under hearsay grounds.

THE COURT: Is that the paragraph beginning, "The Food and Drug Administration said today," is that what you -- is that the paragraph?

MR. BAYMAN: Your Honor, I'll move on to another topic. I'll withdraw it.

THE COURT: All right.

BY MR. BAYMAN:

Q. As part of your work in this case, are you familiar with the plaintiff's expert witness's opinions that GSK somehow hid suicide-related adverse events by using the coding term "emotional lability"?

A. I have heard that, yes.

Q. Do you agree with their assertions that suicide events were -- GSK hid suicide events by coding them as "emotional lability"?

A. No, because they are reported as suicide attempts and suicides.

Q. Doctor, based on your experience as a psychiatrist, what does emotional lability mean?

A. Emotional lability can subsume a number of behaviors: Rapid changes in mood, irritability including behavior changes which could also subsume suicide attempts, things of that nature.

Q. And a phrase has been used in the trial, "coding."

A. Yes.

Q. Coding term.

A. Yes.

Q. Can you explain how this process works?

A. Yes. So coding, think of it as a way of trying to get a bunch of different information to kind of map to a consistent

information so you can compare across different studies. So one example is, an investigator hears from a patient, "I'm throwing up." They write down, adverse event, throwing up. The investigator hears from a patient, "I have upchucked." They write that down. The investigator writes down, "I vomited."

So all of those are the same things, but they're different verbatim terms. So these coding dictionaries have been developed to allow those to be mapped to a common term. So the verbatim gets mapped to a code that can then be understood across different studies and programs like "vomiting" in that case.

So that's what a coding dictionary does. It takes those verbatim or as-said terms and makes them translatable across studies.

Q. And for those of us that are non-technical, when you say "dictionary," you don't mean a Webster's dictionary, you mean a computer database?

A. Yeah, a database that contains all of these codes.

Q. And how was the term "emotional lability" used in GSK's adverse event reporting from the Paxil clinical trials?

A. The coding dictionary at the time of the Paxil clinical trials did not include a code for suicide attempts. It did include a code for overdoses, so overdoses that could be suicide attempts could be mapped to that. So in choosing

where suicide attempts could be mapped to, the emotional lability master code was chosen for the reasons I had outlined before.

Q. Is it correct to say that GSK never informed the FDA about the meaning of the term "emotional lability" or how it was used?

A. No, that's incorrect.

Q. I want to just -- we've seen these before. I want to just do it very briefly, but take a look, if you would, at Tab 14, which is Plaintiff's Exhibit --

THE COURT: All right. We'll take a break now.

(Recess from 2:58 p.m. to 3:15 p.m.)

(Change of reporters, Vol. 15-C.)

[redacted]

(Jury enters courtroom.)

THE COURT: All right. Thank you very much, ladies and gentlemen. Please be seated. We'll resume.

MR. BAYMAN: Thank you, your Honor.

THE COURT: Proceed, sir.

MR. BAYMAN: Your Honor, at this point, I'd move for permission to publish Plaintiff's Exhibit 75. That's Tab 14 in your book, which is admitted already into evidence.

THE COURT: You may proceed.

MR. BAYMAN: Thank you.

BY MR. BAYMAN:

Q. Dr. Kraus, if you'll turn to Tab 14.

A. Yes, the integrated safety study.

Q. Was that submitted to the FDA from GSK or SmithKline Beecham at the time?

A. Yes.

Q. When was that?

A. This was probably submitted in '89, yes, November of '89.

Q. Does it contain summaries of suicide attempts that occurred during the MDD major depressive disorder clinical trials of paroxetine?

A. Yes, it does.

Q. If you turn to page 207, middle of the bottom of the page.

Pull that up, please.

Do you see that?

A. Yes.

Q. And then turn over to page 208a. What's on this page, Doctor?

A. This is a case narrative of an adverse event of a suicide attempt. The first one is overdose. The second one is suicide attempt.

Q. How is the event here, suicide attempt, how is that -- to what preferred term is that coded?

A. Right. In the -- you take a look at the adverse experience, you see at the end something called PT, which is that preferred term, the mapping that we talked about. So, you see listing the suicide attempt, and as we described, we mapped that to emotional lability.

Q. And based on your review of the Paxil data and the regulatory file, have you seen other documents in which GSK has identified suicide-related adverse events as being coded to the preferred term emotional lability?

A. Yes.

MR. BAYMAN: You can take that down.

BY MR. BAYMAN:

Q. Did FDA ever tell GSK to change the way emotional lability was being used in the paroxetine label?

A. No.

Q. Did FDA ever ask GSK to add language to the label to explain how emotional lability had been used?
A. No.
Q. Did FDA ever tell GSK to do anything at all with respect to coding suicide events under the preferred term emotional lability?
A. No.
Q. All right. I want to -- let's move forward in our -- we've kind of been moving chronologically. And I just want to talk to you about 2004. And no document at this point, but are you aware from your review of the Paxil data, including the regulatory file, that in 2004, the FDA requested manufacturers of 10 antidepressant drugs that they strengthen the warning section of those labels to encourage close observation for worsening of depression or emergence of suicidal thinking in behavior in both adults and pediatric patients being treated with these medications?

MR. WISNER: Objection. Leading.

THE COURT: Yeah, it sounds leading. It is leading.

MR. BAYMAN: Okay. Well, I'm just trying to --

THE COURT: It's also rather compound.

MR. BAYMAN: Okay. I was just trying to move along.

THE COURT: Trying to move along.

MR. BAYMAN: Move along, yes, sir.

THE COURT: We appreciate that.

BY MR. BAYMAN:
Q. What was your -- based on your review of the regulatory file and the other Paxil data, what was your understanding of what FDA in 2004 asked antidepressant manufacturers to do with respect to their labels and the issue of suicide?
A. This was an update to the label based on some of their ongoing analyses at that time.
Q. And did GSK comply with the FDA's request?
A. Yes.
Q. And did GSK change the Paxil label in 2004?
A. Yes, according to the FDA's requirements, yes.
Q. And did GSK take any action to alert doctors of the labeling change in 2004?
A. Yes. A Dear Health Care Provider letter was distributed that provided the context and the updated label.
Q. Turn, if you would, to Tab 22, which is Joint Exhibit 7.
MR. BAYMAN: Let's pull that up, please.
Permission to publish, your Honor? It's in evidence.
THE COURT: Yes.
MR. BAYMAN: Thank you.
BY MR. BAYMAN:
Q. Okay. Are you familiar with that document?
A. Excuse me. Yes, I am.
Q. What -- tell the jury what a Dear Health Care Provider letter is.

A. This is a correspondence from a drug manufacturer that goes out to doctors, physicians that would be treating the disease of interest, to provide any updated information that may be important in their understanding, either the benefit or the risk of the medicine.

Q. Okay. Turn --

MR. BAYMAN: If you -- bring up the second page.

BY MR. BAYMAN:

Q. Who signed this letter, Doctor?

A. It was Alan Metz.

Q. And who was Alan Metz?

A. Alan Metz was at that time VP of Medical Worldwide Development North America.

Q. Did you work with Dr. Metz when you joined the company in 2005?

A. Yes, I did.

Q. Let's look at the first paragraph, eight lines, starting with, "These labeling changes."

MR. WISNER: Your Honor, I'm going to object. This is cumulative. We went through in detail this letter and the attached labeling with it with several witnesses now. This is not even 2007 or '10.

THE COURT: There was cross-examination on this by the defendants, as I remember.

MR. WISNER: That's correct.

MR. BAYMAN: Of Dr. Ross, but we have a GSK witness here, your Honor, who will talk about what GSK did in response to the FDA's request. And this is the -- this is when the warnings as to suicide -- this is when the chronology really begins.

THE COURT: All right. You may proceed.

MR. BAYMAN: Thank you.

Can you blow that up, please.

BY MR. BAYMAN:

Q. Okay. It says, "These labeling changes, which have now been finalized, describe that patients with major depressive disorder" --

THE COURT: Excuse me. I want to get the date of this as well.

MR. BAYMAN: Yes, sir. The date of the letter is -- it's May of 2004.

Can you pull that up, Mr. Holtzen.

THE COURT: Okay. 2004.

MR. BAYMAN: Yes, sir.

THE COURT: All right.

BY MR. BAYMAN:

Q. As the language on the screen says that, "These labeling changes, which have now been finalized, describe that patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence

of suicidal ideation and behavior (suicidality) whether or not they are taking antidepressant medications. The changes include a new warning recommending close observation of adult and pediatric patients treated with antidepressant drugs for worsening depression or the emergence of suicidality, particularly at the beginning of treatment or at the time of dose increase or decrease."

Do you see that?

A. Yes, I do.

Q. And did GSK provide the new labeling to the doctors along with the letter?

A. Yes. The new label is included with the letter when these are sent out.

Q. Let's take a -- let's pull up, if we would, pages -- it's 10 and 11 of the labeling. It's 14 and 15 of the exhibit, Doctor.

MR. WISNER: Your Honor, we were told that he would offer opinions. He's literally just reading things that we've read three times.

MR. BAYMAN: I'm getting ready to ask his opinion.

THE COURT: Is this language which was in the 2010?

MR. BAYMAN: Some of it was.

THE COURT: Some of it was removed.

MR. BAYMAN: Some of it was removed, and some of -- a lot of -- most of it was in.

THE COURT: I think you should make that clear, what was left in the 2010 and what was not. I think that I, and -- I'm sure the jury isn't confused, but I'm a little confused about what's in and what's out, so be careful with that, if you would.

MR. BAYMAN: Yes, I will. I'll try to do that.

BY MR. BAYMAN:

Q. Doctor, you testified earlier today that the original Paxil labeling with respect to suicide was giving disease state information.

A. That's correct.

Q. In your opinion, is this disease state information? Is this a disease state warning?

A. No. This -- this warning is related to disease, but also to medication and treatment. As you see, it now applies to dose changes, increases, decreases, and also in terms of discontinuing medication.

Q. Do the -- does the warning reflected here in this labeling -- is it limited to any certain population or age of patients?

A. No. It extends to adult and pediatric.

Q. And is it limited to adult patients under the age of 25?

A. No.

Q. And then let's go to -- yeah, "The following symptoms."

This language, which we've looked at plenty of times

in this case, was this the first -- was this the first time in a clinical -- there was a warning of clinical worsening of suicide risk in the Paxil label that described akathisia?
A. Yes.
Q. And was this language proposed by the FDA, or was this language GSK's language?
A. This is class language from the FDA.
Q. Did the FDA's language in 2004 say anything about whether a causal relationship had been established between the emergence of symptoms like akathisia and suicidality?
A. Yes. They state that a causal link between these symptoms has not been established.
Q. Let's --
THE COURT: This is all FDA-mandated language? This is not GSK's own language?
THE WITNESS: Right. This is the language that was sent to the 10 manufacturers of antidepressant drugs. All of them had to put this in as class language.
BY MR. BAYMAN:
Q. Let's jump ahead then, because the jury -- we've been -- we've been over these labels. Let's look at -- let's move forward to 2005.
A. Is there a tab, or not yet?
Q. Not yet.
A. Okay.

Q. Did FDA require manufacturers to -- in early 2005, to change the antidepressant labels with respect to suicide -- warnings of suicidality?
A. Yes.
Q. Okay. What happened in January of 2005?
A. This was -- I believe it was the time of the advisory committee around the pediatric, which led to recommendations around updating labeling; and that came out in 2005.
Q. Okay. And was a -- was a Dear Health Care Provider letter sent to doctors in February of 2005?
A. Yes.
Q. And was that -- was the new labeling included with the letter?
A. Yes, the new labeling was included.
Q. Tab 23, if you would.
A. Yes.
MR. BAYMAN: Permission to publish Joint Exhibit 6, your Honor.
THE COURT: Yes.
BY THE WITNESS:
A. So, to clarify your question, the FDA came before February, in that January time period. The advisory committee was the year before.
BY MR. BAYMAN:
Q. That was my inartfully-worded question. Okay. Let's blow

this up, please.

This is the February 2005 Dear Health Care Provider letter?

A. Yes.

Q. And turn to, if you would -- the warning was changed. Let's turn to page 4 and 5. Blow that up, please, page 4.

Let's go back, actually. Go back to the black box, please. Okay. Blow that up, please.

Is this when the black box label was added to Paxil and other antidepressant medications?

A. Yes. This is when the boxed warning was added, that's correct.

Q. So, to his Honor's question to you earlier, this would have been new in 2005?

A. Yes, that was new in 2005.

MR. BAYMAN: Okay. Let's then turn, if you would, then, to, Mr. Holtzen, what you had up before with respect to the labeling that was not in the black box.

Can we do the -- get the heading before we pull that up?

MR. WISNER: Your Honor, just for the record, can we just talk about what pages we are talking about.

MR. BAYMAN: Okay. I want the warning section, clinical worsening and suicide risk.

MR. WISNER: So, the black box warning, page 004, is

that what we're doing?

MR. BAYMAN: No, I'm going outside the black box.

MR. WISNER: Okay. So, you were just on page 4, Joint Exhibit 6.

BY MR. BAYMAN:

Q. Now, is this language different now in 2005 than what was there in 2004?

A. Yes. It's been updated based on the new analysis.

Q. Okay. And it talks about the pediatric findings, correct?

A. That's correct.

Q. That's the new analysis?

A. Yes, sir.

Q. And there was a --

MR. BAYMAN: Mr. Holtzen, pull up the phrase you had highlighted earlier, "It is unknown."

BY MR. BAYMAN:

Q. This statement, "It is unknown whether the suicidality risk extends to adults," that was in there before 2004?

A. No, I believe that was new.

Q. So, that's new?

A. Yes.

Q. Okay. And in your opinion, does this labeling address whether there was a risk of suicidality for adults in January of 2005?

A. It addresses it in the sense that it states it's unknown

whether that risk extends to adults.
Q. In your opinion, does it say it doesn't apply to adults?
A. No, it does not say that.
Q. Let's look -- is there language in here about suicidality at the start of paroxetine therapy.
MR. BAYMAN: The second full paragraph, Mr. Holtzen, starts with, "Adults with MDD"?
BY THE WITNESS:
A. Yes. It's a --
THE COURT: I'm going to stop you there. I don't know where you are now.
MR. WISNER: So, your Honor, here's the problem. The exhibit that's up on the screen is actually not Joint Exhibit 6, although I think it has the same text in it, so I don't think it's materially different. But that's the problem. So, it looks a little different in our binders than it does on the screen.
MR. BAYMAN: The language is the same, your Honor. I'm sorry for that. I was trying to get to your point about what came in and what went out.
Do we have --
MR. WISNER: So, your Honor, this is on page -- Joint Exhibit 5 --
THE COURT: Ignore me, Mr. Bayman. Ignore me.
MR. BAYMAN: All right. Well, you asked --

THE COURT: Just go on with your presentation.
MR. BAYMAN: You asked what came in and what came out.
THE COURT: I made a mistake. I shouldn't have asked a question.
MR. BAYMAN: Okay. Just want to be responsive, your Honor.
BY MR. BAYMAN:
Q. Is there language about suicidality at the start of paroxetine therapy in this label?
A. Yes, and this section speaks to it. And it goes to what we talked about before around looking at the initiation of drug therapy, at times of dose changes as well.
Q. Is this disease management language?
A. No, because as I stated before, it's related to changes in treatment of medications.
Q. Let's look down at the third full paragraph on the same page, the label from FDA in 2005 says, "Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established. There is concern that such symptoms may represent precursors to emergent suicidality"?
A. Yes.
Q. In your opinion, what is that -- as a physician, what is

that alerting you to?
A. That's alerting you to the heightened awareness to look at the symptoms they have listed there, given the proposal that they may be related to emerging suicidality. However, there's been no causal link, so it's really just heightened awareness.
Q. And this is new language, correct, that such symptoms may represent precursors?
A. That's correct.
Q. And is there new language in early 2005 about what to tell families and caregivers?
A. Yes, there is.
MR. BAYMAN: Let's go to that, Mr. Holtzen.
BY MR. BAYMAN:
Q. And this is the language alerting families and caregivers for both MDD and other indications, psychiatric and non-psychiatric, to be alerted to the need to monitor the patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above. Those are the symptoms that we saw earlier that included akathisia?
A. That's correct.
Q. And that last sentence, "Families and caregivers of adults being treated for depression should be similarly advised"?
A. Yes, exactly.

Q. Does the language in this part of the label apply only to pediatric patients?
A. No, it does not.
Q. Is it limited to any particular age bracket of adults?
A. No, it is not.
Q. Let's turn to page 6 of the -- this exhibit. You see the precautions section?
A. Yes.
Q. Pull up, if you would, akathisia.

Is this language, this precaution with respect to akathisia, is this new in the 2005 label?
A. Yes, that was added to the 2005 label.
Q. And it says, "The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still, usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment."
A. Yes.
Q. Do you see that?
A. Yes, I do.
Q. Are you familiar with the medical term "akathisia"?
A. Yes.
Q. Tell the jury what that means.
A. Akathisia is -- as it describes here, is characterized by

psychomotor agitation. So, what does that mean, psychomotor? Psycho is some of the internal sense of feeling agitated, but it's accompanied by kind of a physical manifestation. This can include inability to sit still, moving up and down, things of this nature.

It happens, in my experience, most frequently with antipsychotic medicines. So, in schizophrenia trials, I saw this a lot.

Q. Have you treated patients with akathisia?

A. Oh, yes.

Q. Do you know how to recognize it?

A. Yes.

Q. Is that something you were taught in medical school?

A. Primarily in our psychiatric residency is where we would deal with akathisia, since it's related to mainly antipsychotic medications.

Q. Has GSK ever studied the question of whether akathisia in paroxetine patients is associated with an increased risk of suicidality?

A. Yes.

Q. And what did you conclude?

A. In that analysis, akathisia was not associated with an increased risk of suicide or suicide-related adverse events.

Q. Did GSK provide these new labels, the revised Paxil labeling, to doctors along with the letter in 2005?

A. Yes, we provided it.
Q. Let's jump forward to 2006. Now, at this point, you were with GSK, correct?
A. I am with GSK, that's right.
Q. And did there come a time when FDA undertook a comprehensive review of the clinical trial data for adults and suicidality for antidepressants, including Paxil or paroxetine?
A. Yes.
Q. And did the FDA explain to GSK and the other manufacturers why they undertook this review of the adult suicidality data?
A. Yes, they did.
Q. And what did they tell you?
A. It's similar to what you saw in that label. It was unknown whether the risk extended to adults. So, FDA wanted to do a similar review that was done for pediatrics of the adult data to assess whether or not an increased risk was associated with treatment in the non-less-than-18-year-old age group, originally just looking at major depression, but then they extended it to other diseases.
Q. Did FDA identify the types of clinical trials for Paxil from which it wanted data on suicidality?
A. Yes. They wanted -- I spoke a bit to this earlier. They wanted placebo-controlled, so that side-by-side comparison phase of the study. They wanted them to be acute, so those

early treatment studies, and of reasonably short duration, less than 17 weeks, and of sufficient size, 30, such that they could bring meaningful data to the analysis.

And in their request to us, FDA -- obviously, in our New Drug Application, they know all of our studies. They picked out studies that they believed would meet this criteria, asked us to review and provide comment.

Q. Did they actually give you a list by study number?

A. Yes.

Q. Now, how would they know?

A. Well, we submit all of our studies to the New Drug Application, so as our -- remember that slide. As each new indication gets approved, FDA gets all of the studies associated with that, all of the study reports, protocols. So, they're able to understand what might fit their criteria.

Q. So, if I understand it, the original NDA was for major depressive disorders. When you later then submitted for, say, generalized anxiety disorders, you submitted the clinical trial data where patients were being -- who had generalized anxiety disorders were given Paxil or placebo or other comparators, for example?

A. Yes. Every new indication, it all goes into the drug application as Supplemental New Drug Application. So, they have awareness of all the studies.

Q. Now, you said they gave you the list. Did you have an

opportunity to comment on that list?
A. Yes, we did.
Q. And did that -- did you have the opportunity to include other trials that may not have been included?
A. Right. We were able to highlight other placebo-controlled trials that seemed relevant to their request, as well as identify trials that were not appropriate, for example, they were too long, things of that nature.
Q. Did FDA want data from open label or active control trials?
A. No.
Q. Did FDA explain why it didn't want events from open label trials, for example?
A. Yes. They felt that not having that ability to have the control group --
MR. WISNER: Objection. It's either hearsay or speculation.
THE COURT: Yes, sustained as to what they felt.
MR. BAYMAN: No, I said did they tell them.
BY THE WITNESS:
A. They wrote a letter --
THE COURT: You're going to have to rephrase it, sir. It's not what they felt.
THE WITNESS: I can rephrase that, sir. I misspoke there.

MR. BAYMAN: Let's put up Joint Appendix 15, pages 50 and 51. It's in evidence. Pull that up.

BY MR. BAYMAN:

Q. This is in evidence. It's been published before.

A. Right. And this is where they say, "Please do not submit data from active-control-only studies, uncontrolled extensions of placebo-controlled studies, or combination drug studies."

Q. What was your understanding, you and your colleagues at GSK, as to why data from those other studies was excluded by FDA?

MR. WISNER: Objection. Speculation. He can't opine as to why the FDA did something.

THE COURT: No, but he can testify as to his understanding.

MR. WISNER: But the understanding as to why, it's the same question. It's just couched --

THE COURT: All right. The why goes out, but give us your understanding.

BY MR. BAYMAN:

Q. What's your understanding?

A. The understanding is because they were uncontrolled studies, there were confounding variables, as we discussed earlier, that make it difficult to understand whether or not a complex behavior like a suicide or suicide attempts would be related to drug treatment. So, they wanted that control

group, that placebo group in order to answer that question.
Q. What -- explain what you mean by --
THE COURT: I think we've been over this. We've heard about what they want, the type of studies. It's been very thoroughly examined.
MR. BAYMAN: I just want to ask him about confounding.
THE COURT: What?
MR. BAYMAN: Confounding. He used the word "confounding." I want him to explain to the jury what confounding means.
THE COURT: I don't think we need to know what confounding means, do we?
MR. BAYMAN: Well, yeah. It's why they were excluded, because they were confounding -- they could be confounding factors. I just want him to explain to the jury what that means.
THE COURT: Oh, you mean in technical terms?
MR. BAYMAN: Yes, sir. Yes, sir.
THE COURT: Okay.
BY THE WITNESS:
A. There could be instances of additional medications being used so that you couldn't ascertain what may be behind a certain adverse event. The duration of time, as we talked about before, which with an adverse event like suicidality,

without any control group, it's difficult to understand whether that's part of the disease itself or whether it's related to treatment. Things of that nature would have been difficult to understand in the context of an analysis.

So, as we have been talking about, FDA in their request, wanted the placebo-controlled portions so you can see what happens over time in the absence of any active medicine, what happens over time with that active medicine, at the same time, with the same kind of population.

BY MR. BAYMAN:

Q. Have you in your entire career ever seen FDA use the term placebo-controlled portion of a clinical trial to mean anything other than portions of placebo -- well, of clinical trials that have concurrent placebo controls?

MR. WISNER: Objection. Cumulative.

THE COURT: You may answer.

BY THE WITNESS:

A. No. When FDA makes --

THE COURT: You've answered it, sir.

THE WITNESS: Okay.

BY MR. BAYMAN:

Q. I want you -- you're familiar with the opinions of the plaintiff's experts?

A. Yes.

Q. Dr. Ross offered the opinion that a suicide study 083 was

improperly excluded from the 2006 analysis. Are you familiar with study 083?

A. Yes.

Q. Can you describe its design?

A. This was similar to what we talked about before, that kind of randomized withdrawal looking at relapse, where you have a portion of the study where every patient is on Paxil, and that those patients that respond would then go to either stay on that drug or be withdrawn. So, there's an uncontrolled part and then that relapse part.

Q. Can we pull that relapse slide back up, 7036-A that we showed -- got permission to show earlier.

This is the graphic you're talking about?

A. Yes, that's the graphic I was talking about.

Q. Now, based upon your review of study 083, are you familiar with the circumstances of the suicide that occurred during that study?

A. Yes. It had occurred on the left side where there is paroxetine alone without a comparator group.

Q. Should this suicide have been included in your submission to the FDA in 2006?

A. No. It didn't meet the criteria for the analysis.

Q. Should it have been included in your own analysis in 2006?

A. No, for the same reason. The analysis was based on placebo-controlled portions of studies.

Q. Does this mean that the company ignored this suicide?
A. No.
Q. What did the company do when it learned of the suicide in study 083?
A. Suicides, suicide attempts, any adverse events that occur in our studies all are reported into our central safety database. So, every event is captured from every clinical trial that we do.
Q. Okay. I want to move on, move you to Tab 25.
MR. BAYMAN: Defense Exhibit 431, your Honor.
THE COURT: Okay.
BY MR. BAYMAN:
Q. What is that document?
A. This is another FDA talk paper like we described before, where FDA is providing information on an issue that they may be examining. And this one's on reviewing antidepressant use in adults.
Q. And we talked about FDA talk papers. That's something that you and your colleagues rely on for the FDA's official position on whatever the issue may be?
A. Yes.
Q. And that's -- the FDA posts that, posts those talk papers on its website?
A. That's correct.
Q. And it reflects the agency's official views or results of

official investigations?
A. Yes, it does.
Q. And do you and your colleagues regularly monitor these FDA talk papers?
A. Yes, we do. We monitor the website.
Q. And based on the work you've done as part of your responsibilities, did you and your colleagues at GSK rely on this talk paper as part of your ongoing assessment of the Paxil/paroxetine label as it related to suicidal thinking and behavior in adults?
A. Yes.
MR. BAYMAN: Your Honor, I'd move to publish.
MR. WISNER: Objection, your Honor, both on hearsay grounds and relevance. On the relevance issue, I do not believe Illinois law imposes a duty on the FDA to warn. I believe that duty rests with GSK. So, any statements made by the FDA that had nothing to do with GSK cannot possibly be relevant in this case.
THE COURT: What is it that you want to call attention to in the document?
MR. BAYMAN: What the FDA --
THE COURT: What paragraph, so I don't --
MR. BAYMAN: Second paragraph, your Honor.
THE COURT: You're interested in the second paragraph?

MR. BAYMAN: Yes, sir.
THE COURT: Just give me a minute.
MR. WISNER: If it's just the second paragraph, I have no objection.
MR. BAYMAN: Actually, second and third paragraph, your Honor.
MR. WISNER: Oh.
THE COURT: The first bullet? You have -- okay. There's no objection to the second paragraph.
MR. WISNER: Any other parts, I do object to, your Honor.
THE COURT: Oh, you object to the other?
MR. WISNER: Well, he just told us it's the third paragraph.
MR. BAYMAN: Well, the second and the third were the two I was going to ask him about. That's all I was going to do.
THE COURT: Is the third paragraph the one with the bullet?
MR. BAYMAN: It starts, "Adults being treated with antidepressant" -- it's a bullet. It's also --
THE COURT: Okay. Let me read it.
Okay. You may proceed.
MR. BAYMAN: May I publish? Thank you, your Honor.
Do you want to put that up.

BY MR. BAYMAN:
Q. This -- is this information that -- this talk paper is for prescribers also?
A. It's public, so it's on the website, so anyone can see that; but, yes, for prescribers as well.
Q. And what's your -- does this paragraph describe the analysis that the agency was undertaking with respect to adult suicidality and antidepressants?
THE COURT: It doesn't say anything in here about adults, does it? Oh, the second and third line? Okay.
MR. BAYMAN: Yeah.
BY MR. BAYMAN:
Q. It's saying that --
THE COURT: "Begin the process." I Gotcha.
MR. BAYMAN: Okay.
THE COURT: Thank you.
BY MR. BAYMAN:
Q. Take a look at the next paragraph. Did the FDA say anything in this talk paper to healthcare providers about the care of adult patients currently on antidepressants?
MR. WISNER: Objection.
THE COURT: That's a negative question. Sustained.
MR. BAYMAN: Okay. Let me rephrase.
BY MR. BAYMAN:
Q. What does this say -- what did the FDA say in this

paragraph with respect to the treatment of adult patients who are currently on antidepressants?

A. The FDA reiterates points that were existing in the label about adults being treated with these medications, especially for depression, watched closely for worsening or increased thinking or behavior. Close observation of adults may be especially important when antidepressant medications are started for the first time or when the doses are changed. And then adults whose symptoms worsen while being treated with antidepressants, and that can include suicidal thinking or behavior, should be evaluated by their healthcare professional.

And they add that these warnings were already within the label. They were just reiterating them in this talk paper.

MR. WISNER: Your Honor, I again renew my objection this time as well as there's been no foundation that this ever got to Dr. Sachman; and, therefore, it's just a red herring.

THE COURT: Well, it may stand.

MR. BAYMAN: Thank you.

BY MR. BAYMAN:

Q. Did FDA in this talk paper limit adult patients to any particular age group?

A. No.

Q. At this point in time, July of 2005, did the FDA request

any additional labeling changes for Paxil concerning the risk of suicidal thinking or behavior for adult patients?

A. No.

THE COURT: Are you referring to this label -- or this message? Are you referring to this talk --

MR. BAYMAN: Yes, sir -- no, I'm sorry. My question was broader than that at this point in time.

THE COURT: That's what I wondered.

MR. BAYMAN: Yes, sir.

BY MR. BAYMAN:

Q. Okay. Let's move ahead in our chronology. After FDA announced that it was going to do an analysis of adult suicidality data from the clinical trial -- placebo-controlled clinical trials of the various manufacturers, did GSK decide to do any type of analysis?

A. Yes, we did.

Q. Why did you do that if the FDA was going to go ahead and do it?

A. Well, the drug manufacturers were asked to collect the data and to submit to the FDA. So, GSK would have had the paroxetine data going to the -- going to FDA.

So, as we collected the data and as there were new methodologies that were being employed in the FDA analysis based on what it had learned from their earlier analysis in pediatrics, we had the data; and as part of our ongoing

assessment of the safety of the medicine -- as you've seen, we've looked many times at this before -- we used this data to look again at whether there was any increase association of paroxetine treatment with suicidal ideation or behavior relative to placebo.

Q. There's been some testimony in the case about a process by which adverse events were sent to experts at Columbia University for analysis. Could you tell the jury a little bit about that?

A. Yes. So, what were called possibly suicide -- suicidally related adverse events were collected using a process looking at certain words in text strings to go across all the clinical trials. From those, it was -- a case narrative was developed. And we actually had a third-party vendor actually write the narratives for these suicidality-related adverse events.

Those narratives were then provided to external experts to what was called adjudicate or judge whether or not they were an aspect of suicidal behavior. And I think there was a list of nine things that they could have characterized, including suicide attempts, preparation for suicide, suicides themselves, ideation, not related, or not enough information, things like that.

Q. Now, you say a narrative. What do you mean by a narrative?

A. So, it's a description of what happened to that patient in

the study and what happened at the time of that adverse event. So, it's kind of a description. You know, what treatment were they taking? How long had they been on it? Age? Sex? What adverse events had they experienced in the study? What was the adverse event they experienced here? How -- what time did that occur after treatment? What was done? Did the patient stay in study or leave? Those sorts of things.

Q. Now, did I understand you to say that an outside firm prepared the narratives, not GSK?

A. That's correct.

Q. Did GSK control how these narratives were written?

A. No.

Q. Did GSK try to influence how the narratives were prepared?

A. No.

Q. Did GSK try to influence how the experts at Columbia reviewed these?

A. No.

Q. And what were the -- the people that were preparing the narratives, what were they reviewing in order to do the narrative?

A. Well, they would review what we call the case report form from the clinical study.

So, each patient has information associated with their participation in the study that includes the rating scales we talked about, so efficacy, but also includes adverse

events, dose of medicine, things of that nature.

If there was a serious adverse event that was reported, it could also include hospital records and things of that nature that occurred around that time.

Q. Now, why would someone, to use your word, have to adjudicate whether something's a suicide attempt or not? Wouldn't you know?

A. From text strings and from sometimes what was provided by investigators, there wasn't a consistency among how events may have been reported. So, for example, they range from a patient slapping themselves could have been a suicide attempt, or adjudged as one, all the way to a severe attempt, such as an overdose or things of that nature.

So, it was a way to have kind of a common set of eyes with a common set of standards apply whether or not a suicide attempt occurred.

Because sometimes self-harm behavior, hurting oneself can occur without the intent of that patient or subject to want to die. And some of those narratives were able to provide that information for the adjudication as well.

Q. But it was the experts at -- was it the experts at Columbia who were reviewing those narratives and making the determination as to whether this was a suicide attempt or not, or was it GSK?

A. It was the experts at Columbia. They did that

adjudication independent from us.
Q. And the narratives were written, you said, from the case report forms. Is that called raw data?
A. Yeah, that's -- we call it the source material, but, yeah, it's raw data.
Q. All right. Turn, if you would, now to Tab 29.
MR. BAYMAN: Your Honor, this is Defense Exhibit 101. It's admitted into evidence.
Pull that up, please, Mr. Holtzen.
BY THE WITNESS:
A. Which tab was that?
BY MR. BAYMAN:
Q. 29.
A. Okay.
Q. Are you familiar with this document?
A. Yes, I am.
Q. What is it?
A. This is the cover letter for a briefing document that we submitted to FDA that provided the results of the first part of our own analysis of suicidal ideation and behavior.
And that first part of the analysis was the major depression studies. And the reason that was first is FDA initially asked for those studies and then added non-major depression. So, we had kind of two sets of data going through, and this was the first available.

Q. Were you personally involved in this analysis that was submitted to the FDA?
A. Yes, I was.
Q. What did you do?
A. Again, I was the project physician, so reviewed these from a medical, clinical perspective, reviewed the results.
Q. Let's look at the first paragraph, second sentence. "Reference is also made." What does that refer to, that sentence?
A. "Reference is also made to the agency's letter dated December 24th, 2004." This is going to the request that FDA asked us to provide this data for the adult studies to examine this question. So, we're just referring back to that original letter asking for the major depressive disorder studies.
Q. And the placebo -- from the placebo-controlled?
A. Absolutely, from the acute, so that early in treatment part, double-blind, neither the patient nor the investigator knows the treatment, randomized, so that patients by chance get assigned to one of the treatments, and it's placebo or paroxetine.
Q. Go down to the second paragraph. What are you informing FDA?
A. We're letting FDA know that we finished the first part of our analysis, which was the major depression subset.
Q. Did FDA require you to do this analysis?

A. No.
Q. Let's look at, if we can, Tab 30, which is -- I think it's been admitted as Plaintiff's Exhibit 9. It's also Defense 103.
Are you familiar with this document?
A. I may be on the wrong tab. Which tab?
Q. Tab 30.
A. Ah, I had to turn the page. Yes, I'm familiar with this document.
Q. What's this?
A. This is the cover letter for the -- or actually, this is the cover letter for the briefing document for the entire subset -- entire data. So, the major depression as well as the non-major depression.
Q. Were you involved in producing this report?
A. Yes.
Q. And were you involved in analyzing the data?
A. Yes, I was.
Q. How did the number of patients in this analysis in April compare to the number of patients in the one submitted in March?
A. I believe this added approximately two-thirds more subjects, if I recall correctly, but much more subjects were -- a total of about 15,000 subjects in this analysis.
Q. And was that because it included these other anxiety

disorders that we've talked about, like generalized anxiety disorder and OCD and things like --

A. Yes, it included all of those other indications that had been approved for paroxetine.

Q. Turn, if you would, to page 6, the clinical summary.

A. Okay.

Q. From your perspective as a clinician, what are primary and secondary end points in the context of a meta-analysis like this?

A. According to the context of any study, the primary end point is what's defined as the key question to be answered. It's predefined before you do the analysis plan. So, it's the key bit of information in a study.

Q. Let's look at the first bullet. What was the primary end point or objective of GSK's 2006 analysis?

A. The primary end point was of definitive suicidal behavior or ideation, so suicidality across the range.

Q. And what does that include, that spectrum?

A. That includes anything from having thoughts of wanting to kill oneself, to having made preparations to attempt to kill oneself, to a suicide attempt, to a completed suicide.

Q. Why did GSK establish suicidal behavior and ideation combined as the primary end point?

A. There were a couple of reasons. One is that in FDA's prior analysis of the pediatric data, this was the end point

that was able to distinguish a difference -- or evidence of an association between treatment versus placebo, so it appeared more sensitive in the pediatric studies. And also, it was our understanding that FDA would use this as well.

And then finally, ideation and behavior are all important components along the spectrum of suicidality. Patients with ideation or thoughts of suicide are at increased risk of attempts. Patients who have had suicide attempts are at an increased risk of suicide, and so on. So, it's a spectrum effect.

Q. Did GSK try to hide the risk of Paxil-induced suicide by focusing on ideation?

MR. WISNER: Objection. This witness does not speak for GSK, unless that's changed at some point in this.

MR. BAYMAN: He doesn't speak for GSK?

MR. WISNER: Oh, I'm sorry. Is he testifying as a corporate representative? My understanding, he was just testifying as a fact witness.

THE COURT: He may testify.

MR. BAYMAN: Thank you.

MR. WISNER: Sorry, your Honor. I just want to clarify for the record. If this is a Rule 30(b)(6) witness, I'd like to know. That was not disclosed to us. So far, I understand he was just a fact witness.

MR. BAYMAN: He's a designated expert. He's an

employee of GSK. I mean, I think he can --

MR. WISNER: That's fine. Just for the record, he speaks for the company.

THE COURT: Did he give a report?

MR. BAYMAN: He gave the disclosure that I --

THE COURT: Disclosure, but not a report?

MR. BAYMAN: Correct, because he doesn't regularly testify, your Honor. That's why he didn't do an expert -- he's not a retained expert, one who regularly testifies.

THE COURT: He's testifying as a company expert, company official?

MR. BAYMAN: Yes.

MR. WISNER: There's no objection to him testifying as a company expert, but that's significantly different -- is he speaking for the board of directors for GSK, or is he speaking for himself? I don't know.

THE COURT: I think it's clear he's speaking for GSK, isn't it?

MR. WISNER: Good to know. Then no objection.

MR. BAYMAN: He's giving his opinions as an expert who's employed by GSK, and he was involved in the analysis of the data.

THE COURT: Right. He may testify.

BY MR. BAYMAN:

Q. Were you involved in helping establish suicidal ideation

and behavior as the combined primary end point?
A. The end point had been defined prior to my joining the company, so I had not been involved in that.
Q. You were not involved in that, but were you involved in discussions about the results of that primary --
A. Yes, absolutely.
Q. Based on your experience at the company and your involvement in these analyses, did you and your colleagues try to hide anything by including suicidal ideation along with suicidal behavior?
A. No. And as I said, based on --
THE COURT: Okay. You've answered the question.
BY THE WITNESS:
A. No, we did not.
BY MR. BAYMAN:
Q. For adults with major depressive disorder, MDD, what was the result of this analysis for the primary end point, definitive suicidal behavior or ideation?
A. So, you see on the primary end point, there was no statistically significant difference between adults with major depressive disorder treated with paroxetine compared to placebo. So, here you see 31 out of 3,455, 0.9 percent, versus 11 out of 1978, 0.56 percent.
Q. Dr. Kraus, did this analysis show reasonable evidence of an association between paroxetine and definitive suicidal

behavior or ideation for adult patients with major depressive disorder?

A. No, it did not.

Q. And was that true for adult patients of all ages?

A. Yes.

Q. Now, turn if you would, please, to page 8, Section 3.2.

Got it?

A. Yes.

Q. Did GSK also examine this primary end point, which is definitive suicidal behavior or ideation in patients with psychiatric disorders other than major depressive disorder?

A. Yes, we did.

Q. What were the results of this analysis on this primary end point?

A. So, when we looked at all indications pooled, so all of those patients, approximately 15,000 if you add the Paxil and placebo, we found no significant difference between paroxetine treatment versus placebo in terms of risk. So, 0.93 percent for paroxetine versus 1.09 percent for placebo.

When just looking at depressive disorders, which includes major depression, bipolar depression, things of that nature, again, no difference between paroxetine and placebo, 1.77 for paroxetine or Paxil versus 2.08 percent for placebo.

And then finally, when we look at the all non-depression, so this is primarily those anxiety disorders

we talked about, generalized anxiety, PTSD, things of that nature, there was also no difference between Paxil, which was 0.32 percent, versus placebo, which was 0.49 percent.

Q. Dr. Kraus, did this analysis show reasonable evidence of an association between Paxil and definitive suicidal behavior or ideation for patients in these other patient populations?

A. No.

Q. And is that true for adult patients of all ages?

A. That's correct.

Q. Now, did GSK actually examine the data on suicidal behavior and ideation by age range?

A. Yes, we did.

Q. Let's pull up table 2.08.

What is this table?

A. Excuse me. This is a table from the listings of the analysis. This is looking at the number and percent of subjects with the primary end point, definitive suicidal behavior and ideation, and breaking it down by a couple of characteristics. One was baseline suicidal ideation, whether it was present or absent. One by age group, so you can see the different age groups there, less than 18, 18 to 24, 25 to 64, greater than 65; and then also by gender, male and female.

Q. What were the results of this analysis for adults aged 25 to 64?

A. There was no difference in the rate of occurrence of these

events between paroxetine and placebo. You see 0.78 for paroxetine versus 1.14 for placebo.

Q. Is that even nominally protective?

A. The odds ratio is less than 1, so that can be said.

Q. But it was not statistically significant?

A. No.

Q. What does protective mean?

A. Protective means in this instance, a positive effect on reducing suicidal behavior or ideation.

Q. So, not increasing the risk, but reducing the risk?

A. That's right.

THE COURT: Are you saying it reduces the risk?

THE WITNESS: What I'm saying is that odds ratio less than 1 of 0.7 is in a direction of reducing the risk, rather than increasing it.

THE COURT: But are you saying that this shows that?

THE WITNESS: I'm not saying that.

THE COURT: Are you claiming that this shows that?

THE WITNESS: I'm saying there's no difference between treatments.

THE COURT: No difference. But you're not claiming that it's effective?

THE WITNESS: I'm not claiming it's protective.

THE COURT: Protective. You're not claiming it's protective?

THE WITNESS: Right. I was answering the question as to whether .7 points to a protective --

THE COURT: Okay.

THE WITNESS: But I wouldn't make that statement.

BY MR. BAYMAN:

Q. Does it trend in a protective direction?

A. Yes.

Q. But it's not statistically significant?

A. That's correct.

Q. We'll come back to this analysis in a few minutes and other parts of it, but how many different analyses --

THE COURT: And we'll do that on another day.

MR. BAYMAN: Thank you.

THE COURT: I'm sure you're right, though.

MR. BAYMAN: Thank you, your Honor.

THE COURT: All right. Ladies and gentlemen, remember our ruling and your caution about not discussing the case. I know it's tempting, but please don't do it, for yourself, partly for yourself, because I want you all to be in a good position to take the case when we give it to you. And get some exercise and sleep, too, will you?

(Jury exits courtroom.)

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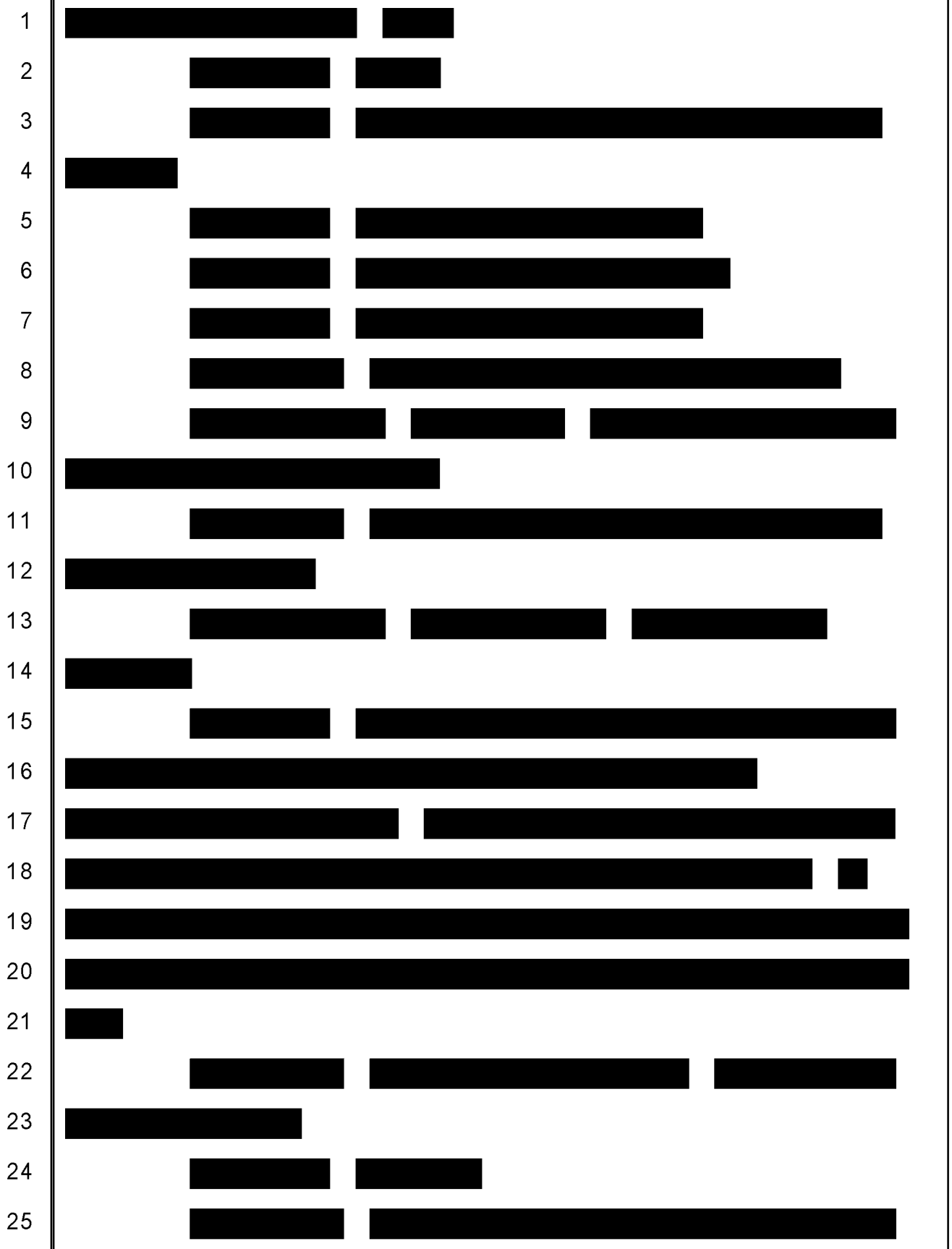

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(Court adjourned, to reconvene 4/10/17 at 9:30 a.m.)

CERTIFICATE

We certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

/s/Judith A. Walsh — *April 6, 2017*

Judith A. Walsh
Official Court Reporter — Date

/s/Charles R. Zandi — *April 6, 2017*

Charles R. Zandi
Official Court Reporter — Date