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

WENDY B. DOLIN, Individually and as Independent Executor of the Estate of STEWART DOLIN, Deceased,	)	
Plaintiff,	)	
-vs-	)	Case No. 12 CV 6403
SMITHKLINE BEECHAM CORPORATION, d/b/a GLAXOSMITHKLINE, a Pennsylvania corporation,	)	Chicago, Illinois April 4, 2017
Defendant.	)	1:30 p.m.

VOLUME 13-B
TRANSCRIPT OF PROCEEDINGS - Trial
BEFORE THE HONORABLE WILLIAM T. HART, and a Jury

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(Proceedings heard in open court, jury not present:)

[redacted]

[redacted]

(Jury enters courtroom.)

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

Ladies and gentlemen, you may be wondering about the length of the trial, as am I. And I'm told by counsel that they expect to finish next week, so we're hoping that everything will move along at that rate. I wouldn't venture to say when though, but next week.

All right. You may proceed.

MR. DAVIS: Thank you, your Honor. Counsel, ladies and gentlemen of the jury.

ROBERT GIBBONS, DEFENDANT'S WITNESS, DULY SWORN.

DIRECT EXAMINATION (Resumed)

BY MR. DAVIS:

Q. Dr. Gibbons, let's pick up where we left off.

MR. DAVIS: Your Honor, I'd ask permission to publish

DX 7035-I, which is a new slide that I handed your clerk over the break. And I've consulted with Mr. Wisner on this.

MR. WISNER: Your Honor, we have no objection. Provided it's in the context of a statistical approach, we have no objection.

THE COURT: All right. Proceed.

MR. DAVIS: Thank you.

BY MR. DAVIS:

Q. Dr. Gibbons, in terms of ranking the evidence as a biostatistician and researcher, can you tell us how you go about ranking the different types of scientific information in order to assess whether or not a medication is increasing the risk of suicidal thoughts or behavior?

A. So, we begin with a large randomized controlled trial, single trial that is -- has the benefits of randomization; and we analyze the randomized part, the double-blind part. And it's important that it's placebo-controlled, so that there are people who are receiving an inert substance like a sugar pill.

The second stage in the hierarchy is to look for consistency across multiple, similarly-designed studies, randomized controlled trials. And we use meta-analysis for that, research synthesis, statistical approaches to combining the information --

THE COURT: Tell the jury what you mean by

meta-analysis so we don't lose you.

BY THE WITNESS:

A. Yes, sir. Meta-analysis is a way of combining the information from multiple studies that are essentially studying the same thing. So, these would be a series of five or 10 or 20, or in the case of the FDA, 372 randomized controlled trials that compared, for example, paroxetine or other SSRIs to a placebo.

And meta-analysis is the statistical procedure that combines that information across that series of studies, comes up with an overall estimate of the effect, maybe a relative risk or an odds ratio, and then describes our uncertainty in that. How much variability is there in that? How consistent is it over the different studies that have been combined?

That's what meta-analysis is. And it's a form of research synthesis, and it's a statistical approach to the combining of information across multiple trials.

From a simple common sense perspective, we want to make sure that one large study we looked at is reproducible over multiple examples of that kind of study. And so this is looking for consistency across those studies.

We then want to know: To what extent does this generalize to the overall population? And there, we look at observational studies. What's an observational -- an observational study is a study where we might take medical

claims data, insurance data, where we know whether or not somebody filled a prescription for paroxetine, as an example, and then we have claims for different events. We might from those claims know whether or not that person made a suicide attempt.

And we look at hundreds of thousands, in some cases millions of these records, and we can determine whether or not people who were taking paroxetine or an antidepressant were different in terms of the rate of suicide attempts that they made relative to people who did not receive antidepressant treatment.

And this kind of strategy can be done in a variety of different ways, both between individuals who took a drug and didn't take a drug, or within individuals during periods of time where they were taking a drug versus times that they weren't taking a drug.

The difference between that and a randomized controlled trial is in a randomized controlled trial, through randomization, we get to balance those people who took the drug versus didn't take the drug. They're assigned to the drug or placebo based on a random process.

In the observational data, they're assigned to the drug based on characteristics that may lead their doctor to prescribe the drug. So, we might expect that the people who are more severely ill will receive a drug rather than

psychotherapy, as an example. So, there's the potential for bias, meaning that there's a potential for alternate conclusions to creep into the analysis.

But the advantage is we can look at very large populations, and we can see: To what extent do the results from the randomized controlled trials from the meta-analysis generalize to the overall population?

Finally, the lowest level on the hierarchy, published case reports, including challenge, de-challenge, rechallenge, uncontrolled healthy volunteer data. These data are important as well. They're important for generating hypotheses that we can then test scientifically using the methods that are above them, randomized controlled trials, meta-analysis, and large scale observational data.

MR. WISNER: Objection, your Honor. Move to strike the portion of his testimony dealing with more severe patients requiring drug, as opposed to psychotherapy. He's not a medical doctor or psychotherapist and cannot offer that opinion.

MR. DAVIS: Your Honor, I don't believe that --

THE COURT: It may stand. Proceed.

BY MR. DAVIS:

Q. You mentioned meta-analysis. Was the GSK analysis done in 2006 on adult suicidality, was that a meta-analysis?

A. Yes, it was.

Q. Was the FDA's analysis in 2006 a meta-analysis?
A. Yes.
Q. Now, tell us -- help us out, Dr. Gibbons. If randomized -- if a meta-analysis is a combination of placebo-controlled, randomized controlled trials, why does it -- and it's a combination or pooling of that, why does it rank No. 2, as opposed to --
THE COURT: Don't talk so fast, sir. The court reporter wants to get every word you say.
MR. DAVIS: Okay. Let me know if I'm going too fast, Charles. Thanks.
BY MR. DAVIS:
Q. Given that meta-analysis is a combination of placebo-controlled randomized trials, why is that on the second level and not at the top of the list?
A. So, a meta-analysis that combines multiple randomized controlled trials is not the same thing as having one really large randomized controlled trial where randomization is done from that particular sample from the population.
So, for example, meta-analyses may include people who received medication for different indications. Some of these people might have had depression. Some of these people might have had a social anxiety disorder. So, there's variability across the studies.
Some of the people may have received paroxetine in

certain studies. Others may have received sertraline, a different antidepressant. So, there's more heterogeneity across the particular medications that are used, the particular population that is sampled in terms of what their diagnosis was. There may be differences between the ages of the people in the different studies.

All of those things can creep into a meta-analysis; whereas, in a large observation -- in a large randomized controlled trial, all of those different features would be balanced in terms of getting the drug or getting the placebo. That's the fundamental difference.

Q. Doctor, can you give the jury an example of where there was a question or hypothesis that was raised in a published case report where it raised the question of whether medication or other exposure caused some type of disorder and then it was investigated by well-controlled studies and that didn't turn out to be the case?

A. Sure.

MR. WISNER: Objection. Relevance. It's not related to antidepressants or suicide.

MR. DAVIS: It's just background information about how the process works, your Honor.

THE COURT: I'm going to sustain the objection. Let's stay on the topic.

BY MR. DAVIS:

Q. In terms of your -- the view of looking at controlled studies, as opposed to published case reports, to assess whether a medication increases the risk of, for example, suicidal thoughts or behavior, as a statistician and a researcher, do you believe that that's the generally accepted view?
A. Absolutely.
Q. The jury has heard about the Teischer and Cole article that was published in 1990 and discussed patients on Prozac who reported suicidal thoughts or behavior. Is that -- is that a case report?
A. Yes, it is.
Q. Now, can that case report make a determination that Prozac or any other SSRI, such as paroxetine, increases the risk of suicidal thoughts or behavior?
A. No, not in and of itself.
Q. Let's turn our attention to the 2006 GSK adult suicidality analysis. When did GSK -- when did that take place?
A. The 2006 study?
Q. Yes.
A. Well, it was published in 2006.
Q. Yes. Now, before -- was GSK the only manufacturer that did that kind of analysis?
A. No. Many of the manufacturers conducted these kinds of research syntheses.

Q. Before that process was started, did FDA give instructions to the antidepressant manufacturers about what information must be used to assess the risk of suicidal thoughts or behavior in adult patients?
A. Yes, they did.
Q. And can we call up, please, Joint Exhibit 13 at pages 50 and 51, Mr. Holtzen.
What were the instructions from the FDA about what information to look at for purposes of assessing the risk of adult suicidality?
A. So, their interest was in the controlled phases of randomized controlled trials that included a placebo comparison group, and they only wanted to see the controlled phases, the phases that were subject to randomization and the patients and the clinicians were blinded to the treatment status of the individuals.
Q. To assess the risk of suicidal thoughts or behavior in adult patients, did FDA ask for adverse event information from either open label studies, open label extension studies, or active control studies?
A. No. They specifically asked not to receive that information.
Q. From the perspective of a biostatistician and researcher who analyzes these kinds of studies, do you believe that that was the right thing to do scientifically?

A. Yes, I do.
Q. Why is that?
A. Well, if we start to add in uncontrolled portions of these studies, it can result in bias in our conclusions. We can get the wrong answer.

These are the highest quality data, the data that are part of the active controlled studies. There's a comparator for every moment during the study where patients are treated with an active medication and compared to a placebo control. The clinicians are blinded, as are the patients.

Q. Can we please call up JX 13-01, second-to-last paragraph of the page.

Is this another instruction from FDA where FDA informed the manufacturers about how to do the study that it wanted done?
A. Yes, it is.
Q. Now, in this particular set of instructions, it says that the FDA only wanted double-blind placebo-controlled trials, and they also wanted information that stopped after one day after the trial concluded.

My question to you, Dr. Gibbons, is: From a statistician -- biostatistician and researcher who has reviewed and analyzed these kinds of studies, was that the right thing to do scientifically?

MR. WISNER: Objection. He's not a medical doctor.

He cannot testify about withdrawal reactions or how a drug affects someone when they're discontinuing a medication. It's an improper opinion.

MR. BAYMAN: I don't think it went to that, your Honor.

THE COURT: To the extent of his knowledge of statistics, he may testify.

MR. DAVIS: Thank you.

BY THE WITNESS:

A. Yes. This is the appropriate time period, so this quote adds in the period of time for the observation and raises the issue of one day after discontinuation, and that is the appropriate time period to analyze the active control part of the study.

BY MR. DAVIS:

Q. Why is that, Dr. Gibbons?

A. After the study is over, both the clinicians and the patients will be unblinded, and now you will know what it was that you were taking; and if you have an expectation, that may influence the likelihood of spontaneously reporting a particular adverse event. It could be a suicide attempt. It could be --

THE COURT: I think we've heard this before.

MR. DAVIS: Okay. I'll move on, your Honor.

MR. WISNER: Move to strike as speculation and

improper opinion. He doesn't know anything. He's not done these trials.

THE COURT: Well, from the standpoint of an expert in the field of these kind of calculations, he may testify. But we've heard this before, so let's not hear over again what we've heard before.

MR. DAVIS: Thank you, your Honor.

BY MR. DAVIS:

Q. When assessing the studies to be included, did FDA's instructions to the manufacturer let the manufacturers decide what studies to include or not include?

A. No. It began with a listing of studies, a listing of all of the studies. FDA reviewed these studies and then contacted the manufacturers to review that list and find out whether or not there were any additional studies that the manufacturer thought should be added or any reasons that the studies that FDA had requested should not be included. That dialogue went back and forth until the final list of studies was selected by the FDA.

Q. And we've got called up joint appendix -- excuse me, Joint Exhibit 13 at 13-047, and are we looking at the instructions from the FDA that basically set out the procedure that you just described?

A. Yes.

Q. All right. Now, according to the instructions that were

given to the manufacturers about how to do this analysis and what data to supply the FDA, did the FDA also inform the manufacturers that if there was a determination that there was an event that should not be included because it was a false positive, was that enough, or did the FDA require more information?

A. So, the FDA wanted a listing of all of the suicidal events, suicidal thoughts, suicidal behavior, suicidal completion. In addition, they wanted to have a listing of the events that the manufacturer felt were false positives, that were events that could have been construed as a suicidal event, but in the opinion of the manufacturer, they weren't.

FDA wanted a complete list of all of those events so that they could review for themselves and determine whether or not those events should be classified as suicidal events.

Q. After it was agreed upon concerning the studies to include and the adverse events to be included both on paroxetine and placebo, what was the next step in the process for how the manufacturers went -- were instructed to go about doing this analysis?

A. So, the narratives for the final listing of events that were agreed upon by the FDA were then sent blinded to Columbia University, to the department of psychiatry, to the group of people that do the blind adjudication of these events using the Columbia suicide classification scale.

So, this is a methodology that's used to review narratives, case reports about a particular suicide event for a given individual and then determine whether or not it was indeed a suicidal event, whether or not it was an example of ideation, preparation, an attempt, or, of course, completion.

So, these data were reviewed by this expert scientific team at Columbia University, and then the reviewers at Columbia did not know whether or not this was a patient who had received placebo or was on an active treatment, so they were not biased in any way, if there was any potential bias.

And those blinded adjudicated data then became the outcomes used in FDA's analysis of those data, meta-analysis.

Q. You mentioned the Columbia classification scheme for suicidality events. What role did FDA play in developing that classification system?

A. The -- this -- that classification system was developed at Columbia by researchers at Columbia University in the department of psychiatry; and it was utilized by the FDA, but the FDA had no part in doing that adjudication.

Q. How would you describe the methodology that was developed by these experts in suicidality at Columbia University?

A. It's the leading methodology available even to this day. It's extremely good work.

Q. I'd like to show you Joint Exhibit 13 at 13-013, Table 3. You mentioned the classification scheme, Dr. Gibbons,

developed by the experts at Columbia University. Is this the categories that were developed?
A. These would be the resulting categories, where a particular event would be categorized, selected for a particular category.
Q. So, for the analysis that GSK had to do -- that GSK did in 2006, what was the primary analysis or end point that was -- that FDA instructed them to use?
A. It would be the combination of the first four categories, so, completed suicide, suicide attempt, preparatory acts towards imminent suicidal behavior, and suicidal ideation.
Q. What was the secondary subgroup analysis?
A. It would be the first three, so it would have excluded suicidal ideation. So, it would have included preparatory acts, suicide attempts, and completed suicides.
Q. From a statistical standpoint as a biostatistician and a researcher in the field, do you have an opinion about whether that was the right assessment to make in terms of identifying the primary end point?
A. Yes, I do.
Q. What's your opinion?
A. I think that was the appropriate primary end point for the following reason. One of the problems in analyzing suicide data is that it's a rare event, and we need extremely large sample sizes in order to have the statistical power to detect

a real drug-related effect if it's there. By including suicidal ideation, we have a more frequent, a more prevalent outcome. The more prevalent the outcome, the more power we have to detect a real drug effect if it is there.

So, I think it was an extremely good idea to include suicidal ideation as a part of the combined end point. I also think it was a good idea to follow as a secondary end point looking at suicidal behavior as a sensitivity analysis.

Q. When you say sensitivity analysis, what do you mean?

A. I mean a follow-up analysis based on the results of the primary analysis.

Q. From someone who's a statistician, who's done research in biostatistics and interpreting these kinds of studies, do you believe that the selection by FDA of suicidal ideation or behavior as the primary end point was arbitrary?

A. No. I believe it was done exactly for that reason, to have greater statistical power --

MR. WISNER: Objection. Speculation as to why the FDA did it.

MR. DAVIS: That wasn't my question, your Honor.

MR. WISNER: He says why they did it. It's the FDA. That's the definition of speculation.

THE COURT: Let's go back to the original question. What was the question? Read it back, please.

(Record read.)

THE COURT: Was what? Arbitrary?
MR. DAVIS: Arbitrary.
MR. WISNER: The problem is with the answer, your Honor. He goes on to say -- sorry. I should let him do it.
THE COURT: He may answer.
MR. DAVIS: Thank you.
BY THE WITNESS:
A. No, I don't think it was arbitrary. I think they made the right selection, for the reasons that I stated.
BY MR. DAVIS:
Q. From a scientific viewpoint of a biostatistician and researcher who has interpreted and analyzed these kinds of studies for a living, do you believe it would have been more appropriate to make the primary end point suicidal behavior, as opposed to suicidal thoughts and behavior?
A. No. I believe the primary end point should have been suicidal ideation and suicidal behavior because it's more prevalent and it would be more -- it will -- there will be more statistical power, a greater likelihood of detecting a real drug effect if there is one.
Q. Let's turn our attention now to the results of GSK's 2006 adult analysis. Did we prepare a slide that shows the -- some of the results? Did you prepare a slide that shows a number of those results?
A. Yes.

MR. DAVIS: All right. Your Honor, I'd ask permission to publish Slide 18, which is DX -- it's 7035-O.

MR. WISNER: This has the same best evidence problem. It has a document on here.

MR. DAVIS: It's a summary that would be helpful to the jury in terms of assessing the evidence that's already in, your Honor.

MR. WISNER: He can show him the document. It's already admitted into evidence, I believe.

THE COURT: What exhibit is it in evidence?

MR. DAVIS: Well, your Honor, it's part of DX 1051, which I don't believe has yet been moved into evidence, but I will if your Honor would prefer me to go that route.

THE COURT: Well, it isn't appropriate to take a slide from a document that's not in evidence.

MR. DAVIS: Your Honor, permission to publish DX 1051. That's the Carpenter article that was used with Dr. Ross.

THE COURT: Is that the one from which you're drawing this data?

MR. DAVIS: Yes, sir.

THE COURT: The Carpenter article was used by Dr. Ross?

MR. DAVIS: Yes, sir.

THE COURT: Okay. You may go to that.

MR. DAVIS: Okay. Can we please pull up the Carpenter article. And if you can go to page 1058, table 4.
BY MR. DAVIS:
Q. Okay. Doctor, how many patients were involved in this particular analysis by GSK in 2006 concerning adult suicidality?
A. Approximately 15,000.
Q. How did that break down between those patients on paroxetine versus those patients on placebo?
A. About 9,000 on paroxetine, and about 6,000 on placebo.
MR. WISNER: Just to keep the record clear, this was Plaintiff's Exhibit 285.
THE COURT: All right.
BY MR. DAVIS:
Q. Did GSK's 2006 adult analysis find an association between paroxetine and completed suicides in adult patients?
A. No, it did not.
Q. Were there any actual suicides in the clinical trials, the placebo-controlled trials that were studied?
A. No, there weren't.
Q. Let's look at page DX 1051 to help us out here, Doctor. It's going to be 1058, left column, last line.
Was there a suicide that occurred in one of the paroxetine trials?
A. There was one suicide that occurred in a 23-year-old man

with social anxiety disorder who received paroxetine.
Q. Were there any patients who suffered from major depressive disorder or any other depressive disorder --
THE COURT: Excuse me. What category was he in? Was he in the placebo or -- he was in the paroxetine group?
THE WITNESS: Yes, sir.
THE COURT: Okay.
BY MR. DAVIS:
Q. Were there any completed suicides in any of the major depressive studies or any other types of depression studies?
A. No.
Q. For this particular analysis that was done by GSK in 2006, does that support the claim that paroxetine increases the risk of suicide in adult patients?
A. No, it does not.
Q. All right. Let's turn our attention to the primary end point or analysis. Again, if we could call up -- if we can call up DX 103, page 110.
MR. DAVIS: Permission to publish DX 103, your Honor?
THE COURT: Is that in evidence?
MR. DAVIS: I believe it is, yes.
THE COURT: All right.
MR. DAVIS: Thank you.
MR. WISNER: What tab is that?
MR. DAVIS: It's page 110, and it's behind Tab 3,

Mr. Wisner.
BY MR. DAVIS:
Q. Okay. Dr. Gibbons, help us out here. What are we looking at?
A. So, what you're looking at is a summary table for all indications. This means all of the different diagnoses that people had in these trials. And we're looking at the primary end point of both suicidal ideation, meaning thoughts, and suicidal behavior.

And what we have at the top that's highlighted in yellow where it says, "Overall, Mantel Haenszel," Mantel-Haenszel is a statistical technique of meta-analysis that combines information across the studies.

We have a rate of a little less than 1 percent for the paroxetine patients, and a little more than 1 percent for the placebo patients. The odds ratio is .9. It is not statistically significant, and it shows that there is no association between paroxetine and suicidal ideation or behavior as a primary end point.
Q. How many paroxetine patients and how many placebo patients were part of this analysis?
A. Again, there were 8,958 paroxetine patients and 5,953 placebo patients.
Q. How would you describe the size of this particular analysis and its ability to detect a difference?

A. So, this is a large number of people, but it's also a rare event. It's occurring about 1 percent. We can see from the confidence interval that it's quite narrow. It goes from 0.7 to 1.3. This means that there is good ability to detect a real effect if it were present.

The confidence or uncertainty in this estimate of the odds ratio, the relative risk between people who are on paroxetine versus people on placebo is very detectible should it go either in a protective direction or in a harmful direction. We're not seeing either of those.

Q. For the primary analysis, did GSK look at whether paroxetine increased the risk of suicidal thoughts or behavior based on the type of disorder that the studies analyzed?

A. Yes, they did. They did that as a series of sensitivity analyses.

MR. DAVIS: Okay. Mr. Holtzen, if we can call --

THE COURT: Wait. Before you leave that, 83 over 8,958, what is 83?

THE WITNESS: 83 is the number of people who had a suicidal thought or behavior.

THE COURT: While on paroxetine?

THE WITNESS: While on paroxetine.

THE COURT: And 65 is the number that they had the same thing on a placebo?

THE WITNESS: On placebo, out of 5,953 patients. So,

those ratios times 100 give you .93 percent for paroxetine and 1.09 percent for placebo.

BY MR. DAVIS:

Q. So, the bottom line, is there a difference seen between paroxetine and placebo in this analysis?

A. No.

Q. Now, going -- if we could pull up --

MR. DAVIS: Mr. Holtzen, if we can pull up the larger -- the other analyses that were on the primary end point.

BY MR. DAVIS:

Q. So, this -- as the jury can see on the screen, what we have here underneath overall, there's all depression, MDD, IBD, dysthymia, bipolar, and a series of other disorders?

A. I'm sorry. This is not the table for the primary end point. This is the table for the secondary end point of suicidal behavior.

MR. DAVIS: Oh, well let's go to page 103. Can we get that called up, Mr. Holtzen? Can we get the right primary end point for that?

THE COURT: Are we still in the article, or are we in some other --

MR. DAVIS: We're in Defendant's Exhibit 103, which is the GSK adult analysis.

THE COURT: Okay.

MR. DAVIS: It will be a couple of pages earlier. It's table 2.01, I believe. It's on page -- it should be on page 110. Okay. Thank you.

BY MR. DAVIS:

Q. Let's get it right. I apologize. Let's go back and look at the overall result for the primary end point. Again, what do we see there for the primary end point of suicidal behavior and ideation that's in table 2.01, Doctor?

A. Again, we're seeing no association between paroxetine and suicidal thoughts or behavior.

MR. WISNER: Objection. Asked and answered. I think we just went over this, like, three times.

MR. DAVIS: I'm not going to cover old ground, your Honor.

THE COURT: Okay.

BY MR. DAVIS:

Q. For each of the additional analyses that were done on the primary end point, how many of them were there?

A. Just in this table?

Q. Yes, sir.

A. 14.

Q. For each one of those, was there any finding of an increased risk or association between paroxetine and suicidal thoughts or behavior?

A. No.

Q. If you're looking at the subgroup analysis in this table that dealt with major depressive disorder and suicidal ideation or behavior, what was the result?
A. The odds ratio was 1.3. It was not statistically significant. It shows no evidence of an association between paroxetine and suicidal thoughts and behavior in patients with major depressive disorder.
Q. So, when you're looking at all the results on the primary end point of suicidal thoughts or behavior, what's the bottom line takeaway from that?
A. We're not seeing an association. We're not seeing any increased risk of suicidal thoughts or behavior at the primary end point of these studies and the taking of paroxetine.
Q. Let's go to the secondary end point. If we could pull up DX 103, page 155, which I think is the table we had up earlier.

Okay. On the primary -- on the secondary subgroup analysis of definitive suicidal behavior, what was the overall result when all of the studies were analyzed?
A. Your -- the overall result -- there's something wrong with this table.

MR. WISNER: This is the MDD analysis. It has a 6.7 risk.

MR. DAVIS: Yeah, that's the wrong -- you have the wrong thing pulled up. Why don't you drop that out. It's the

thing that's highlighted above. There you go.

THE WITNESS: No, it's still not that. This is for the indication of MDD. What you're looking for is the all indication table for the secondary end point.

Oh, that's much better.

MR. DAVIS: Can you look at page 155, Mr. Holtzen.

THE WITNESS: No, it's there.

BY MR. DAVIS:

Q. All right. So, this is looking at all -- what's highlighted is looking at all the studies combined. Can you tell us what this table means and what the results mean, Doctor?

A. So, this is essentially the same table as we saw before, except now we've removed that fourth category from the Columbia classification. We've gotten rid of the suicidal thoughts, suicidal ideations, and are restricting to preparation or worse, so suicidal behavior.

And here again, we have a non-statistically significant odds ratio with a narrow confidence region indicating no association between paroxetine and the secondary end point of suicidal behavior.

Q. On this particular analysis, looking at all the studies and the end point of suicidal -- definitive suicidal behavior, how many patients in the paroxetine group and how many patients in the placebo group?

A. Again, it's the same number. It's almost 9,000 in paroxetine and almost 6,000 in placebo.
Q. Okay. On the secondary subgroup analysis of definitive suicidal behavior, what were the findings when looking at all patients with any type of depressive disorder?
A. No association with paroxetine.
Q. How many patients were in that analysis?
A. This overall analysis, almost 15,000.
Q. No, no, the subgroup analysis of all depression studies.
MR. DAVIS: Can you move that, Mr. Holtzen, so he can see that.
BY THE WITNESS:
A. I'm sorry. So, in the all depression studies, we have 3,720 patients on paroxetine, 2,260 patients on placebo. The overall association is exactly the same. There's no association with paroxetine. It's not statistically significant. And we reached the same conclusion.
BY MR. DAVIS:
Q. Again, did GSK do subgroup analyses where it broke down the studies by the type of disorder that was being studied, for example, panic disorder versus obsessive compulsive disorder versus major depressive disorder, and look at the findings in those particular subanalyses?
A. Yes, they did.
Q. Okay. For those subgroup analyses, was there any one that

found a significant risk?
A. There was one.
Q. Which one was that?
A. That was for major depressive disorder.
Q. Okay. And for the major depressive disorder, what was the finding?
A. The finding was an increased risk with an odds ratio of 6.7. The confidence limit did not include 1. The P value was close to .05.
Q. Now, for all of the other subgroup analyses that were done, were any of those -- did any of those find an association between paroxetine and suicidal behavior or suicide attempts?
A. No, none of the others did.
Q. How many patients were in the major depressive disorder subgroup that had the 6.7 odds ratio finding?
A. There were 3,455 on paroxetine and 1,978 that were on placebo.
Q. So, for the overall number of patients who took paroxetine in this subgroup analysis, how many patients did not have suicide attempts or suicide behavior?
A. The majority. It's less than one half of 1 percent. So, 99.6 percent essentially -- 99.6 percent did not have suicidal behavior.
Q. What would that number work out to be if we had 11 out of

3,455?

MR. WISNER: I have a calculator if you need it.

BY THE WITNESS:

A. Thank you. I don't do arithmetic.

It's roughly -- roughly 55 people.

THE COURT: Let's not do that. Let the record show -- the record speaks for itself.

BY MR. DAVIS:

Q. All right. Now, for those patients who were part of this subgroup analysis for the major depressive disorder finding, did any of those patients actually commit suicide?

A. No, they didn't.

Q. Now, you talked about the importance of consistency earlier. When assessing findings such as this and this kind of meta-analysis, what is your takeaway, given the finding of the -- let me back up.

You talked earlier about consistency and the importance of it. When you look at the primary end point results and the secondary end point results, is there any consistency where you also see other statistically significant increased risks such as the major depressive disorder finding on the secondary analysis?

A. No. This is -- this appears to be an anomalous finding. It's restricted to a single one of 14 different diagnostic breakdowns. This is the result of a subgroup analysis. The

more subgroup analyses, particularly as the sample size goes down and the event is rare, the more likely we are to find an anomalous result.

It's also anomalous from the perspective that it's going in the opposite direction of suicidal thoughts. It's hard to imagine --

MR. WISNER: Objection. Your Honor, he's about to testify about the relationship of ideation and behavior, which is the definition of a medical opinion.

THE COURT: Just stay with the statistics, Doctor.

BY THE WITNESS:

A. It's going in the opposite statistical direction from ideation as it is for suicidal behavior. So, that would be an example of a statistical lack of consistency.

BY MR. DAVIS:

Q. So, is the finding of the 6.7 odds ratio consistent with any of the other primary end point results or any of the other secondary end point results?

A. No, it's not.

Q. Let's take a moment and focus on those 11 patients on paroxetine and the one on placebo. What other evidence is there that this is not an effect showing an increased risk from use of the medication, but rather a product of the statistical analyses that were done?

A. So , if we look at the rate, that odds ratio, we saw that

one anomalous odds ratio of 6.7, suggests a very large difference in the rate between the paroxetine patients and the placebo patients. There are two ways that that can happen. Paroxetine could be really high in terms of the rate, or placebo could be really low.

Now, the rate in the paroxetine patients for that MDD subgroup is .32 percent. We saw that in the -- in the table. The rate on placebo was .05 percent, very, very small number.

If you look at all of FDA's placebo arms and all of the SSRI trials for patients with major depressive disorder, of which there were over 12,000 patients, as opposed to the 1978 patients in the MDD trials, what you see is that that rate is .24 percent. It's four times higher than the placebo arm in GSK's paroxetine studies.

The large odds ratio is not produced by an increase in the rate of suicidal behavior in the paroxetine arm. It's produced by an unusually and unrepresentatively low rate in the placebo arm. And when you compare the paroxetine data to the much larger collection of placebo arms in FDA's randomized controlled trials of the MDD patients, you find no evidence of an association between paroxetine and suicidal behavior.

Q. Now, how many analyses did -- well, let me back up.

Did we prepare a slide that kind of outlined -- did you prepare a slide that outlined that finding that you just

talked about?
A. I did.
MR. DAVIS: Okay. Your Honor, permission to publish DX 7035-BB.
MR. WISNER: Objection. This slide is argument, also cumulative.
THE COURT: What is it? BB?
MR. DAVIS: BB.
THE COURT: BB?
MR. DAVIS: Yeah, two Bs.
MR. WISNER: BB? I thought you said P.
MR. DAVIS: 7035-B as in boy, B as in boy.
MR. WISNER: Oh. No objection, your Honor. It's cumulative, but no objection.
THE COURT: You may proceed.
MR. DAVIS: Thank you.
MR. WISNER: That's not the slide that I'm looking at.
MR. DAVIS: I'm sorry, 7035-CC. I apologize. No, wait a minute.
THE COURT: Wait.
MR. DAVIS: No, it should be -- look at the slide previous to that. Is it -- don't publish it yet, Mr. Holtzen. It's --
MR. WISNER: BB or CC?

MR. RAPOPORT: I think it's AA.
MR. DAVIS: It's BB.
MR. WISNER: I have no objection to this. That's not what he put up.
MR. DAVIS: Yes. Thank you. Yes.
BY MR. DAVIS:
Q. So, does this demonstrative --
THE COURT: Isn't this the same thing we just looked at on the --
MR. DAVIS: Yeah, I was just going to ask him to --
THE COURT: Well, it's on -- we just looked at it, didn't we?
MR. DAVIS: Yes, sir.
THE COURT: All right.
BY MR. DAVIS:
Q. So, does this demonstrative set out what you just described to the jury?
A. It does. You can see that for the placebo arm, in the GSK paroxetine MDD trial for the secondary end point, this subgroup of MDD patients, you can see that the placebo rate is .05 percent. That's extremely low. Whereas, in the lower 12,895 patients who were enrolled in placebo arms for MDD trials in FDA's analysis, it's over four times higher at .24.
If we compare the GSK paroxetine data to the FDA placebo data, we get an odds ratio of 1.33. It's not

statistically significant and shows there's no increased risk of paroxetine relative to a much larger and more representative placebo comparison group.

The effect, the 6.7 that you see in the top middle box, is produced by an unusually low rate in the placebo group, not an unusually high rate in the paroxetine group.

Q. Now, how many analyses were done by GSK in this particular --

THE COURT: Excuse me. A low rate of what, Doctor?

THE WITNESS: Low rate of suicidal behavior.

THE COURT: Okay.

BY MR. DAVIS:

Q. How many statistical analyses were done by GSK?

A. Well over 90.

Q. Can you -- before you pull up the next slide, I would call up demonstrative DX 7035-CC.

MR. WISNER: Objection. This is clearly argument. It states what plaintiffs want. I don't know why it's plural, but it's reflecting our intent, and it's completely argument.

THE COURT: I'll sustain.

MR. DAVIS: Okay.

BY MR. DAVIS:

Q. So, if you have -- given that there were -- how many analyses did you tell us about? 90?

A. More than 90.

Q. When you do that many sub -- that many analyses, what happens? What's the byproduct of that?
A. You're going to get statistical results by chance alone that are statistically significant individually.

So, for every -- if we use a 5 percent level for statistical significance, for every 100 tests we do, we expect to get five of them being statistically significant by chance alone, even if there's no true difference. That's exactly what the 5 percent rate does.
Q. So, what does that tell us about the 6.7 odds ratio finding in the MDD subgroup analysis?
A. Well, it tells us that we would expect at least one statistically significant subgroup analysis by chance alone. We also see that the imbalance is not one for paroxetine being higher for suicide behavior, but lower in the placebo group, which helps explain why this result is significant by chance alone.

Then we also see the disconnect between the primary end point showing no effect and the secondary end point showing an effect.
Q. Okay. Why is the disconnect between the primary end point and the secondary end point important to you?
A. Well, it's important to me because it shows a lack of consistency. All of these different levels of suicidal events, ideation, behavior, completion are on a continuum, and

you don't decrease one of them and increase another.
Q. You -- did you do your own analysis of the paroxetine clinical trial data that was part of GSK's 2006 analysis?
A. I did.
Q. Why did -- tell the jury what you did and why you did it.
A. So, one of the problems with traditional meta-analysis, statistical procedures, meta-analysis, again, combining the information from multiple studies, is that if the event is rare and you don't see any events in a particular trial, you have to take that entire trial and throw it away. It doesn't get into your analysis. This is an inherent problem in traditional meta-analysis.

Newer approaches to meta-analysis allow you to use all of the available data. They don't suffer from that problem. So, I used one of those newer approaches to meta-analysis to include all of the information, even those trials that had no events, which are informative. It's important to know that in 2,000 patients -- or 200 patients on the drug and 300 patients on placebo, there were no events. We're able to use those data as well.

In addition, the newer approaches allow us to incorporate heterogeneity or variability in the treatment effect. As we've seen in these tables, there's a lot of variability. Some are in the protective direction. Some are in the harmful direction. They're all -- you know, there's

variability. We can incorporate that using these newer techniques. So, I applied these newer techniques to these same data.

Q. If we can call up DX 103 at page 157.

Dr. Gibbons, can you tell us what we're looking at here? This is part of GSK's 2006 adult analysis, and certain studies have been highlighted in yellow. Can you tell the jury what's been highlighted and why?

A. So, the studies that are highlighted in yellow have zero events in both arms, so probably almost -- almost a majority of the studies didn't have any events. There were no examples of suicidal behavior in these studies. So, none of those studies actually made it into the meta-analysis; whereas, in the reanalysis of these data that I performed, all of them were included, whether they had zero events in one arm or both arms. It's just a simple advantage of the newer statistical approach to meta-analysis.

Q. When you did your own analysis that you described, what were the results as to the MDD subgroup analysis for paroxetine?

A. My memory is that the overall odds ratio was about 6.3, but now it was no longer statistically significant. There was more uncertainty because there was more of these studies that showed no difference. They both had zero in the analysis.

Q. Again, what is that -- what is that analysis telling you

about whether or not we can -- what is your own analysis telling you about the 6.7 finding?
A. Well, it's telling us that it is no longer statistically significant. Even if it was statistically significant, it's a subgroup analysis. It's one of many, many repeated analyses that could lead to a -- that would be consistent with chance expectations.

But we're seeing that analyzing the complete data set shows that it's no longer a statistically significant effect.
Q. When you did -- did you also apply your more modern statistical analysis program to the results -- the overall results for the 2006 GSK analysis?
A. Yes.
Q. And when you did that, what did you find?
A. I found very consistent conclusions from the data, that there was no association between paroxetine and increased suicidal thoughts and behavior or suicidal behavior alone.
Q. Let's turn our attention to go a little bit more of a deeper dive into these 11 patients that were part of the major depressive disorder subgroup finding.

What age group were the majority of those patients?
A. The majority of these patients were younger. These were patients -- the majority were in the range of 18 to 34 years of age.
Q. And in terms of counting up the majority, between 18 and

30, what -- let me back up, between 18 and 30, how many patients fell in that group?

MR. WISNER: Objection. I believe he said 18 and 34.

MR. DAVIS: I was asking him a different question.

BY MR. DAVIS:

Q. 18 and 30, how many patients fell in that group?

A. I believe there were eight of the patients.

Q. Okay. And so with -- did you -- did you prepare a slide that shows the age distribution of these patients?

A. Yes.

MR. DAVIS: Your Honor, permission to publish 7035-FF.

MR. WISNER: One second, your Honor.

I would object, your Honor. This is a -- this has stuff about Mr. Dolin. Dr. Gibbons shouldn't be talking about Mr. Dolin at all. He hasn't had any opinions or any data about it.

MR. DAVIS: Dr. Gibbons is not talking about anything specific to Mr. Dolin other than his age, your Honor. He's not going to be giving any causation opinion about Mr. Dolin.

MR. WISNER: Then why is it on this diagram? If it's not, then this is argument. It shouldn't be shown to the jury.

MR. DAVIS: Just wait.

THE COURT: Does this show the average age of the

placebo person is 67?

MR. DAVIS: No, your Honor. That's a placebo patient who had -- that was part of the one event.

THE COURT: Was that the age of the placebo patient?

MR. DAVIS: No, your Honor -- yes, your Honor, it is the age of the placebo patient. I'm sorry. Yes.

THE COURT: Well, it's a pretty confusing chart, sir, but I'll let him use it.

MR. DAVIS: Thank you.

BY MR. DAVIS:

Q. All right. Dr. Gibbons, please help us out again and tell us what we're seeing here in this -- in this demonstrative exhibit.

A. Sure. So, what we have here are -- as we saw from the major depressive disorder subgroup, there were 11 patients on paroxetine that exhibited suicidal behavior, and one on placebo. And these are the -- this is the age distribution of those patients.

And just to remind you, there were 3,455 paroxetine patients and 1,978 placebo patients; and these are the 12 events, 11 on paroxetine and one on placebo, roughly close to, not quite two-to-one ratio in terms of the sample sizes.

What we see is that the average age in the MDD patients overall was 46 years old, but the average age of the MDD patients who made a suicide attempt was 30 years old. So,

the ones that are making suicide attempts with major depressive disorder are younger people.

And if we look at the individual ages, we see that the majority of them are in this kind of 18 to 35 age group. Then there's a large point of rarity between the 34-year-old and the 50-year-old and 51-year-old who were both on paroxetine who made a suicide attempt. And then finally, the placebo patient that made a suicide attempt was 67 years old.

So, we see that the majority of these patients who had major depressive disorder and made a suicide attempt were much younger, much more consistent with the young adults than patients Mr. Dolin's age of 57.

If we look at the patients who are in that general age range, we see that there are two out of 3,455 that made a suicide attempt on paroxetine and one out of 1,978. Those are essentially the same rates.

So, this slide illustrates that among people with major depressive disorder, the majority were younger; and in the adult, older adult range, the rate of suicide attempts between paroxetine and placebo arms are essentially identical.

Q. Now, Doctor, based upon your view as a biostatistician and researcher and someone who has spent a career analyzing and interpreting meta-analyses such as GSK's, do you have an opinion on whether or not it's accurate to say that the majority of these attempts, eight of the 11, were in the

younger patients, age 18 to 30?
A. Well, that's consistent with the data, yes.
Q. Okay. And is that -- do you have -- is that statement, in your view, misleading in any way?
A. No. The -- I mean, age is a continuous function. We have all of the ages of all of the individuals. Cutting it into -- into an age bracket is not an unreasonable thing to do, but we know what the ages are.

I'm 61 years old. I know that I'm not 28 years old, 25 years old. There's a big difference.

Q. Now, what about -- what about a statement that if you look at patients who were 25 to 64, and if you count up in that category, there's eight patients in there? Based upon your expertise as a biostatistician and researcher interpreting these types of results, would it be accurate to describe these results in that way?
A. No. These data are clearly clustered in terms of age. I mean, it's a very interesting finding. There are -- the majority of the people who made suicide attempts, they're much younger. We can see that from their individual ages.

Playing around with cut points to try to describe, you know, eight here or eight there is just not being true to the data. The data are clear. The data are clear that there is a clustering. This is related to the younger-aged patients.

Q. Now, for someone who's 57 years old, I think you described this earlier, Mr. Dolin's age is reflected on this particular graphic, is that right?
A. Yes, it is.
Q. Now, as a biostatistician and researcher who has spent a career looking at these kinds of analyses and interpreting them, does this graph, this demonstrative that we've laid out here, does that support the claim that paroxetine increases the risk of suicidal behavior or suicidal thoughts and behavior in patients above the age of 30?
A. No, this does not provide any support for that.
Q. If paroxetine did, in fact, increase suicidal behavior in patients age 57, for example, what would you expect to see in these 11 attempts?
A. I would have expected to have seen a greater age distribution towards the right, more of these suicide attempts, and an overrepresentation in the paroxetine group among people Mr. Dolin's age.
Q. As someone who's spent his career interpreting and analyzing these very type of scientific analyses and as a biostatistician and researcher, do you believe that it's scientifically accurate to say that the 6.7 odds ratio finding and the 11-versus-one finding in this subgroup analysis should be interpreted with caution?
A. Oh, absolutely, for all of the reasons that I've given.

Q. Now, in your view, does the 6.7 -- going back, as a biostatistician and researcher and someone who's looked at populations of people to assess antidepressant risk and suicidality, does this subgroup analysis generalize to the population of real world adult patients?
A. No, not --
MR. WISNER: Objection, your Honor. Move to strike his preface to the question. He's doing it every single time. If he could just ask the question, I think it would move this along faster.
THE COURT: Just a minute.
(Record read.)
THE COURT: Your objection is what? To the reference --
MR. RAPOPORT: He has a three- or four-line preface to his question before he asks the question, talking about things he's done and who he is. It's just cumulative, and it's technically improper.
THE COURT: All right. Put another question.
MR. DAVIS: Okay. I'll make it shorter.
BY MR. DAVIS:
Q. Does the 6.7 odds ratio finding in this MDD subgroup analysis generalize to the population of real world adult patients when it comes to showing an increased risk with the use of paroxetine?

A. No, it does not.
Q. So, is this particular finding in any way applicable to adult patients who were 57 years old, such as Mr. Dolin?
MR. WISNER: Objection. Goes to general causation, improper opinion.
THE COURT: Yeah, sustained.
MR. DAVIS: Okay. Let me see if I can rephrase it.
BY MR. DAVIS:
Q. Is this finding applicable to show an increased risk in adult patients who are between the ages of 50 and 60?
A. No.
Q. Did GSK's 2006 analysis also do analyses based upon the age of the adult patients?
A. Yes.
Q. Okay. Let's turn our attention to those. If we can call up DX 103, table 2.08. If we can find -- call up the larger 25 to 64 finding.
Dr. Gibbons, help us out in terms of what kind of analysis we're looking at here.
A. So, we're looking at the primary end point of suicidal thoughts and behavior. We're restricting the age range for patients 25 to 64. We're seeing an odds ratio -- we're looking at about 12,543 patients in total, and we're seeing an odds ratio of .7, which is in support of a 30 percent decrease. The upper confidence limit is exactly at 1.0, so

it's right on the border of statistical significance.

So, my interpretation of this is that in 25- to 64-year-olds in -- for the primary end point, we're seeing actually a reduction in the risk of suicidal events in patients randomized to paroxetine relative to placebo. This is a very similar result to what the FDA found in their overall analysis of SSRIs.

Q. Let's go to DX 103 --

THE COURT: Before you leave that, why would you split over age 65 out from the other group?

THE WITNESS: This was done by the FDA. The FDA's overall analysis originally looked at all subjects.

THE COURT: But would you do that?

THE WITNESS: Would I do that? Yes.

THE COURT: Okay. All right.

MR. DAVIS: Thank you, your Honor.

BY MR. DAVIS:

Q. Let's look at the next analysis that was age-related for patients 25 to 64, DX 103, page 215.

For this particular analysis, is it looking for patients who were in all depression studies?

A. Yes, it is.

Q. What's the result, and what's your takeaway from it?

A. It's virtually identical. It appears to be a reduction in the rate of these events.

Q. Does this particular -- does this finding show an association between paroxetine and suicidal thoughts or behavior in all depression studies for patients age 25 to 64?
A. It's -- the overall result is not statistically significant, as we talked about before. It contains -- that confidence interval contains the value 1.0; but the majority of the confidence interval is below 1.0, so the direction of the effect is in the direction of being protective, although it's not statistically significant.

THE COURT: It is over 1, though, isn't it.

THE WITNESS: The value 1.0 is contained within the confidence, so it is not statistically significant. If that upper bound was less than 1, then it would be statistically significant.

So, for example, if it went from .4 to .9, then it would be statistically significant because the value 1 is not contained in the confidence interval; and, in fact, the confidence interval in its entirety is below 1.0, which would have made it statistically significant and protective.

BY MR. DAVIS:
Q. So, does the finding of the odds ratio of 0 .7 show an increased risk or a non-statistically-significant decreased risk?
A. There's certainly no evidence of an increased risk, and there is some evidence of a decreased risk.

Q. Okay. Let's go to table 2.09. Here, we're looking at a secondary subgroup analysis for all studies, and looking at patients age 25 to 64, is that right, Doctor?
A. Yes.
Q. So, in this particular subgroup analysis where they looked at definitive suicidal behavior in patients age 25 to 64 and considered all studies, what was the result?
A. Here again, we're seeing evidence of a decreased risk, not an increased risk. The upper confidence limit is right at 1.0, so it's technically not statistically significant, but it's right at that margin; and, in fact, the majority of the confidence limit is below.

So, there is some evidence of benefits, rather than risks, but clearly, there's no evidence of increased risk of suicidal behavior.
Q. Let's go to the next page, page 230 of DX 103, Mr. Holtzen.

And what analysis is this, Doctor?
A. This looks like it's -- this is all depressed patients, and we're seeing -- again for the secondary end point of suicidal behavior, we're seeing exactly the same result, about a 40 percent decrease in the risk of suicidal behavior in patients taking paroxetine relative to placebo controls.
Q. So, was there also an analysis that was done where GSK looked at all non-depression studies on the secondary subgroup

analysis of suicidal behavior?
A. Yes.
Q. What was the result of that analysis?
A. Similar effect.
Q. Similar in the sense of no increased risk?
A. No increased risk.
MR. DAVIS: Okay. Let me go -- if we can call up DX 1050 -- excuse me, PX 285, I believe, but Mr. Holtzen, I think you've got it as DX 1051, but for the record, it will be PX 285.
Yep. Again, we're looking at the Carpenter paper, and if you could call up, Mr. Holtzen, table 6 and the MDD finding for patients age 25 to 64.
BY MR. DAVIS:
Q. Okay. Doctor, you're familiar with this article?
A. Yes, I am.
Q. Now, as a biostatistician and researcher, does this finding that shows eight events on paroxetine and zero on placebo in adult patients age 25 to 64, in your opinion, is that a reliable number for purposes of assessing risk?
A. Well, for all the reasons that I've said so far about the questionable nature of the MDD finding and how it's inconsistent with all other findings, and for a secondary end point where we're not seeing at all in the primary end point, I don't think it's a reliable effect.

And the confidence interval, as we can see, is not even defined, because there were zero events in that -- in the placebo arm.

And we're now in a fairly small margin of the data. We've only got 1500 placebo subjects, 2700 paroxetine subjects, and a fairly rare event.

Q. Are you familiar with what's called a continuity correction?

A. Yes.

Q. All right. Is that a type of statistical analysis that can be done?

A. So, when we compute an odds ratio, we use logarithms, and some of you may be familiar that if you try to take the logarithm of the value 0, it's undefined.

So, one statistical approach that has been used is to add a small number to each one of the cells in the two-by-two table, .5, so that you no longer have to take the log of 0, and it's defined, so you can actually do the computation.

So, this would be an example where someone might use a continuity correction.

Q. And so if you did a continuity -- and have you yourself done that -- a continuity correction analysis?

A. Yes.

Q. All right. So, if you do a continuity correction analysis for this finding, the 8 versus 0, what do you find?

A. So, the overall odds ratio is 9. something, maybe 9.8. It's not statistically significant, unlike this value here that we see. I believe it goes from 0.57 to 170, indicating that there is tremendous uncertainty of the magnitude of the effect. And it includes the value 1 as no longer statistically significant.
Q. So, when you have that big or wide of a confidence interval, how robust and reliable is the finding?
A. Well, you have very little evidence of what the true effect might be.
Q. So, Dr. Gibbons, circling back to round out our discussion about the GSK 2006 adult suicidality analysis, from all of the analyses that we've gone over as well as all the analyses that are contained in that report, does it tell you -- what does it tell you as a biostatistician and researcher in the field of drug safety?
A. We're not seeing any evidence for increased risk of suicidal thoughts or behavior in patients treated with paroxetine.
Q. Let's turn our attention to the 2006 FDA analysis. Was the same type of classification scheme in terms of the events and how they were categorized used by FDA as what GSK did?
A. Yes.
Q. All right. And so did that -- FDA's analysis include adult patients who were 18 and above?

A. Yes.

MR. DAVIS: Permission to publish DX 735 MM.

MR. WISNER: One second, your Honor. I just have to find it.

Your Honor, this is -- I don't know if this is leading or whatever this is.

THE COURT: I can't find it. Yeah, I don't seem to have it here. Give me just a minute.

735 --

MR. DAVIS: M as in Mary, M as in Mary.

THE COURT: This is a summary of opinions?

MR. DAVIS: No, your Honor. It should be -- let me see if I can find it real quick. Thank you.

THE COURT: Your objection?

MR. WISNER: My objection is leading. These are all just facts; and instead of just asking him what he knows and what he says, he's putting it on the screen and having him read it. So, I'd ask that the witness just be asked the question instead of being given slides and fed answers.

THE COURT: I think in the case of this one, I agree. Just go to the question.

MR. DAVIS: Sure.

BY MR. DAVIS:

Q. Dr. Gibbons, with respect to FDA's analysis, how many primary and secondary analyses were done?

Let me back up. Was there a primary and secondary analysis just like what GSK did in its 2006 analysis?
A. Yes. The primary end point was suicidal thoughts and behavior, and the secondary end point was suicidal behavior or worse.
Q. How many different analyses did FDA do?
A. A lot, at least 150, probably more.
Q. Were there subgroup analyses, depending upon the type of indication or treatment for the study?
A. There were subgroup analyses for different diagnoses. There were subgroup analyses for the different drugs. There were subgroup analyses for different age categorizations.
THE COURT: Were these the combined studies? Did these include all the SSRIs or just Paxil?
THE WITNESS: These included -- FDA's overall analysis was for all of the SSRIs, including some SNRIs; but there were also subanalyses. Some of these subgroup analyses just looked at individual ones, like Paxil.
BY MR. DAVIS:
Q. Were there subgroup analyses done on different types of antidepressants?
A. Yes.
Q. How did the FDA go about presenting its findings?
A. They began with the overall findings over -- looking at the primary and secondary end point. And then the second wave

of analyses, age-stratified. They looked at the young adults, 18 to 24. They looked at the adults 25 to 64, and then they looked at the older adults 65 and over.

Q. Did the FDA have an advisory committee hearing in which it publicized the results of its findings?

A. Yes.

Q. As part of that advisory committee hearing, were there experts who came in and talked about -- who were asked by FDA to come in and talk about the results and what they meant?

A. Yes.

Q. Did the FDA's analysis specifically look at paroxetine by itself?

A. Yes.

Q. Was the data that FDA analyzed on paroxetine the same data as GSK had analyzed, or was it different in some way?

A. They were the same data.

Q. Okay. Did FDA have more patient numbers than GSK?

A. In total or just --

Q. Yes.

A. Oh, many more. There was 372 randomized placebo-controlled trials with approximately 100,000 patients enrolled from all of these trials, and that formed the basis of their meta-analysis.

Q. What you're talking about is the -- all the antidepressants in terms of the numbers there?

A. Yes.
Q. Okay. So, in terms of the numbers, did the FDA have more data on paroxetine from other pharmaceutical companies who had submitted data?
A. So, some of these trials that submitted data were placebo-controlled trials, but they also included a comparator, an active comparator arm, which would have been paroxetine.

And GSK would not have had availability -- would not have had those data. Those data were submitted to the FDA and included in the paroxetine-specific analysis as well as the overall analysis.

MR. DAVIS: Your Honor, permission to publish DX 437. That's the statistical report from the FDA's analysis.

MR. WISNER: What tab?

MR. DAVIS: It's behind Tab 5.

MR. WISNER: At this time, your Honor, before anything gets published, I think there's some foundation that needs to be laid, that the witness has seen it, et cetera. As of right now, with the record as it stands, we object to showing him something that hasn't been authenticated or anything.

THE COURT: You said 435, didn't you, sir?

MR. DAVIS: 437. It's behind Tab 5 in your binder, your Honor.

THE COURT: This is the FDA analysis?
MR. DAVIS: Yes, sir.
THE COURT: What --
MR. DAVIS: It's the companion document --
MR. WISNER: Respectfully, Mr. Davis has said that. I don't think there's any testimony about what this document is. That's all I'm saying.
MR. DAVIS: I'm happy to ask the three questions that would establish that, your Honor.
THE COURT: Go ahead.
MR. DAVIS: Okay.
BY MR. DAVIS:
Q. Dr. Gibbons, let me hand you up a notebook that's got some --
MR. DAVIS: May I approach, your Honor?
THE COURT: Yes.
BY MR. DAVIS:
Q. Let me hand you a notebook here. If you could turn to Tab 5.
THE COURT: While he's looking at that, we'll take our recess, ladies and gentlemen.
(Jury exits courtroom.)
[redacted]
(Recess had.)

(Proceedings heard in open court. Jury in.)

THE COURT: All right. Thank you very much, ladies and gentlemen. We will resume.

You may proceed, sir.

MR. DAVIS: Thank you, your Honor, ladies and gentlemen of the jury.

BY MR. DAVIS:

Q. Dr. Gibbons, I think we broke when we were looking behind Tab 5, Defendant's Exhibit 437. Let me ask you a few questions about that exhibit. Was that a document that you reviewed and considered for purposes of forming your opinions in this case?

A. Yes.

Q. Is that a document that reflects analyses that are reasonably relied upon by an expert such as you?

A. Yes.

Q. And is that -- those analyses that are reflected in Defendant's Exhibit 437 authoritative for purposes of what we're here to talk about today?

A. Yes, they are.

MR. DAVIS: Your Honor, move for admission and to publish Defendant's Exhibit 437.

MR. WISNER: Oppose admission, your Honor. I believe under 703, it may be published, but it does not go into the record as admitted evidence.

THE COURT: I think that's correct.
MR. DAVIS: Your Honor, it's the companion document to Joint Exhibit 13.
MR. WISNER: To the extent he's seeking admission, I would object under hearsay.
THE COURT: This is an FDA document?
MR. DAVIS: Yes, sir.
THE COURT: Why don't -- I'll reserve ruling on it, but you can go ahead and publish it for purposes of discussion.
MR. DAVIS: Thank you.
If we can call up Table 14 on Page 29, and Mr. Holtzen, if you could highlight the paroxetine information after you call up that table.
BY MR. DAVIS:
Q. Dr. Gibbons, please help us out again on what we're looking at here for purposes of FDA's 2006 analysis.
A. What we're looking at is a table that describes the primary end point, suicidal behavior and ideation among patients with psychiatric indications for the -- and what's highlighted is the paroxetine group, and we see very comparable rates, around a half of 1 percent of those events in both paroxetine placebo arm and test drug arm, test drug being paroxetine.
Q. So --

A. We're also seeing active control studies that were part of paroxetine. They have a higher rate, a rate of about double what we're seeing in paroxetine.
Q. In this analysis, did we -- did patients taking paroxetine -- let me back up.
In this analysis, did it make a difference in terms of the occurrence of suicidal thoughts or behavior if a patient took paroxetine versus placebo?
A. No.
Q. So how many patients were in the paroxetine arm and how many were in the placebo arm?
A. In paroxetine, there were 8,728 patients. In placebo, there were 5,763 patients.
Q. Now, based upon your review and analysis of the FDA's 2006 adult suicidality data, did the FDA include some studies by the name of 057 and 106?
A. No, they did not.
MR. DAVIS: Okay. Let's turn our attention back to Joint Exhibit 13, and please pull up Table 15, Mr. Holtzen, and if you could pull up the results for all drugs, SSRIs in that first category. There you go.
BY MR. DAVIS:
Q. Okay. So is this Table 15 the FDA's results on the primary end point of suicidal thoughts or behavior?
A. Yes, in adults with psychiatric disorders.

Q. And so what is -- what does this table show in terms of results for paroxetine?
A. It shows that there is no association, no increased risk of suicidal thoughts or behavior or completion in patients treated with paroxetine relative to placebo.
Q. All right. Again, in terms of which direction the risk is pointing, is it pointing towards decreased risk or increased risk?
A. The point estimate is a 7 percent decrease in the risk of patients treated with paroxetine relative to placebo.
Q. Looking at the larger group of SSRIs, was there any SSRI that showed a statistically significant increased risk?
A. No. All of them had confidence intervals that included the value 1.0.
Q. Okay. So if you look at -- and also if you look at the classification of SSRIs where they looked at all SSRIs combined, what was the result?
A. The overall odds ratio was .86, which would represent a 14 percent decrease in the risk associated with SSRIs relative to placebo, not statistically significant. It included the value 1 in the confidence interval.
Q. So what about for all drugs? When all drugs combined were analyzed under the primary end point, what was the result?
A. A very similar result, although this one is now right at the .05 cutoff value, so showing some evidence of a decrease

in the risk of suicidal thoughts and behavior among people treated with all antidepressant medications relative to placebo.

Q. Like GSK's 2006 analysis, did FDA's 2006 analysis also do subgroup analyses?

A. Yes, they did.

Q. Let's turn to one of those subgroup analyses which is in Table 16. Can you pull up the same information?

With respect to all drugs and all SSRIs, what was the finding, Dr. Gibbons?

A. Overall, no significant association with treatment related to suicidal behavior, preparation, or worse, the secondary end point.

Q. What does this table show for paroxetine?

A. It shows a statistically significant increase. The 95 percent confidence interval does not include -- does include -- does not include the value 1. The odds ratio is 2.76 in this subgroup.

Q. Is that the only thing that FDA noted about this particular finding for paroxetine?

A. FDA noted that they had done a large number of comparisons, and it would not be surprising if there would be an occasional statistically significant difference, and they did not believe that it was an effect that should be -- that they would reach a conclusion of a drug safety signal for these data.

MR. WISNER: Objection, move to strike, speculation and hearsay.

THE COURT: It's hearsay. Motion to strike is granted.

BY MR. DAVIS:

Q. All right. Let's go to the statement on Page 23. We've got a statement here, Dr. Gibbons. Can you please read us what this statement by FDA says?

A. "Although the values for some individual drugs are statistically significant at the .05 level," the 5 percent level, "the significance of those findings must be discounted for the large number of comparisons being made."

Q. What does that mean to you as an expert in analyses such as these?

A. It's completely --

MR. WISNER: Objection, speculation.

MR. DAVIS: I'm asking --

THE COURT: Overruled. He's an expert. He can tell us.

BY THE WITNESS:

A. It's a completely legitimate conclusion. They've done well over 150 statistical comparisons, and the occasional statistically significant result is expected given the large number of comparisons that they conducted.

BY MR. DAVIS:

Q. With respect to FDA's statement that -- that the

significance of the findings in Table 16 had to be discounted for the large number of comparisons being made, is that approach generally accepted in the field of assessing statistical data on medications such as those studied by FDA in this analysis?

A. Yes, it is.

Q. Is it scientifically appropriate to ignore this statement and to elevate the 2.76 finding to say that there's an increased risk of suicidal behavior in patients seen taking paroxetine?

A. That would be a scientifically indefensible statement.

Q. Why is that?

A. Well, it is a subgroup analysis. It's an analysis on a secondary end point. It's not seen as being consistent with the primary end point. It's not seen in several of the other antidepressant medications. And it is a -- you know, it's one of a huge number of post-hoc comparisons, comparisons that are done above and beyond the primary analyses that the study was designed to look at.

Q. Would it be appropriate to look at the 2.76 finding in Table 16 and say that this finding shows that paroxetine increases the risk of suicidal behavior more than other -- more than the other drugs that were identified in Table 16?

A. No. Just in the same way as we saw in the previous table for the primary end point, there were some drugs that had odds

ratios that were greater than 1, and FDA did not conclude that they were harmful or different from paroxetine.

Q. Okay. Now, did FDA also look at whether paroxetine increased the risk of completed suicide?

A. Yes, they did.

MR. DAVIS: All right. Let's pull up Joint Exhibit 13 at 042, Table 30, and if we can call up a little bit more, Mr. Holtzen.

BY MR. DAVIS:

Q. In this particular analysis, Doctor, what are we looking at here on the screen?

A. This is a comparison of a summary of FDA's analysis comparing the SSRI arm to the placebo arm for completed suicide.

Q. And it's -- what are the findings?

A. We see that there are -- is one event out of 9,951 subjects and no events out of 7,005 subjects. The statistical comparison of essentially 1 versus zero in these samples is not statistically significant.

Q. So in terms of a difference between, a significant difference between -- or in association between paroxetine and placebo in this analysis, was that shown?

A. No.

MR. DAVIS: Let's also turn to, if we can go back to DX 437, Page 28, Table 13, and if you can pull up -- if you

can pull up the information for "Psychiatric indications."
BY MR. DAVIS:
Q. Dr. Gibbons, can you tell us what we're looking at here and what the significance is to you?
A. So what we're looking at here is a breakdown of the various end points: Completed suicide, completed or attempted suicide, suicidal behavior, and then suicidal ideation and behavior. And basically, what we're seeing is in the first two columns virtually identical rates in placebo which is the first column versus the active treatment groups. All of these are virtually identical for completed suicide, completed suicide and attempts, suicidal behavior, and suicidal ideation and behavior.
Q. So for this particular data table and its results, does it support a claim that antidepressants increase the risk of suicide, suicidal behavior, or suicidal thinking or behavior?
A. No, none of those.
Q. Did FDA also do age-related analyses where it looked at specific time -- ages of patients to assess the risk of suicidal thoughts or behavior?
A. Yes, they did.
Q. Let's look at some of those results, JX 13 at 028, Table 17, please.
Now, for patients -- well, this is again looking at the primary end point which was suicidal thoughts or behavior?

A. Yes, suicidal ideation or worse.
Q. Was there an association of increased risk between antidepressants and suicidal thoughts or behavior in patients older than 24?
A. No, there was no association with increased risk. There was a statistically significant association with decreased risk.
Q. Was there an association of increased risk between antidepressants and suicidal thoughts or behavior in patients aged 25 to 64?
A. No, there was no --
MR. WISNER: I'm going to object, your Honor, to the relevance of this. This is including other sorts of drugs that are not SSRIs whatsoever, so this is just misleading and confusing.
MR. DAVIS: Your Honor, if I may respond.
THE COURT: Does this include -- is this just Paxil?
MR. DAVIS: No, your Honor. This addresses Dr. Healy's claim --
THE COURT: No, I don't care what Dr. Healy said. I don't know what this shows. What does this show?
MR. DAVIS: This is all antidepressants, your Honor.
THE COURT: All antidepressants?
MR. DAVIS: Yes, sir.
THE COURT: Not just Paxil?

MR. DAVIS: It includes Paxil, but it's not limited to Paxil.

MR. WISNER: Benzodiazepines. I mean, we're talking about a whole host of different drugs that really have nothing to do with SSRIs or even affect the serotonin system.

MR. DAVIS: I would --

THE COURT: Well, let's ask the doctor. What drugs were included here?

THE WITNESS: I would have to go back to the original report to see for specifically for this table.

MR. DAVIS: It's behind Tab 2, Dr. Gibbons.

MR. WISNER: It's on the page just before.

THE WITNESS: So this is -- this is the collection of all antidepressants, and it would include SSRIs like paroxetine, SNRIs like venlafaxine, and it also includes tricyclic antidepressants like imipramine and other antidepressants like trazodone. It does not include benzodiazepines.

MR. WISNER: I believe under --

THE COURT: Objection sustained.

MR. DAVIS: If we can go to Tab -- Joint Exhibit 13, and if we can go to JX 13-014, section 5.2.

And while Mr. Holtzen is pulling that up, did FDA in this --

THE COURT: Where are we now?

MR. DAVIS: We are on Page --
THE COURT: No. What document is this?
MR. DAVIS: JX 13, your Honor.
THE COURT: What is it, though?
MR. DAVIS: It's the FDA clinical review that's been admitted.
THE COURT: FDA review?
MR. DAVIS: Yes, sir.
THE COURT: Okay.
BY MR. DAVIS:
Q. My question, Dr. Gibbons, is that: Did FDA publish its overall bottom line from all of its analyses in joint appendix -- excuse me, Joint Exhibit 13?
A. Yes, they did.
MR. DAVIS: All right. Let's turn, if we can pull up Section 5.2.
MR. WISNER: Again, your Honor, I object to this. This is referring again to all antidepressants including tricyclics and a whole host of other drugs that don't affect the serotonin system.
MR. DAVIS: Your Honor, this came in play with Dr. Healy. It's been shown to the jury before.
MR. WISNER: I don't know what he's talking about. We didn't talk about this with Dr. Healy.
THE COURT: Objection sustained.

BY MR. DAVIS:
Q. Okay. Did the FDA analysis, in your view, show that paroxetine increased the risk of suicidal behavior or suicidal thoughts or behavior?
A. No, it did not.
Q. In your view as a biostatistician and someone who has looked at -- as someone who spent their career looking at this, these types of analyses, did it show that paroxetine increased the risk of completed suicide?
A. No, it did not.
Q. Does the scientific data from GSK's 2006 analysis that we've reviewed, is that -- let me back up.

All the FDA analyses that we looked at and went over with the jury, are those consistent with the analyses that GSK did for purposes of assessing suicidality risk?
A. Yes, they are.
Q. Given all the analyses conducted by FDA, how would you describe or characterize the breadth and scope of FDA's analysis?
A. I think that they did an enormous amount of work. They obtained the largest and most representative and highest quality data sets that could be used to draw inferences about the relationship between moderate antidepressants, SSRIs, and risk of suicide, suicidal behavior, and suicidal ideation.

I thought they laid out an excellent plan to

adjudicate the data independently, to obtain and review all events and all -- all of the trials that were conducted by the sponsors. It's a landmark job.

Q. Is there a larger, more robust set of randomized placebo-controlled trial data that's been analyzed by anyone either before or after FDA's analysis?

MR. WISNER: Objection, speculation. He doesn't have access to the vast majority of the drug companies' clinical trial data.

MR. DAVIS: Your Honor, I'll rephrase it.

BY MR. DAVIS:

Q. To your knowledge, Dr. Gibbons, given all of the published literature that's out there that looks at suicidality risk, is there a larger, more robust set of randomized placebo-controlled trial data that's been analyzed by anyone before or after this analysis by FDA?

A. No.

Q. The second category of studies that you mentioned that you looked at which are controlled to assess medications is what you called observational studies, and I'm going to turn our attention now to talking about observational studies.

Are the observational studies that we're going to discuss the type of scientific evidence that experts in your field reasonably rely upon to form opinions?

A. Yes.

Q. And would showing the results of those studies be helpful to the jury in explaining your opinions?
A. Absolutely.
Q. And do you consider the results in those observational studies which we're going to discuss to be authoritative for purposes of assessing the issues we're here to talk about?
A. Yes.

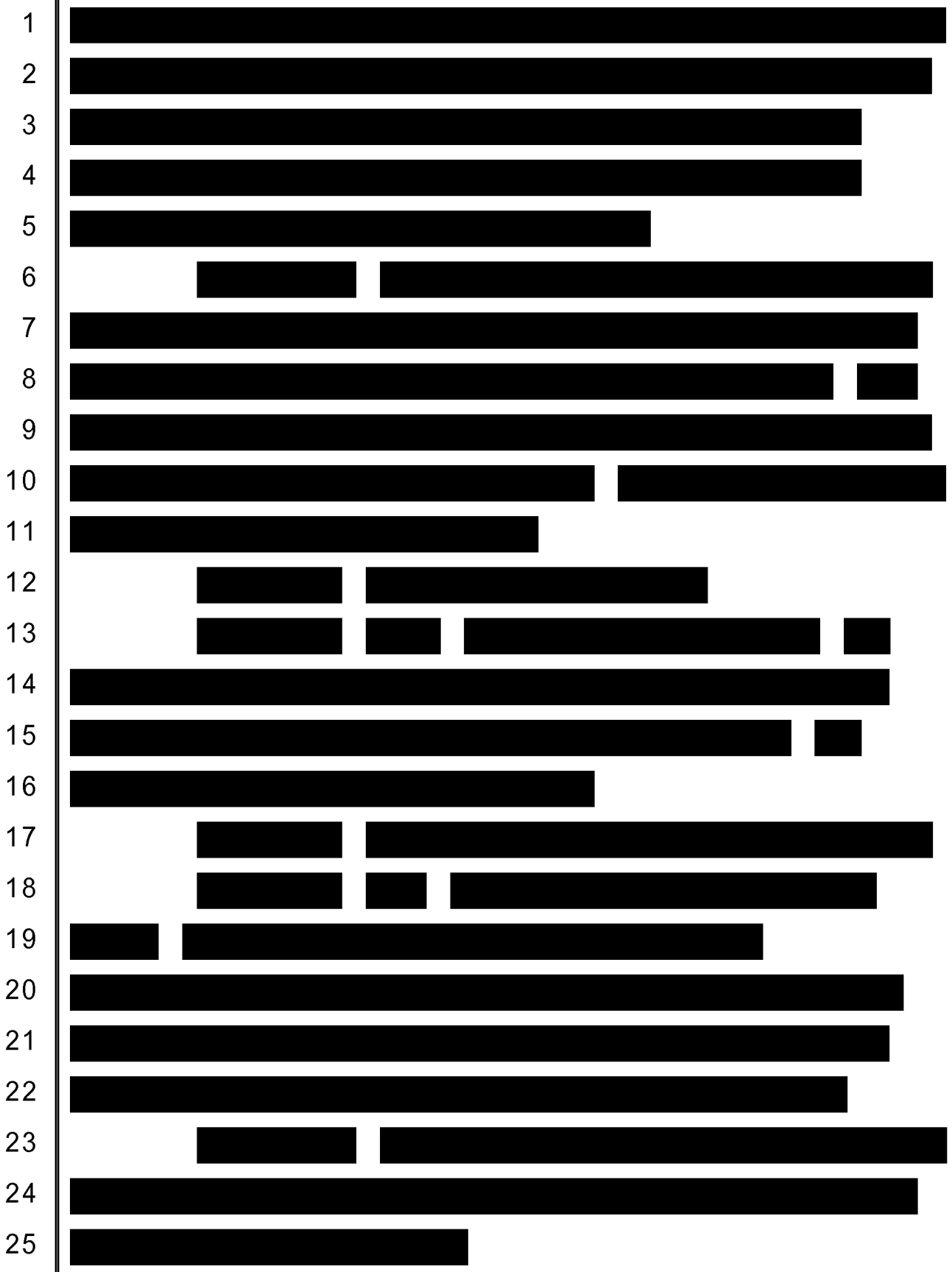
MR. WISNER: Your Honor, I object to this line of questioning. We previously have addressed this in two motions now. You have sustained it both times. This is inadmissible scientific evidence.

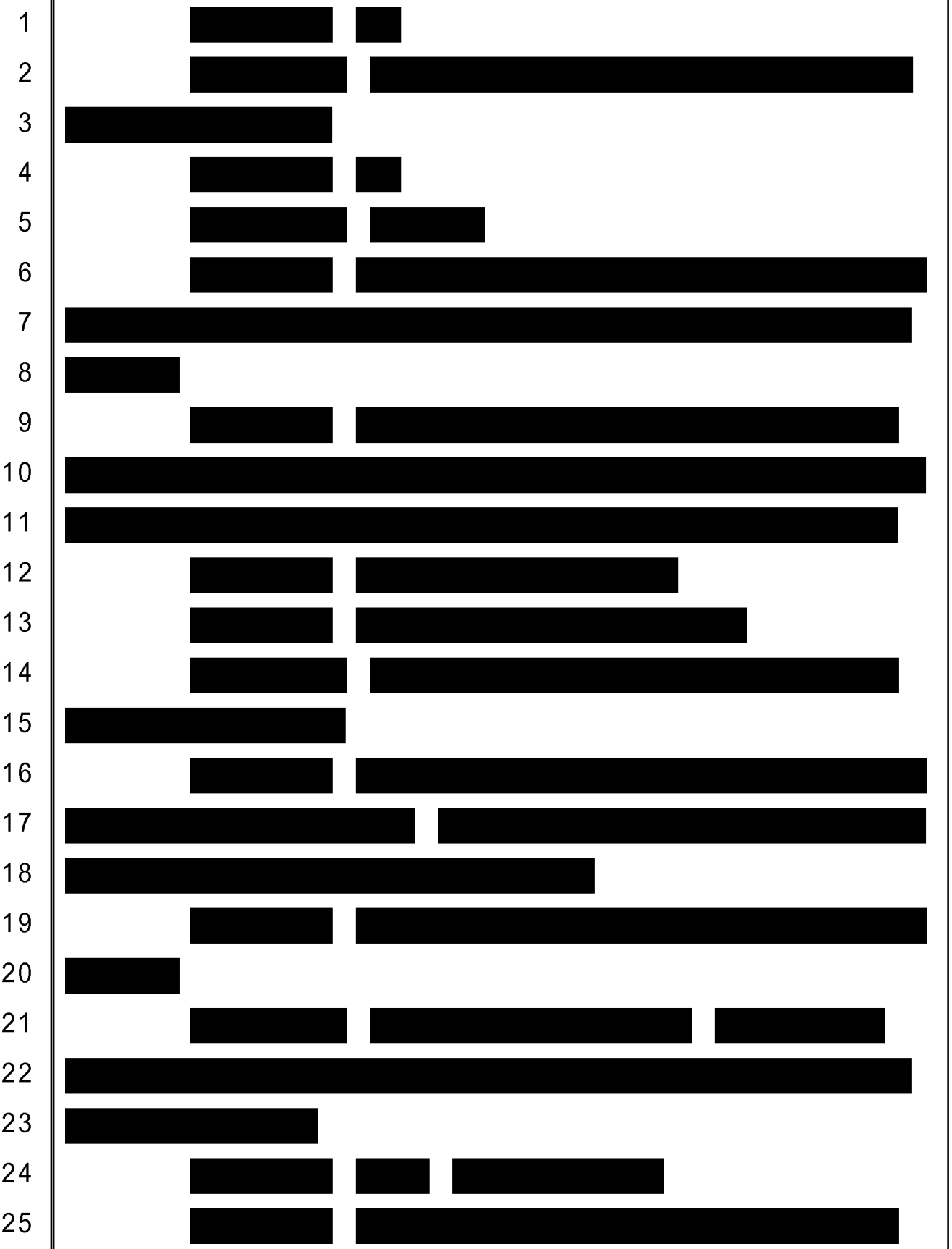
MR. DAVIS: Your Honor, I would ask to be heard because Mr. Wisner is mistaken. You have not ruled upon this.

THE COURT: You've got me mystified, so we've got to find out what you're talking about.

(Proceedings heard at sidebar:)

[redacted]





[redacted]

(Proceedings heard in open court:)

BY MR. DAVIS:

Q. Are you ready to continue, Dr. Gibbons?

A. Yes.

Q. All right. Can you give us a refresher, what are observational studies?

A. So observational studies are large studies where we look at the experiences of thousands, hundreds of thousands, in some cases millions of individuals. In this area, they are typically based on medical claims.

So you go to the doctor. The doctor says, "This patient came to me because of diabetes." The doctor prescribed a medication. You take that prescription, and you fill that prescription. That gets recorded in the medical claims data. These are insurance databases. In some cases, they're like Veterans Administration databases.

So they record all of the diseases that you're treated for, and they record all of the medications that you're given, and they also record things about you: How old you are, are you male or female, what race are you, are you Hispanic, all of these different kinds of things; how long have you been treated for these disorders, have you ever had this disorder before or other kinds of treatment.

And so now we have all of these different claims of diagnoses and prescriptions that are filled, and we can recreate the whole longitudinal pattern of when you took a medication, when you experienced an adverse event, when you got a diagnosis, when you got a particular kind of treatment, did you get psychotherapy, did you get paroxetine at some point in time, did you make a suicide attempt.

We look at these data sets for populations of 40, 50, 100 million people so that we can look at the real-life experiences of what happens when you take a particular drug and what kinds of diagnoses or adverse events do you get after you've taken that drug or compare people who took a drug to people who didn't take a drug and see what kinds of things happened to you. Did you have a heart attack? Did you develop high blood pressure? Did you make a suicide attempt?

So that's the kind of data that we're talking about here. These are very large studies that can actually look at very rare events like suicide attempts or suicides in entire populations.

Q. Have you yourself conducted such studies?

A. Yes, many.

Q. Have you conducted studies where you looked at either antidepressants or SSRIs and suicidality events?

A. Yes, I have.

Q. Let's talk about the study you did. What was the -- what

was the study that you performed?

MR. WISNER: Your Honor, at this time, I'd have to object. There's no foundation laid that these studies are reliable. They involve multiple types of drugs and, quite frankly, they're based on observation after the fact. I mean, this is not reliable scientific evidence. Permission to voir dire on this issue.

MR. DAVIS: Your Honor, I believe I can lay the foundation if there's any question about it.

THE COURT: Why don't you proceed along the lines we talked at sidebar.

MR. DAVIS: I am, yes, sir.

THE COURT: Instead of general questioning of this kind, get specific --

MR. DAVIS: Yes.

THE COURT: -- so we can tell whether or not we're still all on the same track.

BY MR. DAVIS:

Q. Was your study published in a peer-reviewed scientific journal?

A. Yes.

Q. What was your study about?

A. We studied 226,000 veterans --

THE COURT: Is it here attached?

MR. DAVIS: I'm sorry, your Honor?

THE COURT: Is it attached?

MR. DAVIS: It is in -- it's discussed in his report, and it's also part of, it's Tab 7, DX 1 --

THE COURT: Tab 7?

MR. DAVIS: Yes.

MR. WISNER: Your Honor, I have to renew my objection. This is regarding a veterans study. There is absolutely zero evidence that Mr. Dolin served in our armed forces. I don't see how this has any bearing whatsoever on this case.

MR. DAVIS: Your Honor, it's an assessment of the issues that Dr. Gibbons has talked about, and it bears directly on why we're here today.

MR. WISNER: Studying observational effects of antidepressants in suicides in veterans who are suffering from a myriad of psychological conditions that us non-veterans don't suffer from --

MR. DAVIS: Your Honor, I would ask --

MR. WISNER: -- is completely --

MR. DAVIS: I don't think there's a need to read the document. We're going to get into the document after the Court looks at it subject to the Court's --

MR. WISNER: I'm not reading anything. I was objecting to the scientific legitimacy of using this in this trial, your Honor.

(Pause.)

THE COURT: The conclusion of the study takes us beyond where we are today as I read the conclusion. It is not based on Paxil. It's again based on SSRIs. And to the extent that we are focusing on Paxil, it seems to me we're off the track by going into this particular study.

However, if there's something in particular in the study that you want to point out in terms of technique or statistics, I'll let you do that.

MR. DAVIS: I think I can address the Court's concern in about three questions with Dr. Gibbons if you'll permit me.

BY MR. DAVIS:

Q. Dr. Gibbons, did this study that you conducted look at SSRIs and suicide, suicide-related events?

A. Yes.

Q. And did this particular -- in this study, did you report out the results when you looked at people who took SSRIs and people who did not take SSRIs and whether there was a difference in those two groups for suicide attempts?

A. Yes.

MR. DAVIS: All right. Your Honor, I would seek permission to publish the results that are in Table 2.

THE COURT: Mr. Wisner?

MR. WISNER: I was just looking at what Table 2 is, your Honor.

THE COURT: Pardon me?
MR. WISNER: One second.
MR. DAVIS: It's on Page 1047.
MR. WISNER: Again, with all of my objections, to the extent that this is way beyond the scope of this case, if the Court wants to let him read the statistics, I guess I can't stop that.
MR. DAVIS: Your Honor, this refutes Dr. --
THE COURT: Table 2?
MR. DAVIS: Yes. Table 2, Page 1047.
MR. WISNER: And I'd just focus, your Honor, it's the cohort of veterans so --
THE COURT: The objection is sustained.
MR. DAVIS: I'm sorry?
THE COURT: The objection is sustained.
MR. DAVIS: Your Honor, this is the same type of data that Dr. Healy discussed with SSRIs with both Juurlink and the Healy/Fergusson article.
THE COURT: Go into those articles if you want to.
MR. DAVIS: But they are articles and studies that show the -- different results than what Dr. Healy presented to the jury.
THE COURT: Well, sir, I'm not ruling on any of that, and I'm not disagreeing with you as to what you recall, but I am ruling this out because it's a study that deals with all

SSRIs, and I'm fearing that we're going too far beyond the scope of the case that we are adjudicating.

MR. DAVIS: So the objection is sustained?

THE COURT: Correct.

MR. DAVIS: All right, your Honor. Thank you.

BY MR. DAVIS:

Q. Doctor, are you familiar with two observational studies done by a gentleman and researcher by the name of Dr. Gregory Simon?

A. Yes, I am.

Q. And did those observational studies assess whether or not the risk of taking an SSRI was higher in the first few months of treatment?

A. Yes, they did.

Q. Are those studies the type of reasonably -- evidence that experts in your field would reasonably rely upon to form opinions?

A. Yes, they are.

Q. And are those the types of studies that you would reasonably rely upon to assess the risk of taking an SSRI in the first few months of treatment?

A. Yes.

Q. Let's turn our attention to those two particular studies, if you can turn -- if you need it, it's behind Tab 8 of your notebook. But do you consider the Simon studies, the one that

was published in 2006 and the others in 2007, authoritative in terms of addressing the issues we're here to talk about today?
A. Yes, I do.
Q. All right. With respect to the first Simon study that was conducted in 2006, can you tell the jury about how that study was done?
A. This was a study that looked at the initiation of antidepressant SSRI therapy in a large cohort of depressed patients, and what the study found was that the risk of suicide attempts was greatest in the month prior to initiation as opposed to after initiation.

MR. WISNER: At this time, your Honor, I'd move to strike this testimony. Any evidence about there being increased risk of suicidality prior to taking a drug has absolutely no bearing on this case.

MR. DAVIS: Your Honor, one of the issues that Dr. Healy raised and Dr. Glenmullen as well is that after you take one of these medicines, you have an increased risk of suicidal thoughts or behavior. And this study directly bears on that to show that, in fact, something much different is going on with these patients and there is no increased risk. And that's what I want to talk with the jury about.

MR. WISNER: I believe he -- Dr. Gibbons just testified that the greatest increased risk was in the month prior to initiating an SSRI. I couldn't think of a more

irrelevant thing in this case. There was no suicide attempt by Mr. Dolin in the month prior to his initiation of Paxil.

MR. DAVIS: Your Honor, you can't look at these issues in a vacuum. You have to look at whether or not the issue of risk is different before or after taking the medication, and this study directly bears on that.

MR. WISNER: I mean, your Honor, just to put things in context, a lot of people start taking an SSRI or go see a psychiatrist because they made a suicide attempt. So obviously, it's going to be highest just before starting an SSRI. That tells us nothing about the association of the drug, specifically Paxil, and suicide. This is -- this is more of this --

MR. DAVIS: Your Honor --

MR. WISNER: -- you know, going down rabbit holes.

THE COURT: I'm going to sustain the objection.

MR. DAVIS: Your Honor, it's not a rabbit hole. It is something that this expert has relied upon for purposes of his opinions in the case.

THE COURT: Well, I respect him, and I'm sure his opinions are well founded, but not for this case. I'm not ruling on his opinions. I'm ruling on whether or not it's relevant to the issues before this jury and, therefore, I sustain the objection.

BY MR. DAVIS:

Q. Let's talk about another observational study, this one in 2009 by a Dr. Barbui. Are you familiar with that one?
A. Yes, I am.
Q. Did you -- is that the type of information that you would reasonably rely upon to form opinions?
A. Yes.
Q. And do you consider that particular article authoritative for purposes of the issues we're here to talk about today?
A. I do.
Q. Did this particular study have data on paroxetine in adult patients?
A. Yes, it did.
Q. Tell us about how this study was conducted.
A. Can you point me to the tab?
Q. Yes. It's behind Tab 10, Dr. Gibbons.
A. So this was a meta-analysis of observational studies that involved over 200,000 patients with moderate to severe depression. The overall study looked at SSRIs, and it looked at age stratification based on children, adults, and the elderly. The study found statistically significant protective effects of treatments with SSRI on suicide attempts across all of the SSRIs and then --

MR. DAVIS: If we can turn to Table -- Figure 4 on Page 29- -- well, before we do that, your Honor, I seek permission to publish DX 1027 and the figure on -- Figure 4 on

Page 296 which has to do with the paroxetine data.

THE COURT: All right.

MR. WISNER: No objection to that.

THE COURT: You may proceed.

MR. DAVIS: Okay. If we can call that up --

THE COURT: The page again? 296?

MR. DAVIS: Yes, sir.

BY MR. DAVIS:

Q. So I think you mentioned, Dr. Gibbons, that this particular observational study involved over 200,000 patients with moderate or severe depression?

A. Yes.

Q. So when -- and what we have called up is Figure 4. What were the results for paroxetine in terms of completed suicide or attempted suicide in adults taking that medication?

A. There was no evidence of increased risk of people taking paroxetine and either making a suicide attempt or dying by suicide.

Q. Are you familiar with an observational study by Dr. Olfson that was published in 2006?

A. Yes.

Q. Is that a study that you relied upon to form your opinions in this case?

A. Yes.

Q. And for purposes of that type of analysis, is it the type

that experts in your field would reasonably rely upon?
A. Yes, it is.
Q. Do you view it as authoritative for purposes of the issues we're here to talk about today?
A. I do.
Q. Can you describe this particular study?
A. Can you remind me which tab I'm looking at?
Q. Yes. That would be Tab 11.
A. So this was a large case control study. It involved Medicaid beneficiaries across all 50 states. And there was an overall analysis in adults age 19 through 64 years of age and --
Q. Can you turn to Page 869, Table 3? And before we show that, can you tell me if that -- if this study had information on adults who took paroxetine?
A. Yes, it did.
MR. DAVIS: And so, your Honor, permission to publish DX 1273 and the table, Table 3.
THE COURT: And what page is that on?
MR. DAVIS: 869.
MR. WISNER: No objection since it has actually Paxil on it -- paroxetine. Sorry.
THE COURT: Table 3?
MR. DAVIS: Yes.
THE COURT: Okay.

MR. DAVIS: Thank you.

BY MR. DAVIS:

Q. All right. For starters, what age ranges are we looking at for purposes of analysis for paroxetine that's up here on the screen in front of the jury?

A. 19 to 64.

Q. And what was the results for whether or not there was an increased risk of suicide attempts in adult patients?

A. There was no association between taking paroxetine and suicide attempts in this large Medicaid database.

Q. For this study, did it also have information on paroxetine and completed suicide in adult patients?

A. Yes, it did.

Q. Let's go to Table 5 on Page 870. Again, Dr. Gibbons, what age range are we looking at for purposes of this analysis?

A. 19 to 64.

Q. And for the results for paroxetine and completed suicide, was there an association between the two?

A. No significant association, no increased risk.

Q. So does this study support the claim that paroxetine increases the risk of suicide attempts or completed suicide in adult patients?

A. No, it does not support that.

Q. Okay. For the previous observational study that we looked at, the Barbui study in 2009, did that observational study

support the claim that paroxetine increases the risk of suicide attempts or completed suicide?
A. No, it did not.
Q. Let's turn our attention to Olfson 2008. That's behind Tab 12. Are you familiar with this article?
A. Yes, I am.
Q. Did you read -- did you review and rely upon it in terms of forming your opinions in this case?
A. I did.
Q. Is the information that's in this article the type that would -- experts in your field would reasonably rely upon to form opinions?
A. Yes, it is.
Q. And do you believe that the information and data that's in this study is authoritative for purposes of what we're here talking about today?
A. Yes, I do.
Q. Is this a different observational study than the previous one we talked about?
A. Yes, it is.
Q. And did this observational study look at whether or not there's an association between SSRIs and the risk of suicide attempts in the first three months of treatment?
A. Yes, it did.
MR. DAVIS: Permission to publish, your Honor, DX

1275.

THE COURT: All right.

BY MR. DAVIS:

Q. If we can look at Table 2, are we looking here at results for adult patients, Dr. Gibbons?

A. Yes, we are.

Q. And was there an increase in risk for suicide attempts in the first three months of treatment with SSRIs in this particular study?

A. No, there was not.

Q. Okay. And when these researchers assessed whether suicide attempts increased as the dose of the medication went up, what did they find?

A. They found no dose response relationship.

Q. So what does that tell us?

A. It says that as the exposure, the amount of dosage of the medication that people received increased, the rate of suicide attempts did not increase.

Q. What was the results in this study for all adult males taking antidepressants?

A. For any antidepressant, the odds ratio was .85, and the confidence interval included the value 1.

Q. And what were the results for adult males specifically? Did it show a protective effect? Did it show a decreased risk? Did it show increased risk?

A. That's not on this part of the slide.

MR. DAVIS: I think we can go down a little bit, Roger. It's a little bit further down.

THE WITNESS: This study found a statistically significant decrease in the risk. It was about one-third of the risk in males, in adult males, relative to those that did not take an SSRI.

BY MR. DAVIS:

Q. Okay. Are you familiar with an observational study that was authored by Dr. Leon?

A. Yes.

Q. Did you review and consider that study to form your opinions in this case?

A. I did.

Q. Is that study the type of information that experts in your field would reasonably rely upon?

A. Yes, it is.

Q. For purposes of the issues we're here to talk about today, do you consider that study authoritative?

A. I do.

Q. Can you describe what kind of study this was and how the data was assessed?

A. So this was a very unusual study. This was a study that was originally funded 27 years ago, actually longer than 27 years ago, by the National Institute of Mental Health. It was

a collaborative study on the psychobiology of depression, and it studied a cohort of about 1,000 patients who were treated, who were treated for severe depression.

And what was unusual about this study is that they were able to follow these subjects up for a full 27 years. And they were able to compare the rates of suicide attempts and suicides during periods of treatment with antidepressants versus treatment, periods of treatment without antidepressants.

Q. And when -- and so for purposes of their analysis, did they look at whether there's an association between antidepressants and either suicide and suicide attempts?

A. Yes, they did.

Q. And what did they find?

A. They found a 20 percent reduction in the likelihood of a suicide attempt or a completed suicide during those periods with antidepressant treatment relative to those periods of time where patients were not treated. And that difference was statistically significant.

Q. Are you familiar with an article by Dr. Barbui who published the article we talked briefly about earlier in -- he published one in 2009. He also published an article in 2008. Are you familiar with the 2008 article?

A. Yes, I am.

Q. Okay. Let's talk about that particular analysis. Did

that study look at the same -- let me back up. Did that article take some data from FDA's 2006 analysis and study it?
A. Yes, it did.
Q. For the end point that that study used, what was it?
A. It was all of the categories from the Columbia classification including those categories of events unknown or undetermined.
Q. So had -- did they call that grouping suicidal tendencies?
A. Yes, they did.
Q. And is that a recognized end point that's been validated?
A. No.
Q. To your knowledge, has anybody else ever used that type of end point to make assessments for risk for paroxetine or other SSRIs other than the authors in the Barbui article of 2008?
A. This is the first time I've ever seen it.
Q. And do you believe that that measure is a reliable -- that they utilized of suicidal tendencies was a measure by which one could properly and appropriately conduct an analysis?
A. No.

MR. WISNER: Objection, improper opinion. He's talking about suicidal tendencies and whether or not that's an improper evaluation. He doesn't have the medical know-how to make that determination.

THE COURT: You can cover that on cross-examination.

MR. WISNER: Okay.

THE WITNESS: The --
THE COURT: He said no. Another question.
BY MR. DAVIS:
Q. Why not?
A. Because the categories that were included were categories that the group at Columbia defined as being too unreliable to be included. These were also the same categories that were excluded in the analysis performed by the USFDA.
Q. Are you familiar with an article by the name of Juurlink that was published in 2006?
A. Yes.
Q. Okay. What were the ages of the patients in that particular study?
A. They were all older than 65.
Q. And how do those patients compare -- so those patients were all older than someone in the 50 to 60-year range, obviously?
A. That's correct.
Q. So did the authors make any statements about whether their findings applied to younger patients?
A. They indicated that they did not.
MR. DAVIS: All right. Your Honor, permission to publish PX 259. This was an article that had been previously used in plaintiff's case.
THE COURT: You may proceed.

MR. DAVIS: Thank you. Mr. Holtzen, if you could call up P 259-7.

MR. WISNER: Your Honor, we're just going to have a maintaining objection to this. This was not cited ever in his expert report.

THE COURT: Wait. Whose report?

MR. WISNER: His. It was never disclosed in his report.

THE COURT: The witness's report?

MR. WISNER: That's correct. Dr. Gibbons never cited this in his report as well as actually quite a few other ones, but this one in particular he did not cite. When it was shown to him in his deposition, he had never seen it before.

THE COURT: When it was shown to him at his deposition, he never saw it before?

MR. WISNER: Right, yes. And he said, "I have no opinion."

THE COURT: But it was referred to during the plaintiff's case?

MR. DAVIS: Yes.

THE COURT: You may proceed.

MR. DAVIS: Thank you.

Let's call up P 259.7 -- I'm sorry. That's not the right one. It's on Page 819, left-hand column, first full paragraph.

MR. WISNER: Completely different exhibit. There we go.

MR. DAVIS: Okay.

THE COURT: Are we in two different exhibits now?

MR. DAVIS: We've got the right one now.

MR. WISNER: Yeah, we flashed a previous exhibit just now that wasn't this one.

BY MR. DAVIS:

Q. All right. So what's up here on the screen is a statement from the Juurlink article that says, "We used administrative data and had no direct measure of antidepressant doses or adherence."

I don't want to ask you about that, but instead I want to ask you where it says, "and the applicability of our findings to younger patients is not known." Did I read that right?

A. Yes, you did.

Q. And so do you agree that in terms of whatever findings they made about the medications that they studied is not applicable to younger patients?

A. Yes.

Q. Now, did the authors in this article make any comments about whether the suicides that occurred were likely due to depression rather than the medication?

A. They did.

Q. Let's look at that, if we can call up PX 259 at Page 817. Okay. Is this another statement where it says, "Many suicides during the first month of treatment likely result from depression itself rather than an adverse effect of treatment"? Is that --

MR. WISNER: Objection. That's an incomplete sentence.

THE COURT: It's an incomplete sentence. Finish the sentence.

BY MR. DAVIS:

Q. Okay. "The actual risk of suicide due to antidepressant therapy is probably far lower."

My question to you, Dr. Gibbons, is: Given this statement, what significance is it of you when you look at this particular article and try to make an assessment of what it means?

A. Well, I think you have to kind of look at the article and what it is that they're attempting to do. This is a study that looked at a large cohort of elderly patients, 65 and over, and broke down the rates of suicide by month. And what they found was that there was an increase, almost a fivefold increase in the rate of suicide in the first month which then disappeared in following months. It was a case-controlled study.

So what a case control study is doing is it's comparing cases which in this case are people who completed

suicide to patients who did not complete suicide, and then it compares the rates of treatment of those patients between those two groups.

In this case, it used 4-to-1 matching. So for every case of suicide, there were four people who were included who didn't commit suicide. They tried to match on a series of things that are available in administrative data. Obviously, the thing we really want to match on is the severity of depression and, of course, the severity of depression is not known in an administrative database.

MR. WISNER: Objection, complete speculation. He has not seen this data. He's read the same article I have.

MR. DAVIS: Your Honor, I think he's interpreting the article.

THE COURT: I think he is, too. He may answer.

And you may cross-examine.

BY MR. DAVIS:

Q. Did this article, Dr. Gibbons, have any data that -- specifically on paroxetine?

A. No.

Q. And so in terms of whether it can tell us whether paroxetine increases the risk of suicide or suicide attempt, can it do it?

A. No.

Q. So what did it assess? Did it assess SSRIs as a group?

A. It looked at -- I want to make sure that I'm accurately answering that question. Which tab?
Q. It would be behind Tab 19.
A. This was a comparison of the rate of suicide, the rate of -- this was a comparison between SSRIs and all other classes of antidepressants. So what these -- what these authors did is they compared, they looked to see whether or not SSRIs were distinct from people who took a different class like a tricyclic antidepressant, was there something special about SSRIs in their association with suicide, this elevated rate of suicide they uncovered in the first month.

And so it was a comparison of SSRIs to all other classes of antidepressants. There wasn't a paroxetine versus tricyclic antidepressant comparison in this study.
Q. All right. So did GSK's 2006 adult analysis analyze whether paroxetine increases the risk of suicidal thoughts or behavior in adults over the age of 65?

MR. WISNER: Objection, asked and answered five times.

THE COURT: Yes, it's covered.

BY MR. DAVIS:
Q. All right. In terms of this -- given that the Juurlink article doesn't look at paroxetine patients and the GSK 2006 analysis does look at paroxetine patients, which one of the two are you going to focus in on and think is more reliable?
A. Well --

MR. WISNER: Objection, leading.
THE COURT: It's somewhat leading, but you may answer.
BY THE WITNESS:
A. The paroxetine trials conducted by GSK are more relevant to this question.
BY MR. DAVIS:
Q. To your knowledge, has the Juurlink analysis -- let me back up. Has the Juurlink analysis been replicated in other control studies?
A. There have been two attempts to replicate this finding of an increased risk in that first month following treatment. The first was a study conducted by the FDA where they looked at completed suicides in all of the short-term randomized control trials, similar period of time, one month, two months. The results of that study found no increased risk of completed suicide in patients taking SSRIs versus any other class of medications or --
MR. WISNER: I'm going to object to hearsay. What is this document he's talking about?
THE WITNESS: It's the Hammad paper 2006.
MR. WISNER: Then objection, hearsay.
THE WITNESS: We've --
THE COURT: All right. I'll sustain. Let's go on.
MR. DAVIS: Your Honor, it's the same document that Dr. Gibbons talked about early in his examination, the 2006

Hammad paper that was published to the jury. I don't believe that the objection is a proper objection.

THE COURT: Was that paper previously presented?

MR. DAVIS: Yes, sir. It went up on the screen, I believe.

Did it not, Doctor.

THE WITNESS: Yes, sir.

MR. DAVIS: Yes.

MR. WISNER: Well, then can we see the document? I mean, best evidence here, your Honor.

THE COURT: I'm a little confused. You're going to have to clear it up on cross-examination.

MR. WISNER: Okay.

MR. DAVIS: So just so the record is -- Dr. Gibbons's testimony stands?

THE COURT: It may stand.

MR. DAVIS: Thank you, sir. Thank you.

BY MR. DAVIS:

Q. You mentioned the other -- you mentioned two studies where it wasn't replicated. What's the other one?

A. The second study was conducted by Schneeweiss and his group from the FDA sentinel network, so another FDA study. And this was a study that compared SSRIs as a group to other classes of antidepressants and also individual SSRIs to the other class of SSRIs and other classes of medication.

This was done in approximately 280,000 patients. This was a cohort study, not a case control study. And that study found that there was no difference in risk between SSRIs as a class and other classes of antidepressants and no difference between paroxetine in particular and other SSRIs or other non-SSRIs in completed suicide rates.

And that analysis was conducted over a long period of time but also plotted out for every single month. And there was no evidence of an increased risk, not twofold, threefold, fourfold, or fivefold, no increased risk during that first month period. So it did not replicate the result originally found by Juurlink.

MR. WISNER: Objection, hearsay.

THE COURT: Well, you may cover it on cross.

MR. WISNER: I don't even know what he's talking about. He's talking about a magic study. Do we have the document?

MR. DAVIS: I'll just go to my next question.

THE COURT: Is there a document to support this?

MR. DAVIS: I don't have it in the notebook, your Honor, but he's familiar with it. He just spoke about it.

MR. WISNER: It wasn't -- is this in his expert report?

MR. DAVIS: May I ask the next question?

THE COURT: Is it in his report?

MR. DAVIS: I don't remember, your Honor. Schneeweiss, I don't know.

MR. WISNER: I'm at a bit of a disadvantage. I don't have the document. I don't know if it's in his report. Is it? That's not it.

It's not in his report, so we can't just bring up studies that no one has talked about before. I can't cross-examine him. I don't know what he's talking about.

THE COURT: All right. I'm going to sustain the objection. Go on to something else.

MR. DAVIS: Thank you, your Honor.

BY MR. DAVIS:

Q. All right. The Healy/Fergusson article, are you familiar with that article?

A. Yes.

Q. And did FDA specifically assess the data in the Healy/Fergusson article?

A. They did.

MR. DAVIS: Now, if we can please call up JX 13, 043, Mr. Holtzen. All right. And if you can, pull up that table. All right.

BY MR. DAVIS:

Q. Dr. Gibbons, as part of the FDA's review of adult suicidality issue, did it also review the results from the published article in Healy/Fergusson?

A. Yes, they did.
Q. And did the Healy/Fergusson article have any analyses that were specifically assessing paroxetine?
A. No.
Q. So can the Healy/Fergusson article tell us whether paroxetine either causes -- excuse me. So can the Healy/Fergusson article tell us whether paroxetine increases the risk of suicide or suicide attempts or fatal suicide attempts?
A. No.
Q. And what did the Healy/Fergusson article assess?
A. It was a comparison of a number of randomized control trials. It initially looked at a very large number of trials. Only half of those trials, a little less, actually ended up in the analysis.
Q. So in terms of what medications, did it group all SSRIs together as a group?
A. Yes, it did.
Q. And so for the result of fatal suicide attempts, what did that analysis find as to all SSRIs? And if you need that, that's behind Tab -- it should be behind Tab -- I'm not sure I have it behind a tab.
MR. WISNER: Objection to "fatal suicides" as vague. Are we talking about suicides here?
MR. DAVIS: That's the description from the article itself. I think Mr. -- Mr. Wisner should know that --

THE COURT: Well, we don't have the article here now, so I think we're all at somewhat of a disadvantage, so we'll recess until tomorrow morning at 9:30, ladies and gentlemen. Thank you very much.

(Proceedings heard in open court. Jury out.)

[redacted]

[redacted]

(Proceedings adjourned from 4:30 p.m. to 9:30 a.m.)

C E R T I F I C A T E

We, Charles R. Zandi and Judith A. Walsh, do hereby certify that the foregoing is a complete, true, and accurate transcript of the proceedings had in the above-entitled case before the Honorable WILLIAM T. HART, one of the judges of said Court, at Chicago, Illinois, on April 4, 2017.

/s/ Charles R. Zandi, CSR, RPR, FCRR April 4, 2017

/s/ Judith A. Walsh, CSR, RDR, F/CRR April 4, 2017

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