(Change of reporters - Volume 2-C:)

[redacted]

(Jury enters courtroom.)

THE COURT: All right. Thank you very much. Ladies and gentlemen, please be seated. We will resume.

You may proceed, sir.

BY MR. WISNER:

Q. Dr. Healy, in the next part of this diagram, it says, "What This Study Adds." What's the purpose of this portion of your article?

A. Again, it's to briefly orient the reader, who isn't going to spend much time reading the entire thing, as to what the key points are.

Q. When was this published?

A. This was 2005.

Q. And the Juurlink article, when was that published?

A. That was the same year or 2006, one or the other.

Q. Can you please turn your attention to Exhibit 182 in front of you.

A. Sorry, this is going to take me just a moment.

Right. 182, I have that.

Q. All right. What is Exhibit 182?

A. This is an article in a journal called *BMC Medicine*, and it's by Ivar Aursnes and colleagues.

Q. How do you say her last name?

A. It's a he, and he's Ivar. I'm not exactly sure how -- now, I've met the man. He's now dead. He was close to death when he wrote this article, but I can't remember how to -- actually how to --

Q. I'm going to call him Dr. Aursnes. Is that okay?

A. Fine.

Q. Are you familiar with this article, Doctor?

A. Yes, I am.

Q. Is it an article that you cite to and rely upon in tendering your testimony for this case?

A. Yes, it is.

Q. Is this article published in a reliable medical journal?

A. Yes, it is.

Q. And is the article itself reliable, in your opinion?

A. I believe it is, yes.

Q. Okay. So, the last article, the one we were talking about a second ago --

MR. WISNER: Your Honor, permission to publish portions of this article under Rule 18, 803(18).

THE COURT: Yes. You may proceed.

BY MR. WISNER:

Q. Okay. Doctor, now the previous article we looked at, that was looking at all SSRIs, is that right?

A. Correct.

Q. Okay. Let's look at this one. What is this one

specifically relating to?
A. This one is looking at Paxil trials.
Q. Let's open it up here, the abstract. It gives the background. It says, "Inclusion of unpublished data on the effects of antidepressants on children has suggested unfavorable risk-benefit profiles for some of the drugs."
I'll stop right there. What does that sentence mean?
A. Well, it refers to the fact that there is -- I mean, this is the year after -- well, actually, just let me check. This is published what year? This is -- yes, it's also 2005, and this is the year after the question of the use of antidepressant drugs in children and the risk that they might pose in terms of children becoming suicidal and going on to a suicidal act was a hot button issue for FDA and for the wider mental health community.
And part of the issue here was that it appeared that there was a great deal of data --
MR. BAYMAN: Objection, your Honor. This is the subject of a motion *in limine* again about the pediatric data, and now he's getting into it, as opposed to giving historical context.
THE COURT: Yeah. We did say that we weren't going to go into -- generally into the pediatric problems associated --
MR. WISNER: Yes, your Honor. This is just the

background of this article, which relates to adults. This is not a pediatric article.

THE COURT: So, we're not going into the pediatric suicide issue.

MR. WINSNER: Fair enough.

MR. BAYMAN: And Dr. Healy was getting ready to get into the issue. That was my objection, your Honor.

THE COURT: I understand, sir. And that's why I'm cautioning counsel to remind him of our prior ruling.

Proceed, sir.

BY MR. WISNER:

Q. Doctor, let's not get into the drugs causing kids to kill themselves. Okay? Let's focus on adults here.

The next sentence here says, "Recent meta-analyses of studies on adults have indicated similar effects. We obtained unpublished data for paroxetine that have so far not been included in these analyses."

Do you see that?

A. I do, yes.

Q. I'll just take a pause for a second. What is paroxetine?

A. That's Paxil. That's the generic name for what's -- for a drug that has the trade name over here Paxil, but a lot of different trade names elsewhere in the world.

Q. What's paroxetine called in the United Kingdom?

A. The trade name's Seroxat.

Q. In the clinical trials for paroxetine internally to GSK, do they call it paroxetine or Paxil?
A. They -- they can do either. I mean, they can use the UK trade name if the work was done in the UK, the U.S. trade name over here, or they can use the generic name.
Q. From a physician's perspective, is there a difference between paroxetine or Paxil?
A. No.
Q. So, now, it says, "We obtained unpublished data for paroxetine." Do you know what these authors are referring to?
A. Well, they've clearly got -- and I didn't know at the time this piece of work was done -- some unpublished data on Paxil. It was clear -- what I was actually trying to say before at the first sentence, one of the things that people had become clear about was there was a lot of unpublished data, whether you're looking at children's trials or adults' trials or whatever. There was a lot of data unpublished.
Q. All right. It goes on to read, "The documentation for drug registration contained 16 studies in which paroxetine had been randomized against placebo." Can you please translate that for the jury?
A. Yes. These -- they're referring here to the fact that in their searches, that looking at the clinical trial portfolio that GSK, or SmithKline Beecham as they were then, would have submitted to the FDA in the U.S. or MHRA in the UK or EMEA in

Europe, given a portfolio of clinical trials that were done on people who were depressed or people with OCD or other anxiety disorders for which the company was seeking indication.

Q. Is that what's referred to by registration trial?

A. Registration, yes. This is where the company is trying to seek an indication, an approval from FDA to make the claim that our drug could be an antidepressant.

Q. It goes on, "We've registered the number of suicides, suicide attempts, and ideation." So, what is that referring to, those three different groups?

A. Well, these are completed suicides, suicidal acts, and suicidal ideation. Now, for them to register that, they're not looking at the Hamilton scale that I've mentioned before, just whether the questions were asked about whether a person had ideas or thoughts about harming themselves, but an ideation event is where we've got a crisis. The person has come in and made it clear they're thinking about harming -- actually harming themselves.

This will often lead to them being removed from the clinical trial.

Q. I've seen this phrase in a couple of documents. I want to make sure I understand what it is. What is a fatal suicide attempt?

A. That's where you end up dead.

Q. Is there anything different between a fatal suicide

attempt and a suicide?
A. No. I mean, it's -- it is conceivable that you might be able to describe a fatal suicide attempt where the person has made an attempt to kill themselves in possibly all but one case out of 100 would lead to them being dead, being described as a fatal suicide attempt, but usually it means the person is dead.
Q. Okay. In the conclusion, it says, "Our findings support the results of recent meta-analyses. Patients and doctors should be warned that the increased suicidal activity observed in children and adolescents taking certain antidepressant drugs may also be present in adults."
What is your understanding of this conclusion, Doctor?
A. They're saying that there have been concerns about these drugs being given to children. The concerns should not be confined just to children, but other age groups may have the same problem. And, in fact, the first indications there was a problem came from adults, not from children.
Q. Why, Doctor, are researchers looking at children as being different than adults for the purposes of suicide? Why does that matter?
MR. BAYMAN: Your Honor, once again, we're getting into children and why children are different. This gets right at the heart of the motion *in limine*.

THE COURT: But is it going to relate to the testimony here?

MR. WISNER: Yes, your Honor. I mean, the black box warning relates to children. It's the first thing on the label, so --

THE COURT: You may answer.

BY THE WITNESS:

A. There is, in my opinion, no difference between adults and children. The problem was outlined first in adults and not children.

The risk portfolio looks exactly the same in adults and children. The clinical trial portfolio, the Juurlink articles, and the other, look much worse than anything that has ever been done in children.

The one difference in the case of children would be that wherein adult trials, the drugs can be shown to be of benefit, in children, that hasn't been as clear to date.

BY MR. WISNER:

Q. Now, it refers to -- I'm sorry. Let me call that back out. It refers to in here supporting recent meta-analyses. Do you see that, Doctor?

A. I do, yes.

Q. Do you know what she's referring to here?

A. Well, these are the kinds of articles like the one you put up earlier, the Ferguson article, and the kinds of work that I

and other colleagues have done even before the Ferguson article, where you try and get either a large number of the clinical trials from a source like the FDA, for instance, which will often -- if you go into the FDA documents that are in the public domain, you can find trials that haven't been published.

The Ferguson article looked at all the published trials. Some of the other work I've done have done things like go into the FDA documents and look at the trials that are in there, the suicidal acts linked to those that haven't actually been published.

Q. In your opinion, Doctor, does this article lend support to your meta-analysis that there's a relationship between SSRI use and adult suicide?

A. I believe it does. And one of the interesting things about this article, while in some respects it looks like they're doing just the same kind of thing that I've done and other people have done, and what I've done, I have to stress I think pretty well every person in the jury could have done, this is a little different. They take a completely different statistical approach to the one that anyone else ever took with this issue.

It's a thing called a a Bayesian approach, and if you guys don't know what that means, well, I'm not sure I know, either. Because a great deal of work in this area, as I say

people in the jury and the court here could have done a lot of what you hear me say. But this is a little different. It took a very unusual approach, and the thing about it was that it found the same answer taking this approach to the one that I and others had found taking the much more straightforward approach that we took.

Q. Now, Doctor, are you aware of whether or not GSK actually responded or critiqued this article?

A. Well, they did clearly. I think there was a degree of response that was in the public domain. But there was a follow-up article by this group where they said -- it had been clear that there was an interaction between GSK and themselves, that GSK had thought the approach they took wasn't -- well, it was unorthodox and unusual and perhaps not the one that GSK would have taken.

But they respond and say why they believe the approach they took was of value, and people should perhaps be taking this type of approach more often. And they stood by their views as to what the findings were.

Q. Now, is this a common practice for a drug company to make a critique against an academic publication?

A. Well, it's not awfully unusual. I mean, these things can happen. It's a little unusual, I guess, for it to be quite as extensive as this. It's not a response that GSK appeared to have published in an academic forum. The reason we know about

it in an academic forum is Dr. Aursnes and his team, they tried to lay out the two points of view, GSK's point of view and their own point of view in a follow-up article.

Q. Now, Doctor, if you could turn to Plaintiff's Exhibit 217 in your pile there.

A. I have to tell you, as I tell you, I've slightly messed these things up so finding anything is -- I don't think you should have ever let me loose on these, frankly, but do you know which one it is? I'm supposed to be looking for a number.

Q. It's 217, Doctor.

A. No, no, no, but -- roughly --

Q. I have a copy right here. I'm going to walk it up to you.

A. All right. Thanks a lot.

Ah, right, yes. Sorry. Okay. I've just put that on the floor. That's why I wasn't finding it. Okay. Sorry about that.

Q. All right, Doctor. I don't want to know what your office looks like.

What is Exhibit 217?

A. Well, this is the follow-up article that I referred to where Dr. Aursnes laid out his point of view and his team's point of view, the approach they took, and the GSK point of view, as they understood it, at least. And they explained why they held on not just to the approach that they took but to

what they thought the data showed.
Q. Is this a document that you cited to and relied upon in offering your testimony?
A. Yes, it is. This was a group who aren't linked as being anti drug or pro drug or anything. This is an independent safety monitoring group.
Q. And is this the same journal that published the original one?
A. No. This is -- it's from the same group of journals, but it's not actually out of the same journal.
Q. Okay.
MR. WISNER: Your Honor, permission to publish this exhibit to the jury?
THE COURT: You may proceed.
BY MR. WISNER:
Q. All right. Then let me just clarify my misunderstanding. What is BMC Psychiatry? What does that refer to?
A. Well, BMC is the group of journals. It's Biomed Central. And one of the things that they were big on was the idea -- they were mainly trying -- they hoped to produce articles that were open-access and, where possible, where the data came with the article.
Q. Now, what does it mean when an article is open-access, Doctor?
A. Well, that means that it's not behind a pay wall, that you

don't have to subscribe to the journal. You don't have to be a member of the professional body. You don't have to pay to get it, that it's just there and anyone can access it. The jury could access it.

Q. Why are some journal articles open-access and others not?

A. Journals are a business, and when one's -- when the open-access -- some of them charge the authors to get their publications there, but often that will be built in to the cost of a grant. When the authors try to get a grant, they say, "We do want to publish the results and we want to make it widely available, so we're going to include the cost of the publication in the grant."

Q. Now, this abstract right here is for -- well, before we get into it, quickly, this process of drug companies or even other academics raising questions about methodology and trying to discuss the issues, is that part of the scientific method?

A. Yes. There should be debate, and, you know, people should challenge these things. You can, of course, challenge too far. You can just try to keep a debate going when maybe it will have resolved earlier.

Q. Now, this process of engaging in scientific debate, is that appropriate in the context of such a serious side effect like suicide?

A. Well, I think the issue -- yeah, so if the concern is with the safety of patients, often we should act as though the risk

is real and warn about it and have the debate afterwards, rather than have a perpetual debate before the issues get resolved and then we warn.

Q. All right. The background to this article says, "Following our previous publication, we have received critical comments to our conclusions as well as new data that are strengthening our findings."

Do you see that?

A. Yes.

Q. What does that mean?

A. Well, clearly, there was input from GSK, and it will have been reasonably sophisticated input. And they've obviously thought about the whole thing, but maintain that the approach that they took was still a reasonable one to take and have further data which they believe strengthened the case.

Q. Do you know if the new data that they were considering was similar data that GSK had developed in 2006?

A. Yes, it appears to be the same data.

Q. And this is the data that was put and presented to the FDA in what's called a briefing document, is that right?

A. Yes.

Q. Okay. We're going to get to that later. I just wanted to highlight it here.

Now, it says down here in the results, it says, "We found that the comment to our article by GSK representatives

contained errors, misunderstanding, and unwillingness to accept Bayesian principles in the analysis of clinical trials."

Do you see that?

A. Yes, I do.

Q. What does that mean?

A. Well, they are, as I say, taking a different approach towards the data. It's one that a lot of people think is maybe a better approach to the conventional approach that we take. There's a lot of people who are true Bayesian believers.

THE COURT: You better tell us, Doctor, about Bayesian principles, if you can in a few minutes.

THE WITNESS: I don't know that I can, your Honor. It's one of these complex things that --

THE COURT: Is it a mathematical formula?

THE WITNESS: Well, it isn't. It's an entire approach towards statistics, and it's not the one that's the mainstream within the field. Now --

THE COURT: But is it math? Are we talking about --

THE WITNESS: Oh, yes, it's math.

THE COURT: All right. That's enough now. We've got it.

THE WITNESS: Okay.

THE COURT: I'll leave it to Mr. Bayman.

BY MR. WISNER:
Q. Do you think it's appropriate to examine data from all forms of statistical approaches?
A. Yes. I mean, it's always useful when different statistical approaches converge and give the same outcome. I mean, I think the data was very strong before this group took this approach, but it's always -- I mean, if the data hadn't turned out, rather, if they took this approach and it hadn't shown the risk that people like me taking a much straightforward or the more usual approach have taken, then that would have been food for thought for everyone.
Q. And, Doctor, this leads to a sort of general fanatic question I have about looking at risk. Do you ever think it's appropriate to not look at something?
A. No. The whole point behind a scientific method, whatever approach you take, and there's a lot of different approaches you take, but at the heart of everything is the fact we should have access to the data, and our efforts are to try and explain the data that's in front of us.

One of the biggest problems in all of this is that no one has access to the data. Everyone here, even this group, are working from data that GSK have put in the public domain, but that's not necessarily the full data set.
Q. Now, in this conclusion, it says, "We were in our previous publication, with preliminary data and a Bayesian approach,

able to raise a concern that suicide attempts might be connected with the use of paroxetine. This suspicion has now been confirmed."

Do you see that?

A. I do.

Q. What does that mean, Doctor?

A. Well, again, they're saying their views have firmed up. They're claiming to have come to this with an open mind, to have seen a very clear safety signal before. They now have more data, and they think the results are pretty conclusive.

Q. The -- when you look at whether or not a -- sorry.

When you look at whether or not a piece of medical literature is reliable and something that you consider, do you take into consideration who authored it?

A. Yes. At the end of the day, you really want everybody's input, company's input, non-company people's input. You want the doctors' input. You want the patients' input.

I think objectivity doesn't come from a mechanical exercise. It comes from everybody with different biases and completely different points of view getting to look at the data and figuring out, well, how do we explain this, until we get to a point where everybody thinks this is the only way to explain it.

Now, that gets harder and harder to do if the data is not -- as I keep repeating, while these -- this group here and

others are working from more and more data, maybe better and better data, no one's working from the complete data set.

And if there's any evidence that any company -- there's an old saying --

MR. BAYMAN: Your Honor, objection. He's -- again, we're getting into company conduct and allegations of hiding data, which is the subject of a motion *in limine* which you granted.

MR. WISNER: Your Honor, he didn't even mention the defendant. He's talking about looking at authorship. I don't see how that's company conduct.

THE COURT: You may answer.

BY THE WITNESS:

A. Let me quickly put it like this. There's an old saying you've all heard, and I'm sure it's changed since it was used first. For all I know, it may have come from here in Chicago. If I owe the bank a million pounds, I've got a problem. If I owe the bank a billion pounds, the bank has a problem.

If companies are shown to hide the data --

MR. BAYMAN: Your Honor, now he's saying companies and hiding data. This is in violation of a motion *in limine*.

MR. WINSNER: We'll move on, your Honor. I think the point's made.

THE COURT: All right. Move on.

BY MR. WISNER:

Q. All right. Doctor, do drug companies, for example, like the defendant, publish journal articles?
A. They do.
Q. And do they state who they are when they publish them?
A. Well, often the list of authors may not be the true authors, and in all cases in the case of these articles, there's no access --
MR. BAYMAN: Objection, your Honor. This is also the subject of a motion *in limine* that you've ruled on.
MR. WINSNER: I'm not sure which motion --
THE COURT: I haven't heard all the question. Have you finished the question?
MR. WISNER: I'm just asking him about whether or not drug companies publish literature and whether or not the authors are who they say they are.
MR. BAYMAN: And that's the subject of your motion *in limine*, your Honor.
MR. WINSNER: I'm not sure what motion he's referring to, your Honor.
THE COURT: That's kind of a general question. Be specific. Sustained your objection.
BY MR. WISNER:
Q. Doctor, putting aside ghost authorship, okay, we're not going to talk about that. Let's talk instead about do drug companies publish literature?

A. Yes.
Q. And do employees of drug companies put their names on that literature?
A. They may be there, or they may have a big involvement and their names not be there.
Q. Now, is there some sort of inherent conflict of interest if a person who's employed by GSK is making statements to the medical community about the product they're selling?
MR. BAYMAN: Same objection, your Honor.
THE COURT: Overruled.
BY THE WITNESS:
A. There's clearly a conflict of interest, but I'm not against conflict of interest necessarily. I don't mind that GSK have a view or that I have a view. The problem I've got is if we don't have access to the data so that an independent group like the jury can decide whether they think GSK is right or I'm right.
You know, it's the lack of access to the data that makes conflict of interest a big problem, rather than just it's a big problem in its own right, if you see what I mean.
BY MR. WISNER:
Q. So, it's fair to say, then, that notwithstanding the conflict of interest of company authors, you still consider it?
MR. BAYMAN: Objection. Leading, your Honor.

THE COURT: Overruled.
BY THE WITNESS:
A. Yes.
BY MR. WISNER:
Q. Because you consider everything, is that right?
A. Yes. Oh, yes, sure. I mean, you know, I wouldn't rule things out of hand just because they come from one of the companies.
Q. We went through a couple of journal articles of various meta-analyses that were done. Were any of those people employees of GSK?
A. You mean the ones that we've just referred to? No.
Q. All right. Doctor, I want to move on to another section here. And we've touched on it a couple of different times throughout your testimony, but I think I want to sort of clarify and crystallize it for the jury.

What types of data have you really looked at to examine the risk of Paxil and suicide?
A. I think you've got to look at every kind of data and the biological data of what we know about what actually happens in the brain, and what we know are -- know we don't know about what the drugs can do and things like this are things we have to take into account.

The clinical reports, maybe from patients, even reports that are just on the Internet when people describe

what happened to them; the reports written by doctors or combinations of doctors and patients together; the clinical trial data, whether it's placebo controls or whether they're controlled by other antidepressants; the trials in healthy volunteers; the trials in patients; the trials in patients who are depressed; the trials in patients who are anxious; and other studies like the Juurlink one you've seen which are cohort studies, which are also controlled.

There's a wide body of data here; and if anybody's trying to work out what's actually going on, they need to take all of it into account.

Q. All right. Doctor, I heard you mention four different types of data, and I want to go over what they are with the jury so that we can understand what they are.

If you could turn to Exhibit 35 in your pile there.

A. Guess what. I have it.

Q. Look at that. What is Exhibit 35, Doctor?

A. Well, this looks like a way to explain the different approaches, for instance, that I believe you should take on the issue. You should be looking at data from all the different kind of sources that you can.

Q. And these are the types of data that you reference and discuss in your expert report in this case?

A. Yes. This leaves out the brain research that I referred to, but it's more the clinical research.

Q. All right. And would using this diagram aid you in explaining to the jury the different types of studies and data that you looked at?
A. Yes.
MR. WISNER: Your Honor, permission to publish Plaintiff's Exhibit 35 for demonstrative purposes only.
THE COURT: All right.
BY MR. WISNER:
Q. All right, Doctor. This chart says four types of data. The first one references clinical observation. What is that?
A. That's when I, for instance, would give a drug, in this case Paxil, to -- it could be a person who's anxious, a person who's depressed, or a healthy volunteer. And I get observations from the person who's on the drug, or I may observe things actually myself. For instance, if they become restless, I may observe it, but the person themselves may not be as aware of it.
What you're looking here to get is the best possible description of the event you can, because for anything else you're going to do, whether it's clinical trials or genetic studies or whatever, we want the best descriptions we can have in order to make sure when we go on to do a study that we've got -- the people who have been looked at all have the same condition.
Most of what we know about a drug comes from clinical

observation like this. It doesn't come from control trials. Most of the things that we know that Paxil does come simply from clinical observation like this. When GlaxoSmithKline maybe gave the drug to healthy volunteers, what their own employees said in many instances, "This drug does this to me, it causes genital numbing, it causes nausea, can cause this, that, and the other, it interferes with my sleep," this is where we get most of the information that we have about a drug.

Q. Do you think clinical observation is an important thing to consider in assessing whether a drug can cause a suicidal type of reaction?

A. Very important. And it was -- it's not just medical observations. A lot of what got doctors thinking this was an issue came from the people put on the drug who came back to people like me and said, "Hey, Doc, this is different. I've been suicidal before. This is different."

A lot of what we get, a great deal of what we get, the observations come from the people on the drugs because they're inside their own body and they know what's happening better than anyone else does.

Q. Do you think it's appropriate to discount clinical observation?

A. You can't. You'd discount most of what we know about a drug if you were to do that. If you were to just go by what

we pick up from controlled trials, which are not designed to give you a good view about what this drug is actually doing, you'd know vastly less about what the drug does.

Q. Let's go to the next one here, healthy volunteer studies. What is a healthy volunteer study, Doctor?

A. A healthy volunteer is just a normal person who has no condition at all, at least not the condition that you might be thinking of giving the drug for later. Like, they aren't going to be depressed, they won't have any nervous problem if the drug you're looking at is an antidepressant. Normally they won't have anything wrong with them at all.

Researchers like me can use healthy volunteer studies to tease out what is it that antidepressants actually do. Companies have to do healthy volunteer studies, and often 30, 40, 50, 60 of them or more even before they bring the drug on the market, because they want check and see, "If we give this drug with alcohol, for instance, what happens? If we give this drug when people are driving cars, what happens?" They don't put you out in a car on the road if this drug is untested. They have driving simulators, and they test these things out. They want to see combinations of the drug with other drugs you might be taking.

So, this is the reason for doing them. They may be brief and last for just one day. They may last for two or three weeks. They will recruit people who are younger and

people who are older. And they'll often follow up with the person afterwards after he's stopped the drugs to see what actually happens during the next few weeks.

Q. What value do you get from taking a perfectly healthy, non-depressed person and putting them on Paxil? What do you learn from that?

A. Well, you learn a lot about the drug. You see, most people when they hear the word "drug trials" think this is what happens in hospitals when we give drugs to patients who are depressed or have got diabetes or whatever. That's not, strictly speaking, a drug trial.

It's not a trial of the drug because you've got a mixture of the condition and the effects of the pill, and it can be very hard to tease out what's being caused by the drug and what's being caused by the pill. But if you give the drug to people who've got nothing wrong with them, this is a trial of the drug, and you see much more clearly what it is the drug has done.

Q. Does this -- healthy volunteer studies, are they particularly helpful when the side effect you're looking for is a side effect of the condition you're treating as well?

A. Absolutely. This can make it very, very clear. In the case of -- and this applies -- it isn't just the antidepressants, and it isn't just the issue we're looking at today. There's a large number of drugs that can cause exactly

the same kind of problem as the condition that we're trying to treat you for. This is -- the diabetes drugs can cause your blood sugar to go the wrong way, you know, for some people.

So, these are issues where healthy volunteers can be particularly important. And it's very much the case in the case of the antidepressant group of drugs that these have been very helpful.

Q. Have you ever conducted a healthy volunteer study?

A. I've actually conducted a few healthy volunteer studies, yes.

Q. And what have you -- specifically with SSRIs?

A. Yes.

Q. What have you learned from them?

A. Well --

Q. I'm sorry, Doctor. What have you learned from them as it relates to suicide?

A. Yeah, in our healthy volunteer trial, we found that two of our healthy volunteers became suicidal on the SSRI that they were given; and this was a blinded trial, so the people didn't know they were getting an SSRI, and we didn't know they were getting an SSRI. There was a different drug in the mix completely. But it was only when these people went on the SSRI and not on the other drug that they became suicidal.

This was a very striking finding to me. I've had a chance to review a lot of other healthy volunteer studies.

Based on this, my confident conclusion would be if we had a jury of 10 of you, which we do have, let's say we had a jury of 20, then for sure if we were to give every one of the jury an SSRI, at least one of the 20 would become suicidal, possibly a higher number.

Q. And this is regardless of these people having a psychiatric condition? These are healthy people?

A. Yes. And that's in a sense what makes it easier to see what's going on, because in the case of people who are depressed, you may have people who are suicidal to begin with, where the drug is tremendously helpful and they stop being suicidal. So, you know, it gets a lot more complicated when you're dealing with people who have the same problem that the drug can cause.

Q. Did GSK conduct healthy volunteer studies for Paxil?

A. They did, yes.

Q. Have you reviewed them?

A. I have.

Q. What have you seen?

A. My view is that you see the same problems in the healthy volunteer studies that you see in the clinical populations also. People can become agitated, become nightmarish, apprehensive. And in the GSK healthy volunteer trials, there was one individual who later committed suicide. Whether we can say it was linked to the drug or not is another question.

Q. When these healthy volunteers, they're given Paxil and they get this reaction, what happens when these healthy people are taken off of Paxil?
A. Well, it -- the reaction can endure, or they can be relatively okay on Paxil and have problems when they stop. And the complaints from people who have took it to begin with, when they stop Paxil having been on it for two weeks can be, "I'm feeling anxious. I'm feeling depressed. I'm feeling tired, fatigued. I'm having bad dreams," so a lot of the kinds of symptoms of people who are depressed.

If you were to present these to your doctor, she would say, "You're depressed. I need to give you an SSRI." Well, in natural fact, they can be linked to the treatment as well, either going on the treatment or withdrawing from it.
Q. So, if a patient -- a healthy person is given Paxil, becomes agitated, and then that agitation ceases when you stop taking Paxil, what does that tell you as a scientist?
A. Well, this moves on to the next -- well, to a specialized form of clinical observation.
Q. But I'm talking about in healthy people, Doctor, what does that tell you?
A. Well, either in healthy people or people who are -- people who have a clinical problem, this is the most conclusive way to prove cause and effect. If the problem appears from the drug and clears up when you halt the drug, and then maybe

reappears if you expose the person to have the drug, this is a more powerful way to illustrate cause and effect than controlled trials or any other method.

Q. So, that's for healthy people. Let's look at doing that sort of study in depressed people. The next one here is a challenge, de-challenge, rechallenge study. Before we get into using this diagram to explain it, Doctor, can you tell us what challenge, de-challenge, and rechallenge means?

A. Yes, I can. Perhaps the best way to illustrate it was something I learned in Chicago a few years ago. I've been here a few times. The first time I was here was 20 years ago. But about four or five years ago, I was here for a meeting, and somebody else talking about these issues said, "Oh, this is the Christmas tree light bulb test. This is the way to remember it."

In the old days -- it doesn't apply as well now, in the old days when you had Christmas tree lights, at least in Ireland and probably here, when they were real bulbs, little bulbs but real, sure as eggs are eggs, when you took the Christmas tree lights down from the attic at Christmas time and put them on the tree and plugged them in, they didn't work.

So, what my father used to do, I can recall, was go and unscrew each bulb until he unscrewed one and they came on. And you'd screw it back in again, and they'd go off again.

So, you remove the dud bulb. And this is challenge, de-challenge, rechallenge in reverse.

Exactly the same thing happens with a drug. If I give you a drug and you turn blue and grow feathers, that's challenge. If we remove the drug and the thing clears up, that is de-challenge. Now, not all conditions will. For instance, you can't do this if people are dead from suicide. You can't do this if the drug causes you to break a leg. Your leg is still going to be broken.

But if you become agitated and suicidal on a drug, when you're being given the drug, and you remove it and it clears up, that's de-challenge. And then if you think it's safe, you can do what Carol Locke and Tony Rothschild did and give the person the same drug again and see what happens; and if the thing comes back, that's very like what my colleague, as I said, called the Christmas tree light bulb test.

Q. So, let's talk about the challenge step. When you're talking about a challenge, de-challenge, rechallenge study, are you typically referring to depressed patients?

A. No. This is the universal approach towards adverse events across the board. Whatever drug you're looking at and whatever condition, whether it's a cardiac condition or an orthopedic condition or a mental health condition. It's embodied in the federal judicial manual as the way to approach cause and effect.

Q. Now, specifically when it comes to looking at challenge, de-challenge, rechallenge studies for antidepressants and SSRIs, do you typically start off with a cohort of depressed patients like we have here in this diagram?

A. You do and you don't. Let me explain.

Q. Okay.

A. That's an Irish answer, in case you didn't know.

What -- the first article that I wrote was a challenge, de-challenge, rechallenge article, but only on two patients. We gave them the drug. They became suicidal. The problem cleared up when we removed the drug and reappeared when we gave them a different SSRI. That's challenge, de-challenge, rechallenge in just two people. The -- that shows you conclusively the drug caused the problem, but it doesn't give you any idea how often this problem is likely to happen.

You can expand it up, as one of the other companies in the field did at one point when there was an issue about all this. They said, "We're going to run a randomized control trial. We're going to put into this a bunch of patients who have become suicidal on an antidepressant" --

MR. BAYMAN: Your Honor, objection. That's subject to a motion *in limine* on the Beasley protocol that your Honor granted involving Eli Lilly.

BY THE WITNESS:

A. I can reframe it.

MR. WINSNER: Yeah, no problem, your Honor. We're not referring to a Lilly protocol or that they should have used it. This is a completely different line of questioning.

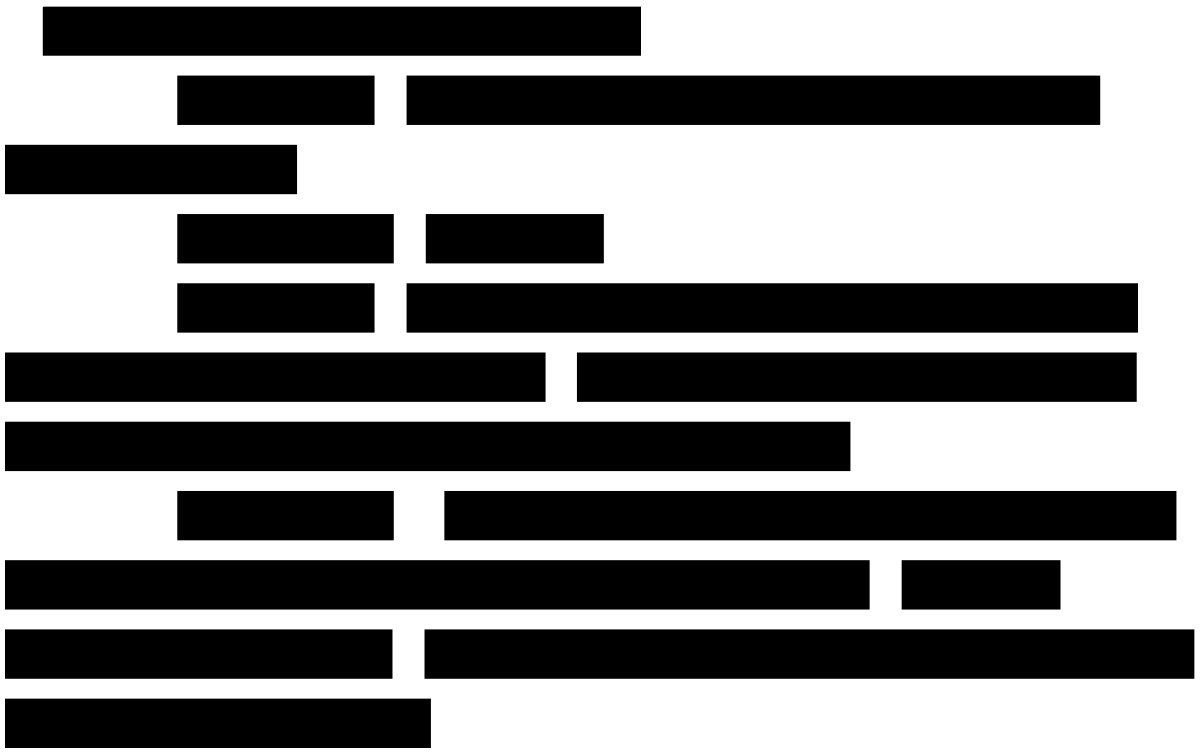
THE COURT: Is this the Lilly protocol?

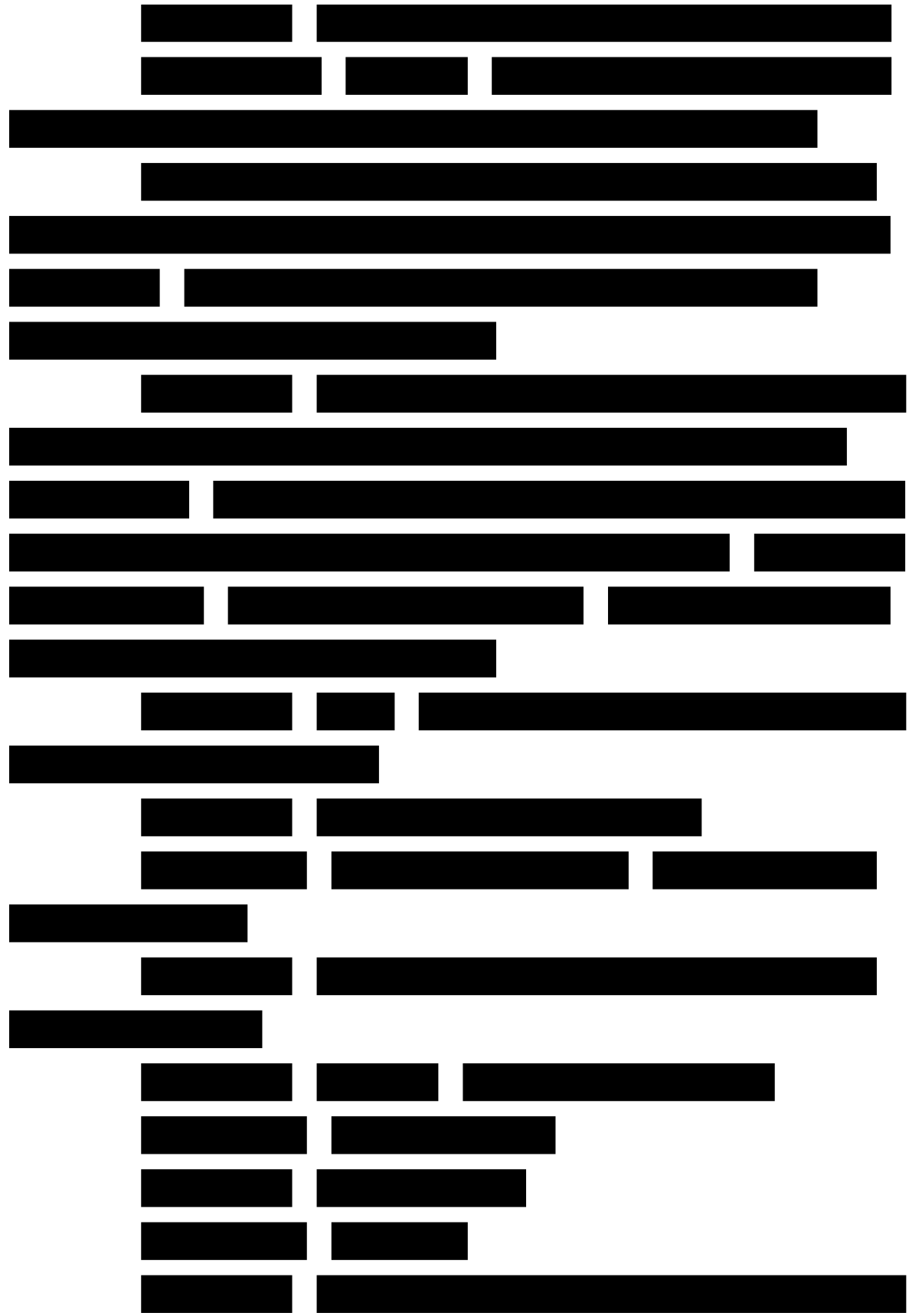
MR. BAYMAN: It's the same methodology. That's exactly what he said.

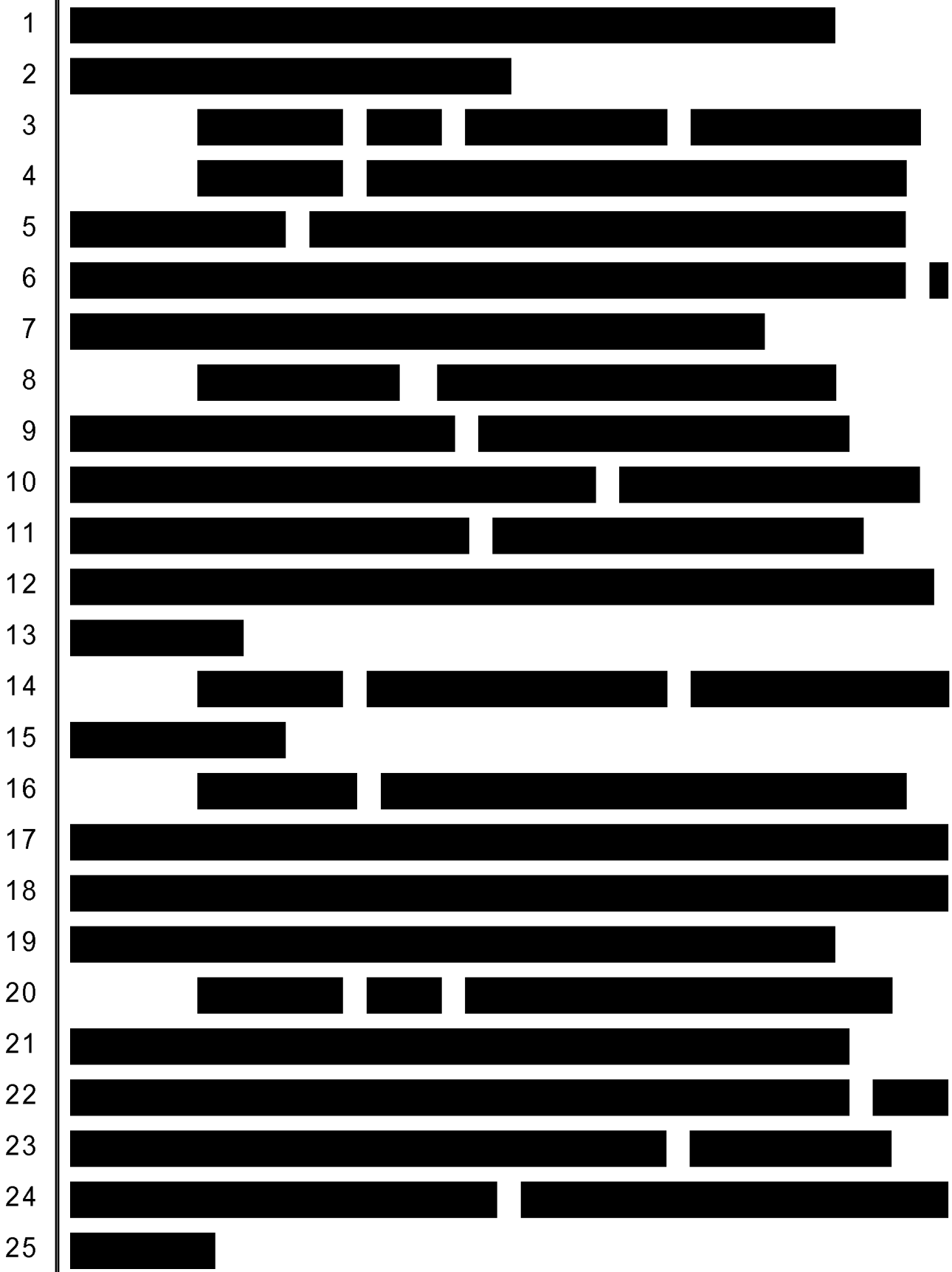
MR. WINSNER: Yeah, but he wasn't referring to it. They're the ones who made this an issue, not us. He was just answering a question about how you could do a clinical trial with challenge, de-challenge, rechallenge, nothing to do with Lilly.

MR. BAYMAN: Could we get a sidebar?

THE COURT: Yes.







[redacted]

(Proceedings heard in open court, jury present:)

THE COURT: Getting close, ladies and gentlemen.

All right. Go ahead.

MR. WISNER: Thank you, your Honor. Long day.

BY MR. WISNER:

Q. All right. So, Doctor, I just want to ask you about -- I'm not asking about a specific study or anything like that, but how could you design a challenge, de-challenge, rechallenge study as it relates to -- period? How would you do that?

A. Sure. You could design the same kind of thing. You could say David Healy and his patient may be -- two patients may be some odd freaks, although a bunch of other people have

described the same challenge, de-challenge thing and this problem. You could say, "We really want a much bigger group of people. We want to run a controlled trial where people get exposed to the drug, and if there's a problem, the drug gets stopped, and then they get re-exposed." This could be done.

The FDA at one point said this is a good idea, but it's never been done.

Q. Now, you did mention that it had been done on a smaller scale, is that right?

A. Only in the case --

MR. BAYMAN: Your Honor, same objection as before. This is not theoretical.

THE COURT: Move on, sir. Let's move on.

MR. WISNER: All right.

BY MR. WISNER:

Q. Have you seen any challenge, de-challenge, rechallenge case reports done before?

A. There's a large number of them in the field. The other place where it comes into play is when companies run clinical trials and patients in them go on to a suicidal act or become suicidal or drop out of the trial because they become suicidal, the company monitors or asks to determine, "Did our drug cause the problem or not?"

MR. BAYMAN: Your Honor, objection again.

THE COURT: Overruled, sir.

Go ahead, Doctor.

BY THE WITNESS:

A. They're asked to decide: Did the drug cause the problem or not? And they take exactly the same approach as I'm taking here -- or as I took with the patients I have. They look at, well, is there any evidence that -- well, first of all, they look and see: Did the problem happen after the patient went on the drug? Was there any hint of the problem there before? After they went on the drug, did it clear up when the drug was stopped? And is there any evidence, then, that the patient got exposed to this drug or a similar drug, and did the problem come back?

They also look at issues linked into the dose, whether the problem wasn't there at the start but appeared when the dose got put up.

Company personnel -- the only point I'm making is company personnel took exactly the same approach towards trying to decide did the drug cause the problem as I do. The thing is, you see me publish and say, "Look, I think this indicates the drug can cause the problem. It may be very rare, but it can cause it." You don't see company publications like that.

BY MR. WISNER:

Q. All right. Well, you mentioned several times in this area of challenge, de-challenge, rechallenge Rothschild and Locke.

Do you recall that, Doctor?
A. I do, yes.
Q. Who is Rothschild?
A. Anthony Rothschild is a doctor who was working at Harvard shortly after the first reports came out of Harvard of Prozac causing a problem. And this was by a different group of people.

Dr. Rothschild was working with a woman called Carol Locke, who I understand to have been the senior author on the paper, but between them they wrote a paper which is referenced in quite a few of the papers you've seen today, Locke and Rothschild. And this was looking at a person who was suicidal on Prozac -- well, three people, where two at least having been given Prozac do things like jump off buildings and are seriously injured; but because there is all sorts of things put in place to keep them safe afterwards, when the problem is cleared up, when the Prozac is out of their system, they take the opportunity to re-expose, with the person's consent, and the people then describe, "The problem comes back when I get re-exposed to this drug."

And a further factor which company personnel will take into account when they're trying to work out if this happens in a clinical trial, Dr. Rothschild and Carol Locke introduced an antidote, which you've heard me talk about, a beta blocker called Propranolol; and in two of their cases, at

least, this seemed to help a lot.

Again, company monitors, if there's any evidence that something has been done to alleviate the problem, if there's any evidence of an antidote, this again goes to the standard approach that everybody takes to determining cause and effect.

And company monitors do it with individual cases. Although they're in clinical trials, they still have a duty to do this with individual cases. Or if any of the jury would get in touch with GSK, they would want to do the same thing. They would want to ask exactly the same questions. Were you on anything else? Did it happen after you went on the drug? Did it clear up after the drug was stopped? Did you go back on the drug? What happened?

And they have an obligation to follow you up. And based on that, they will often say, "We believe that our drug has caused a problem," even if your own doctor has said, "No, it didn't."

Q. All right. Well, do you know if Anthony Rothschild is involved in this case at all?

A. I understand he may be involved in this case. I'll have to wait and see.

Q. What capacity?

A. He's one of the expert witnesses for GSK.

Q. I see. Do you know Dr. Rothschild personally?

A. We have met many, many years ago. Actually, I met

Dr. Rothschild first 20 years ago. I can date it rather precisely.
Q. Why is that, Doctor?
A. Oh, well, the -- yeah, no, just -- I had -- the issue of Prozac causing people a problem had become a big one.
MR. BAYMAN: Your Honor, hearsay.
MR. WISNER: Yeah, let's not go there.
THE COURT: Let's not go back there. Let's stay with the issues.
MR. WISNER: Let's not go there.
BY MR. WISNER:
Q. Would you recognize a copy of the Rothschild article that we're referring to if you saw it today?
A. I thought we put it up earlier. Did we not?
Q. No, we haven't.
A. Well, yes, I would.
Q. Please take a look at Plaintiff's Exhibit 88.
THE COURT: The number again, sir?
MR. WISNER: 88.
BY MR. WISNER:
Q. Have you got it, Doctor?
A. Well, my filing system has broken down again, I hate to say. I'm a little worried that you may need to help me out again, because it's not coming to hand.
Q. One second. I'll get you one.

THE COURT: Here you are, Doctor. My system isn't much better than yours, but I don't want to have you sort all of your papers.

THE WITNESS: Thank you, your Honor.

MR. WISNER: Thank you very much, your Honor.

THE WITNESS: Actually, there's two papers here. I'd better give you this one back.

BY MR. WISNER:

Q. All right. Have you got Exhibit 88 in front of you, Doctor?

A. Yes, I do.

Q. Great. Plaintiff's Exhibit 88, what is it?

A. This is a paper that appeared in a journal called *The Journal of Clinical Psychiatry*. It's called, "Re-exposure to Fluoxetine After Serious Suicide Attempts by Three Patients: The Role of Akathisia," and its authors Anthony J. Rothschild and Carol A. Locke.

Q. Is this one of the articles that you cite to and rely upon in your expert report?

A. Yes, it is.

Q. And is this a reliable article, in your opinion?

A. Well, yes, it is. With all of these things, as I indicate, you know, the trick is you want people to look at every article from every point of view. This, I think, is a good article, but you wouldn't hang an entire case on just one

article. But it is, well, I thought when I read it first, a very compelling article.

MR. WISNER: All right. At this time, your Honor, permission to publish Exhibit 88 to the jury?

THE COURT: Yes, you may proceed.

BY MR. WISNER:

Q. All right. So, let's start with the first page here, Doctor. You mentioned this was written by Rothschild and Locke. Do you see that?

A. Yes, I do.

Q. Is there any significance about the fact that Rothschild is listed first?

A. Not necessarily, no.

Q. Okay. Now, if you look at this, it has a section that says, "Case Reports." Do you see that?

A. Yes.

Q. What are case reports?

A. Well, case reports are where a doctor, or these days increasingly a doctor and a patient, say, or a few doctors and a few patients will report on a problem or an issue that they're seeing, or it can be a good outcome, where it's not in the clinical trial literature. You know, drug X may be used to treat condition Y, but, in fact, we're seeing some good outcome or bad outcome maybe when drug X is being used to treat a completely different condition that nobody knew

anything about.

One way or the other, what you've got is a group of doctors and patients looking at something happening on the drug and trying to take into account everything else that could explain what they're seeing and coming to a conclusion that we think this drug, for instance, has caused that outcome, whether a good or a bad one.

Q. That leads me to a question while we're here on the Rothschild article.

Do you think it is appropriate, if you're investigating whether or not a drug caused someone's suicide, to start off with the belief that it couldn't possibly have caused the suicide?

A. Well, I think in some respects, it would have been very difficult in Boston at that time not to think that these drugs could cause a problem, you know, because some of the first reports had come from Boston. So, I'm sure this was an issue for Dr. Rothschild and Locke. They were alerted to it in a way that a few others weren't.

But these reports were coming in, you have to appreciate, from all sorts of places. They came in from both Harvard and Yale; and they don't usually agree on anything, but they were coming from both universities.

Q. But methodologically, putting aside the context of the article for a second, but methodologically, do you think it's

appropriate, if you're going to look at whether a drug caused someone's suicide, to start off with the belief that it's not possible a drug could cause someone's suicide?

A. I don't think you have to do that at all. As I've said, the single greatest way we discover most things about drugs are from people saying, "Hey, this is happening to me." And that doesn't happen if you're intensely skeptical. You have to be open to the possibility that the drug is causing it.

It isn't just problems. The single best way to discover new drugs is because patients or doctors recognize something new happening. And the unfortunate thing is, a lot of people say you shouldn't pay heed to case reports. You should only pay heed to controlled trials. And as that culture has grown, we've ended up with less and less new drugs. The supply of new drugs has begun to dry up because we're not paying heed to observations like this.

Q. All right. Well, let's look at the discussion here. We're on page -- the second page of it. And I want to actually go through this first paragraph written by Dr. Rothschild. It reads, "Three depressed inpatients, 25 through 47 years of age, were re-exposed to fluoxetine." What's fluoxetine, Doctor?

A. That's Prozac.

Q. Okay. "Were re-exposed to fluoxetine after having previously made a serious suicide attempt while taking the

drug. This is the first report, to our knowledge, of patients restarted on fluoxetine after a previous suicide attempt during fluoxetine treatment. We observed that all three patients developed severe akathisia while taking fluoxetine, and they stated that the development of this syndrome in the context of their depressive episode is what precipitated their prior suicide attempts. When re-exposed to fluoxetine, the patients again developed akathisia and suicidal ideation. The suicidal feelings abated when the akathisia was treated by the discontinuation of the fluoxetine or the addition of propranolol."

Do you see that? I probably said that wrong.

A. Yes.

Q. Okay. Walk the jury through what that paragraph is saying by Dr. Rothschild.

A. Well, there's been a prior challenge with the drug, and the person has become suicidal. The drug has been removed. When you get to read the case history in detail, when you see the fluoxetine has been removed, the problem clears up. The person still needs treatment. In this case -- well, in these three cases, they've had the opportunity to re-expose the person to fluoxetine in part because other treatment options weren't available to these patients. They were quite unusual patients in that respect, but also because as I said to you earlier, one of them, a woman in particular, was in a

wheelchair, so it was rather easy to make sure that she couldn't repeat what she'd just done, which was jump off a building, although what she made clear was, "I'm having exactly the same feelings that led me to do this before."

Q. In the next paragraph and a half down, it reads, "Akathisia has been implicated in the development of suicidal ideation, homicidal ideation, and violence." Do you see that?

A. Yes, I do.

Q. What is homicidal ideation?

A. That's where you've got thoughts of violence not just towards yourself, which leads to your own death, but thoughts of violence towards others.

Q. Is -- we've talked about violence and suicidality associated with akathisia. What is Dr. Rothschild referring to here?

A. Well, the fact is that the state gives rise to people having horrific and unusual impulses. People sometimes end up in a state of fear, but they also end up in a state where they're afraid of the impulses and thoughts that they're having. It's not just that I might take an overdose and end up dead. It's I might kill myself in an awful way, or I might kill others.

Q. All right. I want to start -- it crosses over two pages, so it reads down here, it says, "In both cases, sui-," do you see that, Doctor?

A. Yes, it's --
Q. Okay. "In both cases" -- and then I'll read the rest here. "In both cases, suicidal ideation appeared suddenly, concurrent with the development of akathisia, and disappeared when the akathisia was treated."

What does that tell you as a scientist?

A. Well, again, the key thing is that it happens after you give the drug. One of the other things is -- but again, we know that these people are very susceptible. These are people who are going through a bad reaction and appeared to have one very quickly.

This again ties -- if there's a big delay between giving the drug and the akathisia happening, while that can certainly happen on the drug, it becomes a little harder for an outside observer or the person themselves to make the linkage.

In this case, clearly -- I mean, it's just generally when we're trying to work out what happens with these things, if there's a close temporal link between giving the drug and the problem happening, people are more likely to figure out, "Ah, there is a causal link here."

Q. If you read down farther, and I'll highlight this part, it says, "Shaw and colleagues reported a case of suicidal and homicidal ideation and akathisia in double-blind neuroleptic crossover study."

MR. BAYMAN: Your Honor, we're now getting into drugs that are not even in the class of the medicine that's at issue in this case, so I object.

THE COURT: All right. We'll recess now until tomorrow morning, ladies and gentlemen. We'll resume at 9:30. And we will ask you to remember all of the admonitions that I gave you about the case. And don't forget us between now and then, either.

(Jury exits courtroom.)

[redacted]

[redacted]

[redacted]

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[redacted]

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[redacted]

[redacted]

(Court adjourned, to reconvene 3/16/17 at 9:30 a.m.)

CERTIFICATE

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

/s/Gayle McGuigan — *March 15, 2017*

Gayle McGuigan
Official Court Reporter — Date

/s/Charles R. Zandi — *March 15, 2017*

Charles R. Zandi
Official Court Reporter — Date