THE SUPERIOR COURT OF THE STATE OF CALIFORNIA
FOR THE COUNTY OF ORANGE

- - -

BEVERLY SMITH, on behalf of herself and all others similarly situated and on behalf of the general public,

Plaintiff,

vs.

Case No.: 04 CC 00590

SMITHKLINE BEECHAM CORPORATION, dba GLAXOSMITHKLINE, a Pennsylvania Corporation, and DOES 1-100, inclusive,

Defendants.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

- - -

PAMELA BLAIN, Individually and as Personal Representative of the Estate of TREVOR KYLE BLAIN, II,Deceased,and on Behalf of All Those Similarly Situated; TONYA D. Brooks, Individually and on Behalf of ALL of Those Similarly Situated; RONALD BLAIN, Individually; LEX BROOKS, Individually;Cheryl Brooks, Individually

Plaintiffs,

vs.

Case No.: 06-1247-JD

SMITHKLINE BEECHAM CORPORATION d/b/a/ GLAXOSMITHKLINE, a Pennsylvania Corporation,

Defendant.

DEPOSITION OF
NEAL RYAN, M.D.
PITTSBURGH, PENNSYLVANIA
OCTOBER 5, 2006

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STATE OF MINNESOTA
COUNTY OF HENNEPIN
- - -

Leigh Ann Engh, Darcene and Greg) Lensing, on behalf of the general) public, themselves and all others) similarly situated)
Plaintiffs,)
vs.)Court No:
)PI-04-012879
SMITHKLINE BEECHAM CORPORATION,) d/b/a/GLAXOSMITHKLINE, a) Pennsylvania corporation,)
Defendants.)

Deposition of NEAL RYAN, M.D., taken on behalf of the Plaintiffs at Professional Suites, US Steel Tower, Suite 600, 600 Grant Street, Pittsburgh, Pennsylvania, commencing at 9:14 a.m., Thursday, October 5, 2006, before Michele A. Kohar, Certified Court Reporter.

A P P E A R A N C E S

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I-N-D-E-X

WITNESS: NEAL RYAN, M.D.

WITNESS WAS INSTRUCTED NOT TO ANSWER
(NONE)
INFORMATION TO BE SUPPLIED:
(NONE)

PITTSBURGH, PENNSYLVANIA; THURSDAY, October 5, 2006; 9:14 A.M.

VIDEOGRAPHER: Good morning. This is October 5, 2006 at approximately 9:14 a.m. The videographer is Martin Murray of Investigative Videography, 121 Glenwood Avenue, Pittsburgh, Pennsylvania, 15209.

We are located at 660, USX Tower, Pittsburgh, Pennsylvania 15219. We are here to videotape the continuance of Day Two of the deposition of Dr. Neal Ryan to be used at time of trial or for any other reason in the Superior Court for the State of California, the County of Orange, Case Number 04-CC-00590. We have Beverly Smith, et. al, Plaintiffs versus SmithKline Beecham et. al Defendants.

Also in the United States District Court for the Eastern District of Pennsylvania Case Number 06-1247JD. We have Pamela Blain, et. al Plaintiffs versus SmithKline Beecham Corporation, et. al, Defendants.

Also in the State of Minnesota, County of Hennepin, District Court Fourth Judicial District, Court File Number PI-04-012879 we have Leigh Ann Engh, et. al, Plaintiffs versus

SmithKline Beecham, et. al, Defendants.

At this time would counselors please identify themselves and who they represent.

MR. MURGATROYD: My name is Skip Murgatroyd and I represent the Plaintiffs in each of these actions.

MS. CONNELLY: Pam Connelly representing Dr. Neal Ryan.

MR. DAVIS: Todd Davis representing GlaxoSmithKline and also present, but not entering an appearance, is Amor Esteban from Drinker & Biddle.

VIDEOGRAPHER: Please proceed.

Neal Ryan, M.D.
having been previously sworn, was examined and testified as follows:

EXAMINATION

BY MR. MURGSTROYD:

Q. Good morning, Doctor.

A. Good morning. **09:14:33**

Q. You understand you're still under oath?

A. Yes.

Q. Okay. And I understand that after the deposition concluded yesterday you went to look for the slides that you thought you may still have 09:14:44

regarding the presentations you've given on Paxil in the treatment of depression, youth with depression? 09:14:44

A. I went to look for the presentations I've given. Some of the presentations were not primarily about that, but did include a couple slides on Paxil. They were about larger topics. I brought all of those. 09:14:58

Q. Okay. And I'm going to mark some of them for the record and ask you to take a look at them, and I believe your Counsel -- or actually that's fine. It's easier -- well -- I'm trying to think of the most efficient way of doing this. I'm going leave the tags on the different pages that I've tagged. Do you see that? 09:15:13

A. Sounds good. 09:15:33

Q. Okay. And before I do that, in terms of these presentations, what was the purpose of these presentations? Did they vary from presentation to presentation or did they generally have the same purpose for each one? 09:15:50

A. The purpose of all of them are -- well, basically the purpose of them was to present scientific data in the field that I was describing, which was primarily the treatment of depression or treatment -- diagnoses, treatment and course, and 09:16:05

psychophysiology depression in some of them. 09:16:05

So larger topics about depression in children and they included some data on Paxil trials and typically the other antidepressant trials in children. 09:16:16

Q. Okay -- and --

A. I'm sorry. I took a pause there. It sounded like I had stopped.

These were all presented -- every one of them were presented to audiences of primarily psychiatrists and psychologists, child psychiatrists, all to professional audiences and they were presented as scientific presentations. 09:16:22

(Ryan Deposition Exhibit No. 41 was marked for identification.) 09:17:16

Q. Let me show you what I've marked as Exhibit 41.

MS. CONNELLY: For the record, this is titled Presentation of Neal Ryan. It's dated April 1999. 09:17:35

BY MR. MURGATROYD:

Q. Doctor, can you identify for the record what that document is, please?

A. Yes. It's a presentation that I did for a symposium for psychiatrists. It was held in 09:17:43

Barcelona. This one, unlike the large majority of the others, was sponsored by a pharmaceutical company. This is sponsored by Pfizer. 09:17:44

Q. Okay.

A. So I prepared the slides on this entirely of my own preparation. They did format the slides. They did not tell me what content to present. They didn't edit my slides. 09:17:50

Q. Is that document authentic?

A. Yes. 09:18:11

Q. And, again, you created that, correct?

A. I created that document from the Power Point slides from that talk, yes.

Q. And at that presentation, did you discuss paroxetine in the treatment of adolescents? 09:18:20

A. Yes.

Q. Okay. Who were -- only had the symptoms of major depressive disorder or for all types of illnesses?

A. The data that we had in this was -- the only data available was what I presented, was the study we've been referring to as 329. There were no other paroxetine studies available in the world at the time so that's what all I presented. 09:18:33

Q. Okay. And what did you in that presentation, what did you state the results of your study were? 09:18:48

A. I don't keep any -- I don't -- the slides are obviously shorthand for what you talk about. 09:18:50

Q. Sure. 09:18:59

A. So all I have at this point are the slides.

Q. Right.

A. So the slides that I have related to the paroxetine study. Our first slide that describes -- it's a slide entitled "Paroxetine Multi-Site Adolescent MDD Study. 09:19:05

Q. That's study 329? Correct?

A. That's correct.

Q. Okay. And I'm just looking for the results of the efficacy. 09:19:16

A. Right. So it has -- it's a single slide that discusses paroxetine out of six times -- you know, something like 50 or 60 slides here and it has -- so there's one single slide discussing paroxetine. It has four bullet points. The first bullet point says: It was an 8 week randomized trial. The second bullet point describes the dosage that was given in the three treatments; paroxetine, imipramine and placebo. The third point says 09:19:29 09:19:41

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paroxetine was superior to placebo on measures of effect, global improvement and remission of depressive symptoms, and the fourth point says imipramine not superior to placebo on any outcome measures. 09:19:44 09:20:01

Q. Okay. Thank you. Let's go to the next one. So in that presentation you did not come out and say that Paxil is effective for the treatment of adolescents with major depressive disorder? Correct? 09:20:11

A. To the best of my knowledge in all of these I gave a more balanced discussion, which was it worked that on some of the indicators and not on others. That would have been scientifically correct. 09:20:22

(Ryan Deposition Exhibit No. 42 was marked for identification.)

MR. MURGATROYD: Okay. Let's look at the next one.

THE WITNESS: So you get that one back, right? 09:20:28

MR. MURGATROYD: Actually, the court reporter does.

MS. CONNELLY: We leave it with this pile.

THE WITNESS: Thank you. 09:20:28

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MS. CONNELLY: The next one is a presentation dated July '99. 09:20:28

BY MR. MURGATROYD:

Q. Okay. And for the record, can you identify what that document is, please? 09:20:35

A. Sure. This was an invitation to give grand rounds at the University of Texas in Galveston, the Department of Psychiatry, July '99.

Q. And what, for the jury's purposes, edification, what is a grand round? 09:20:44

A. Sure. A department will invite a scholar in some area to talk about their area of scientific research, typically, you know, 10 to 20 per year. Most of the department will attend that.

Q. Okay. And this was actually where Dr. Wagner, one of your coauthors works, correct? 09:21:07

A. That's correct.

Q. Okay. And did she invite you down to give that lecture?

A. It was Dr. Chris Thomas who's in the child division who works with Dr. Wagner invited me. I don't know whether she was in the chain of approval of that or not. 09:21:14

Q. Okay. And that document is authentic, correct? 09:21:28

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A. Yes. 09:21:29

Q. And it was prepared by you also?

A. Yes.

Q. And I noticed that -- and correct me if I'm wrong -- that incorporated slides that had been previously created from Martin Keller? Is that correct? 09:21:31

MR. DAVIS: Object to the form; no foundation for that.

THE WITNESS: It incorporated slides? I think that in fact it did incorporate a slide of -- let me look for it. The slide that was -- let's see -- I do not know that they were presented for Dr. Keller, but the two slides I believe that were prepared originally from -- by GSK were a slide that shows the maps of where the investigators were and the slide that shows the so-called, quote "study design", which shows the three arms. I used those because they contained the correct data, and it was easier than redoing them myself. 09:21:48 09:22:07 09:22:18

BY MR. MURGATROYD:

Q. Okay. And some of the balance of those slides were used by Martin Keller in earlier presentations, earlier than your? Correct? 09:22:33

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MR. DAVIS: Object to form. 09:22:33

MS. CONNELLY: Object to form. There's no evidence in the record containing that assertion in your question.

BY MR. MURGATROYD: 09:22:35

Q. Well, I'm just -- do you recall that?

A. I have no knowledge of whether Dr. Keller used these slides before I did.

Q. Okay. Let's see if we can sort that out.

A. Okay. 09:22:44

VIDEOGRAPHER: Can we go off the record?

MR. MURGATROYD: Sure.

VIDEOGRAPHER: At this time we're going off the record. The time is 9:25 a.m.

(Pause in Proceedings.) 09:23:26

VIDEOPERATOR: We are now back on the record. The time is approximately 9:25 a.m.

(Ryan Deposition Exhibit No 43. was marked for identification.)

BY MR. MURGATROYD: 09:24:05

Q. Okay. Let me show you what I've marked as Exhibit 43.

A. Okay.

Q. And can you identify for the record what that document is, please, sir? 09:24:31

A. E-mail from Jim McCafferty to myself dated October 13, 1998. It contains an attachment, Power Point attachment. It says, "Hi Neal. Good to talk to you again", and this is from Mr. McCafferty. "And thanks for allowing your name on the ECNP poster. Marty's APA presentation is attached below. Please confirm receipt." 09:24:31 09:24:58

Q. Okay. And let me show you what I've marked as -- and so the record's clear that was one of the documents that you produced in this litigation, correct? 09:25:11

A. Yes.

Q. And so that's an authentic document?

A. My staff and office produced it. I assume it's an authentic document. 09:25:24

Q. Do you have reason to think it's not?

A. No, I have no reason to think it's not.

Q. Okay. And that was a document that you received, correct?

A. I'm sorry? 09:25:35

Q. That's a document you received? You personally received that document? Correct?

A. That was a document e-mailed to me, that's correct.

Q. Okay. Great. Let's take a look at 44. 09:25:39

(Ryan Deposition Exhibit No. 44 was marked for identification.) 09:25:39

MS. CONNELLY: Can I ask a question? Are there supposed to be pages that are supposed to be blank? 09:25:52

MR. MURGATROYD: That's how I got them form you, Pam. That came up as a question in Dr. Keller's deposition as a matter of fact.

BY MR. MURGATROYD:

Q. And can you identify for the record, sir, what that's documents is? 09:26:05

A. It is a document that appears to come from us with slides and I assume then that it's the attachment to this e-mail --

Q. And -- 09:26:28

A. -- certainly not slides I've prepared, because it's not my style in slides.

Q. Okay. That's fine. Now, if you would, can you go to the -- can I see that document, please? 09:26:41

A. Sure. Of course.

Q. Thank you. Let me show you -- it's page number 3543. That's the page for your convenience. Now, you see that the slide that you're talking about, the location, the map of the United States 09:27:11

that's in there, correct? 09:27:14

A. Right. Yes.

Q. Okay. Now, do you see the slide above that talks about the results of the study?

A. Okay. Yes. 09:27:22

Q. And can you read those into the record?

A. It says, "Paroxetine superior to placebo on measures of affect, global improvement, and remission of depressive symptoms."

Q. Okay. Wait. Stop right there. 09:27:29

A. Yes.

Q. Now, that's what you said in your first -- in the first presentation we've marked today? Correct

A. That's correct. 09:27:35

Q. Okay. Now, the next one, please?

A. "Imipramine not superior to placebo in any outcome measures."

Q. Okay. And the next one, please?

A. "Paroxetine is an effective treatment for MDD in adolescent outpatients." 09:27:37

Q. Okay. Now, let's go to the -- there's a tagged portion of the exhibit I gave you?

A. Yes.

Q. Do you see that? 09:27:46

A. Yes. 09:27:46

Q. And does that talk about the results of 329?

A. Yes, it does.

Q. And can you read that into the record, please? 09:27:58

A. Sure. "Summary-Efficacy. Paroxetine superior to placebo on measures of affect, global improvements and remission of depressive symptoms. Imipramine not superior to placebo on any outcome measure, and paroxetine is an effective treatment for MDD in adolescents outpatients." 09:27:59

Q. Is there any difference between those two slides?

A. Not in the bullet points at all. 09:28:16

Q. Okay. So would you agree that, you, in that presentation before you used the slide, that had been prepared for Martin Keller?

MR. DAVIS: Object to the form of the question of, "been prepared for Martin Keller". There's no foundation for that. 09:28:22

THE WITNESS: I agree with that, because that slide that was in Dr. Keller's office -- because this slide reflected my consensus. I used the wording on the slides, but I took 09:28:37

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responsibility for it once it's in my presentation. 09:28:41

BY MR. MURGSTROYD:

Q. Okay. So now at this grand rounds -- again, that's where -- that's a gathering of physicians, correct? 09:28:48

A. Yes.

Q. And would be also psychologists and social workers and so forth?

A. Yes. Faculty members at the University of Galveston, Texas. 09:28:52

Q. Okay. And obviously it's slides that are projected onto the wall for -- that different people see?

A. Right. 09:29:03

Q. So obviously the people, if they're paying attention, saw the slide that said that Paxil is an effective treatment for adolescents? Correct?

MS. CONNELLY: Object to the form. He can't say what other people may or may not have seen. 09:29:20

BY MR. MURGATROYD:

Q. Well, is available? That statement was, available for all the people there to view, correct?

A. Yes. 09:29:24

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Q. Okay. Now, do you recall actually saying those words too? 09:29:24

A. I typically don't read the words but talk through them, but certainly.

Q. That's fine. Thank you. All right. Let's go to the -- I think I got out of order. What was the last one? 09:31:20

A. You have 42, 44 and 43. I think you're up to 45.

Q. Thank you. 09:31:20

(Ryan Deposition Exhibit No. 45 was marked for identification.)

Q. Okay. Let me show you what I've marked as Exhibit 45. Doctor, can you identify for the record what that document is? 09:31:43

A. Yes. This was a grand round that I did at the University of Belfast in Northern Ireland in 1999, and so I did a Multi-R presentation that included all kinds of stuff including a little bit on antidepressants in children -- and adolescents -- my apologies. 09:32:01

Q. And in that presentation you included the slides, I guess? Did you keep using the same slides over and over again?

A. Certainly I don't remake most of the 09:32:14

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slides. So some of the slides change. Some don't. 09:32:16

Q. Okay. Well, let's go to the ones that are tagged there. Actually, before we do that, that document is authentic, correct?

A. Yes. 09:32:26

Q. And you prepared that?

A. Yes.

Q. Okay. Great. Do you see where I have one of the tags?

A. The first tag, yes. Which slide would you like me to discuss? 09:32:31

Q. Is that the slide we discussed earlier? Does that show the Martin Keller slide as being used again in this presentation?

A. It was a slide representing work we had done jointly; so yes, I was using a slide on work we'd done jointly -- 09:32:44

Q. Okay.

A. -- correctly representing that work.

Q. Okay. Now, let's go to the next tag. The second one, please? 09:33:01

A. Yes.

Q. Turning to the next page.

A. Okay.

Q. Okay. Does that have the results of -- 09:33:05

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did I do the tag? My apologies. Here we are. Summary efficacy. Okay. Can you read that into the record, please? 09:33:07

A. Sure: Summary-efficacy. Paroxetine superior to placebo on measures of affect, global improvement and remission of depressive symptoms. Imipramine not superior to placebo in any outcome measures. Paroxetine is an effective treatment for MDD in adolescent outpatients. 09:33:14

Q. Okay. So that's the same slide that we saw earlier, correct? 09:33:29

A. It's a slide -- it's a slide on work that I had done that I represented as correct. It was the best data available then and it was cited correctly. It was a slide that we had seen earlier in my work. It's different from the slide in the -- in the thing you presented me from Dr. Keller only in the title. 09:33:35

Q. Okay. And it says that paroxetine is an effective treatment, correct? 09:34:03

A. Yes, which it was at the time that this was written, I think, the best estimate of the data.

Q. Well, actually, at the time that was written you were aware of the Study of 337? Correct? 09:34:11

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A. Yes. **09:34:11**
Q. Okay. And 377 clearly showed that Paxil was not effective? Correct?
A. Not correct.
Q. Okay. It showed that Paxil was not effective? 09:34:18
A. Not correct.
Q. Okay. Did 377 reach statistical significance with any of the primary efficacy variables? 09:34:26
A. No, but it's obviously disingenuous and scientifically wrong to say that shows it's not effective.
Q. Well, the study failed? Correct?
MR. DAVIS: Object to the form. 09:34:37
THE WITNESS: Actually, again, that brings back an issue we discussed before that a failed study has a different meaning than that.
BY MR. MURGATROYD:
Q. It's a negative study? 09:34:41
A. It was a negative study, yes.
Q. Negative meaning it didn't show efficacy to a statistically significant --
A. That's correct. That's scientifically, scholarly and every way you want to look at it **09:34:58**

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different than strong evidence that it does work. It simply did not show that it did work. **09:34:59**
Q. Okay. And let's go to the second -- to the next tag I have on that document.
A. Huh-huh. **09:35:11**
Q. And do you see that box right next to it that talks about extrapyramidal?
A. Yes.
Q. And what was the purpose of that box?
A. The purpose of this box was to talk about one group of symptoms that you can get with all SSRIs in adolescents and adults. To remind them of that possibility. **09:35:18**
Q. Okay. And it --
A. It was in with a group of slides -- where a number of slides I was talking about a number of side effects one can get with SSRIs. One more slide. **09:35:29**
Q. Okay. And are these side effects that are known to be caused by SSRIs? 09:35:46
MR. DAVIS: Object to the form.
THE WITNESS: These are side effects that are associated with SSRIs, yes.
BY MR. MURGATROYD:
Q. Okay. And is akathisia one of those? 09:35:59

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A. Yes. **09:36:03**
Q. And can you tell the jury what akathisia is?
A. Motor restlessness. Feeling that you've got to move. Feelings of being restless. **09:36:11**
Q. And does it have an internal component?
A. I'm not sure what you mean.
Q. Does -- well, you say motor restlessness. Can you have akathisia without --
A. It could be the feeling of restlessness as well as the moving itself, yes. **09:36:14**
Q. Okay. And how does that -- a patient who experiences akathisia, is it a discomforting sensation?
A. Yes. **09:36:33**
Q. And can it be severe?
A. Yes.
Q. Okay. And have you read the different medical literature that states that it could be associated with suicidality if left untreated? 09:36:44
MR. DAVIS: Object to the form.
THE WITNESS: I have read articles hypothesizing that this may be related to suicidality. To the best of my knowledge that is simply hypothesis with almost no supporting 09:37:01

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data. 09:37:03
BY MR. MURGATROYD:
Q. Okay. Is that an issue that you've personally studied?
A. We did systemically akathisia in these studies and that showed the rate of akathisia was very low. I don't remember that we had any in this particular study. **09:37:09**
Q. No. My question was: Did you -- have you personally studied the association between akathisia and suicidality? 09:37:16
A. No. I read the literature.
Q. Okay.
A. I mean, I have not done a research study to address that question. **09:37:28**
Q. Okay. That's fine. And would you agree, sir, that Paxil can cause akathisia in some people who take it?
MR. DAVIS: Object to the form.
THE WITNESS: My knowledge of the literature suggests that all the SSRIs can cause it in some people who take it including Paxil. 09:37:41
BY MR. MURGATROYD:
Q. Okay. Thank you. Let's go to the next -- 09:38:29

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now I'm totally lost. Wait a minute -- 44, correct, 09:38:29
or I'm way out of order.
MS. CONNELLY: Next is 46.
(Ryan Deposition Exhibit No. 46
was marked for identification.) 02:47:32
BY MR. MURGATROYD:
Q. That's what I thought. Okay. Great. Let me get rid of these.
Doctor, can you identify for the record what that is? 09:38:31
A. This is a grand rounds that I did at Cornell Medical School in March of 2000.
Q. Okay. Where is Cornell Medical School located?
A. It's on the Harborside in Manhattan. 09:38:43
Q. Okay. And, again, this is a grand rounds where you're talking to other physicians?
A. That's correct. I'm talking to faculty and residents at Cornell.
Q. Okay. So that would be -- 09:38:59
A. It would be physicians, psychologists, social workers, residents in psychiatry primarily.
Q. Okay. And also professors too, correct?
A. Yes.
Q. Okay. Now, how was it that you were asked 09:39:07

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to do this presentation. 09:39:11
A. I do not remember who invited me on that. They -- again, they, you know, most departments of psychiatry would have 10 to 15 grand rounds per year and they simply invite different people to speak on 09:39:28 different topics as they think may be interesting.
Q. Okay. And there's a tagged portion of that slide presentation?
A. Yes.
Q. And, actually before -- that document's 09:39:37 authentic, correct?
A. Yes.
Q. And you prepared it?
A. Yes.
Q. Okay. And you see the summary efficacy 09:39:43 box?
A. Yes.
Q. Can you read that into the record, please?
A. Sure. Titled, Summary-Efficacy. Bullet point one, "Paroxetine superior to placebo on 09:39:43 measures of affect, global improvement and remission of depressive symptoms."
Bullet point two. "Imipramine not superior to placebo on any outcome measure."
Bullet point three, "Paroxetine is an 09:39:50

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effective treatment for MDD in adolescent 09:39:50 outpatients."
Q. Okay. So, again, this is the -- you're using the same slide that -- it's the same message that you had given in the earlier presentations that 09:40:11 paroxetine is an effective treatment for MDD in adolescent outpatients, correct?
A. That's correct. That's a message I thought was scientifically correct from all the data available at the time. It's the same message. 09:40:24
Q. Okay. So now let's go to the next Exhibit which I'll mark as 47.
(Ryan Deposition Exhibit No. 47
was marked for identification.)
Q. Okay. And can you identify for the 09:40:50 record, sir, what this Exhibit is?
A. This is a slide presentation that I did for a talk at the American College of Neuropharmacology in December of 2000.
Q. Okay. And is this document authentic? 09:41:07
A. Yes.
Q. And was it prepared by you?
A. Yes.
MR. DAVIS: Excuse me. Is it December of 2000 or is there -- 09:41:14

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THE WITNESS: There's two 09:41:18 separate documents. One is 2000 and one is 2003.
MR. DAVIS: Thank you, Dr. Ryan.
BY MR. MURGATROYD: 09:41:26
Q. And did you --
MR. DAVIS: I don't have the 2000. That's where I got thrown off. Oh, yes I do. I stand corrected.
BY MR. MURGATROYD: 09:41:33
Q. What is the American College of Psychoneuropharmacology.
A. It is a professional organization of senior researchers in psychiatry, psychopharmacology and basic neuroscience of psychiatric disorders. 09:41:44
Q. Is it just researchers or is it also doctors who actually go out and treat patients?
A. Mainly researchers. Almost exclusively -- to be a member you basically have to be a researcher. It would be very few clinicians. 09:42:03
Q. Okay. Can you also treat patients, also?
A. Yes. Some of the people would treat patients.
Q. Okay. And when you made this presentation was this funded by the ACNP? The American College 09:42:14

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of Psyconeuropharmacology is also known as the ACNP, correct? 09:42:18

A. That's correct.

Q. And was your trip funded by this organization? 09:42:24

A. I am trying to remember back. I was not -- if you remember, they don't fund anything. If you're not a member they pay $500 towards travel costs which won't defray the whole cost. They don't give you any honorarium and I don't think I was a member yet. I am a member now. So either I got $500 towards travel total, which would have been a net loss, but helpful, or I got nothing for it. 09:42:43

Q. Okay. And did you use the same slide in this presentation that said paroxetine is an effective treatment for MDD in adolescent outpatients? 09:42:52

A. Yes indeed.

Q. Okay. Let's go to the next one.

(Ryan Deposition Exhibit No. 48 was marked for identification.) 09:43:18

Q. Have you had a chance to review it?

A. Yes.

Q. Okay. Can you identify it for the record please? 09:43:37

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A. Yes. This is a presentation that I did at a retreat for investigators trying to understand child depression and anxiety disorders at Cold Spring Harbor in February of 2001. 09:43:39

Q. Okay. And, I'm sorry, can you repeat that again? 09:44:03

A. Sure. This was a retreat for investigators studying the question of child depression considered broadly at Cold Spring Harbor in February of 2001. 09:44:05

Q. How were people invited to that?

A. The cosponsors. They were the co-organizers of it. Boris Birmaher, and I'm forgetting the other one, decided which researchers to invite. 09:44:18

Q. Okay. And did you use the same slide in this presentation that we discussed earlier that says that Paxil is an effective treatment for MDD in adolescent outpatients?

A. Yes, indeed, because in February of 2001 it still is the best data. 09:44:33

Q. Okay. Let's go to the next slide.

(Ryan Deposition Exhibit No. 49 was marked for identification.)

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BY MR. MURGATROYD: 09:44:44

Q. Okay. Can you identify for the record what that document is, please?

A. Yes. This is a presentation that I did at the request of the National Alliance on Mental Illness, which is a consumer organization of psychiatric -- an organization of psychiatric patients run by them in July of 2001. 09:45:16

Q. Okay. And by this time the results of 701 were known, correct? 09:45:29

A. Not to me.

Q. Okay.

A. Or not to the world at large I believe.

Q. Okay.

A. Do you have any data that anybody else knew them at that point? 09:45:41

Q. I'm asking if you knew?

MS. CONNELLY: No. Your question was as fact.

THE WITNESS: You said they were known. 09:45:44

BY MR. MURGATROYD:

Q. Well, the results were completed. For -- GSK had completed the study. That's what I meant.

A. But to your knowledge nobody else in the world knew it at that point so that was misleading, 09:45:58

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right? 09:45:58

Q. I asked: The results were completed? Do you understand the question?

A. No. You said the results were known at this point. 09:46:07

Q. Okay. So --

A. So that was clearly a misleading question, right?

Q. Well, I'm trying to find out whether or not you knew them? Did you know that? 09:46:09

A. You knew that I couldn't possibly know them at that time, right.

Q. Why? Why could you not know about it? You're out talking and telling people this drug's effective. GSK knows it's not. Don't you think you should have been told that? 09:46:16

MS. CONNELLY: I'm going to have to object here. We're getting to the point of argument. Your fundamental first question was misleading in that it contained a fact which is not in evidence in this deposition. 09:46:20

If you want to ask the straightforward question as to whether or not the witness had knowledge at the relevant time feel free to ask it. 09:46:33

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BY MR. MURGATROYD: 09:46:35
Q. You were doing work with GSK?
A. Not at this point, as you know.
Q. Is that true?
A. I was -- I don't think at this point I was doing any work with GSK, was I? 09:46:44
Q. Well, let me ask you this: How did you find out the results of 377?
A. They told me, but -- and we gave you the data on that one. 09:46:50
Q. Oh, okay.
A. And I saved all the net study and I told you that.
Q. Okay. So you're saying GSK did not give you the data on 701? 09:46:59
MR. DAVIS: Object to the form.
THE WITNESS: Yes. They did not.
BY MR. MURGATROYD:
Q. And when did you find out about 701?
A. We discussed that yesterday. 09:47:07
Q. Then remind me.
A. It was in the FDA report.
Q. And not until the FDA report were you aware of 702's existence?
A. To the best of my knowledge, yes. 09:47:18

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Q. And nor you were aware of those results until you read it from a source other than GSK? 09:47:18
MR. DAVIS: Object to the form.
THE WITNESS: I think I saw it first there and then on the GSK web site, but there was no data out there on 701 at the time. 09:47:28
BY MR. MURGATROYD:
Q. Do you believe that was important data for physicians such as yourself to have?
MR. DAVIS: Object to the form. 09:47:41
THE WITNESS: Yes.
BY MR. MURGATROYD:
Q. Okay. Now, referring -- going back to that exhibit right there.
A. Yes. 09:47:43
Q. What number is it again?
A. Your Exhibit 49.
Q. And you said that's a presentation before NAMI, N-A-M-I?
A. That's correct. 09:47:48
Q. And is that a consumer group?
MS. CONNELLY: Asked and answered.
THE WITNESS: Yes. That's correct.
MR. MURGATROYD: Okay. I didn't ask if it was a consumer group. 09:48:03

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MS. CONNELLY: He already testified. I never heard of it and now I know it's a consumer group, because he said it five minutes ago. 09:48:03
BY MR. MURGATROYD: 09:48:07
Q. Okay. I'm just clarifying. It's a consumer group, right? It's not physicians?
A. Right. I think that's the third time. Yes, it's a consumer group.
Q. Okay. I wanted to make sure I know who the audience is. So does the audience consist of consumers? 09:48:11
A. Yes.
Q. Okay. And how was it that you made this presentation? 09:48:20
A. They invited me to give a talk to their audience, to their -- to the -- and these would be obviously to the representatives to the regional NAMI organizations and other interested NAMI members. 09:48:28
Q. Okay. And did you give the same slide presentation regarding the -- with the statement that Paxil is an effective treatment for adolescents with MDD?

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MS. CONNELLY: Object to form. Are you asking him if the entire slide presentation was the same or whether that one particular efficacy slide was the same? 09:48:46
MR. MURGATROYD: That one particular efficacy slide? 09:48:58
THE WITNESS: Fine. Yes. I discussed a number of things including bipolar disorder, mood stabilizers, lithium, and I did, as you say, include the slide which we discussed before giving the details on the outcomes of the study in terms of which things it was superior on, and my overall assessment at the time is that it was an effective treatment. 09:49:05
BY MR. MURGATROYD: 09:49:20
Q. And in any of the slides that we've covered so far, did you tell your audience that Paxil had failed to reach statistical significance on the majority of the primary and secondary end-points? 09:49:28
MR. DAVIS: Object to the form.
THE WITNESS: That -- obviously a slide talk is a synopsis of the data. I think that the way -- the thing -- the quote "fact" you just presented is misleading and would have 09:49:41

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mislead the audience, and so I was giving them my best professional opinion on how to summarize what the data meant. 09:49:43

BY MR. MURGATROYD:

Q. Okay. You didn't answer my question so I move to strike it. 09:49:50

My question was: Did you ever tell any of the audiences that we've discussed so far that Paxil did not achieve statistical significance on the majority of the primary and secondary end-points? 09:50:01

A. I think that would have mislead my audience.

Q. So is the answer, you did not?

A. I think that would have seriously mislead the audience. I think one would have to be a complete idiot to tell people something like that. I did not. 09:50:16

Q. Thank you. Now --

A. I think it would be unethical to put something that's misleading in a talk. 09:50:29

Q. I'm sorry. You think it would be unethical to tell an audience that Paxil failed to achieve statistical significance on the majority of the end-points that were predefined before the breaking of the blind? 09:50:46

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MR. DAVIS: Object to the form; mischaracterizes the data. 09:50:48

THE WITNESS: Yes. I don't think that is what the data showed. I think that -- I think that -- I think that you have an obligation to present fairly what the data showed and an obligation to give a fair conclusion so I think that twisting the data to make it -- to make it look worse than it was would be unfair. You can't -- if you present a whole paper you can have complicated discussions. When you're doing a slide you have the obligation to get, you know, in two minutes in a talk that's 60 minutes, to get the to stuff out there in a clear way. 09:51:03 09:51:14 09:51:26

BY MR. MURGATROYD:

Q. Okay. So you think it was important to tell the audience that it passed on three efficacy variables? Right? That's what you have in this sticker slide? 09:51:37

A. I don't know. Let me go back and look. I think we have four in there.

Q. Okay. And you don't think it was important that all the other ones that it failed on, you don't think that information should have been 09:51:59

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given to the audience? 09:52:01

MR. DAVIS: Object to the form.

THE WITNESS: Yes. But understand why I think that requires larger context, which is that -- 09:52:07

BY MR. MURGATROYD:

Q. Doctor. Okay. You answered me.

A. I need to answer your question. I am giving you an answer which will be misleading if you don't let me finish. 09:52:14

Q. I have one question for you.

A. Okay. I'm still trying to finish the prior one, sir.

Q. Go ahead. Finish it. Fine.

A. That this was the first time that anybody had looked at those particular psychosocial outcome measures in a direct depression treatment study, and the improvement in sort of psychosocial things tend to lags the clinical improvement. So the fact that those were negative was a disappointment, but didn't change the weight on whether this compound worked or not. So do you say to average those in? You know, that you have to average those in and you should have averaged those in? That's just wrong. 09:52:20 09:52:35

Q. Well, that's your opinion, and I think 09:52:50

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there's people that would disagree with you and I think you've read people who disagree with you, correct? 09:52:52

MS. CONNELLY: Objection. You're testifying now. 09:52:58

MR. DAVIS: I agree. Move to strike the last question.

BY MR. MURGATROYD:

Q. Do you agree that people have disagreed with what that just said in writing in journals? 09:53:03

MS. CONNELLY: Object to form; there's no facts in evidence.

MR. MURGATROYD: Well, we'll get to it.

MS. CONNELLY: There's factual assertions embedded in that question. 09:53:11

BY MR. MURGATROYD:

Q. Fine. Do you agree with that, sir?

A. I'm sorry? To the question again?

Q. Do you agree that people, your colleagues, disagree with the statement that you just made, and have made that in writing in journals? 09:53:18

MS. CONNELLY: Object to the m; it embeds factual statements which are not in evidence, and if you want to present a different question or evidence then he can answer that question. 09:53:26

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MR. MURGATROYD: He can answer that question. We'll present the evidence later. 09:53:26
MR. DAVIS: I join in that objection.
THE WITNESS: Fine. I am not aware of anybody who disagreed with the statement I just made in writing. 09:53:37
BY MR. MURGATROYD:
Q. Okay. We'll get to that. Now, remember yesterday we talked about -- we added up the variables in your paper and it came up to 11? Do you recall doing that? 09:53:43
A. Yes.
Q. Okay. And you testified only four of those variables reached statistical significance in favor of Paxil? 09:53:59
A. Yes.
Q. And we also talked about -- actually we talked about other variables that were analyzed regarding that study that didn't make it into your paper, right? 09:54:11
MR. DAVIS: Object to the form.
THE WITNESS: Yes.
BY MR. MURGATROYD:
Q. okay. And have you had a chance to go back and look at how many other variables that Paxil 09:54:16

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failed to reach statistical significance on? 09:54:18
A. No. I didn't go back and review anything last night other than doing the work to pull these.
Q. Okay. But you're aware that there are others that Paxil failed to reach statistical 09:54:28
significance on that were analyzed, but not included in your paper? Correct?
A. Yes.
Q. Okay. And so saying that it -- 4 passed -- Paxil passed statistical significance on 4 09:54:39
out of 11 is actually an incorrect statement, because it was actually 4 out of a larger number? Correct?
MR. DAVIS: Object to the form; mischaracterizes the data. 09:54:50
THE WITNESS: I don't think there's -- I don't think that -- let's see -- you were the one that asked about the 4 out of 11 so what's your question?
BY MR. MURGATROYD: 09:55:03
Q. There was actually more than 11?
MS. CONNELLY: I have to object to the form. In the other questions you were pointing to the paper and said, how many are there in the paper -- 09:55:11

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MR. MURGATROYD: I understand. 09:55:11
MS. CONNELLY: -- and said it's 4 out of 11, and now you're trying to say the witness was mischaracterizing it when it was your question based on the paper. 09:55:16
MR. MURGATROYD: No. I'm not saying that. In fact --
THE WITNESS: You said I mischaracterized it.
MR. MURGATROYD: No, I didn't. Those weren't the words out of my mouth. 11:59:58
MS. CONNELLY: I think. Let's just --
MR. MURGATROYD: If you want to argue about it that's fine.
THE WITNESS: Fine. Read it back, please. 09:55:39
MR. MURGATROYD: Doctor, you're not running this deposition.
BY MR. MURGATROYD:
Q. How many variables --
MS. CONNELLY: He's entitled to ask for something to be read back. 09:55:39
THE WITNESS: Am I entitled to ask for it to be read back?
MR. MURGATROYD: No. You're not. Not my question, because you've already answered it. 09:55:39

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MS. CONNELLY: You know what, let's take a break if we're going to be argumentative and abusive. It's not productive. We're on a limited time here. 09:55:39
MR. MURGATROYD: Fine. 09:55:39
MS. CONNELLY: Let's take a quick break right now before you ask a question.
MR. MURGATROYD: No. I don't care if --
MS. CONNELLY: I don't want to hear the -- Counsel asks for a break. 09:55:39
THE WITNESS: I would like a break.
MR. MURGATROYD: Go ahead and take a break.
VIDEOGRAPHER: At this time we're going off the record. The time is 9:57 a.m. 09:55:52
(Recess taken.)
VIDEOGRAPHER: We're no back on the record. The time is approximately 10:07 a.m. Please proceed.
BY MR. MURGATROYD: 10:05:43
Q. Before we took a break, Doctor, we were talking about the number of efficacy variables that were left out of your paper, correct?
MR. DAVIS: Object to the form.
THE WITNESS: Yes. 10:06:13

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BY MR. MURGATROYD: 10:06:13
Q. And do you know what the total number is that were left out of your paper that failed to reach statistical significance in favor of Paxil?
MR. DAVIS: Object to the form; it's been asked and answered. 10:06:22
THE WITNESS: No.
BY MR. MURGATROYD:
Q. Okay. Now, yesterday we did talk about Dr. Stober asking that four efficacy variables be added and analyzed, correct? Do you recall that? 10:06:26
A. I recall that.
MR. DAVIS: Objection to form.
BY MR. MURGATROYD:
Q. And let me show you Exhibit 13 again. 10:06:31
MR. DAVIS: And just so the record's clear, added and analyzed for the study, not added and analyzed for the paper because that mischaracterizes what that document says.
MR. MURGATROYD: I said added and analyzed for the study. I didn't say for the paper. 10:06:44
MR. DAVIS: Just so it's clear.
BY MR. MURGATROYD:
Q. Do you see that? We talked about four --
A. Yes. 10:06:58

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Q. The first four? 10:06:59
A. Yes.
Q. And what are those four again.
A. "Analyze HAM-D results using its four factors." 10:07:03
Q. Okay.
A. So subscales of the HAM-D. The anxiety/somatization.
Q. Right.
A. Sleep, cognitive disturbance and psychomotor slowing. 10:07:03
(Ryan Deposition Exhibit No. 50 was marked for identification.)
Q. Okay. And now let me show you what I've marked as Exhibit 50, which is the Final Clinical Report in its entirety with the exception of its appendices, and I want to turn your attention to Table 22, which is found on page 74 of the report. 10:07:20
MS. CONNELLY: Plaintiffs Exhibit 50 is a GSK produced document. It looks like it's subject to the protective order. 10:07:52
MR. MURGATROYD: I think we agreed that the only part that it's subject for are the first two pages, correct?
MR. DAVIS: That's true. 10:08:03

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MS. CONNELLY: Do you want the witness to review this document or just the table? 10:08:03
MR. MURGATROYD: Just the table.
BY MR. MURGATROYD:
Q. Do you see that Table 22 on page 74 of that report, sir? 10:08:09
A. 22, page 74. Yes, I do.
Q. And does it discuss an analysis of the four efficacy variables that we just discussed?
A. Yes, it does. 10:08:24
Q. And can you determine from those tables whether or not the four efficacy variables proposed by Mr. Strober reached statistical significance in favor of Paxil?
A. It's Dr. Strober. He's a Ph.D. 10:08:44
It looks like in observed cases the first one reaches significance. Not in the last observation carried forward, so that's anxiety/somatization reaches it in one of the two analysis. 10:08:59
Q. The one I'm concerned about is, last observation carried forward.
A. I'm sorry. I thought you asked -- tell me the question you asked before.
Q. How many of the four variables proposed by 10:09:07

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Dr. Strober reached statistical significance in favor of Paxil -- 10:09:13
A. Right. I was answering that question --
Q. -- in regard to last observation carried forward? 10:09:22
A. That's a different question.
Q. I understand.
A. Okay. None of the four.
Q. Okay. Now, whose decision was it to not put the results of Dr. Strober's variables in your paper? 10:09:29
A. I can't imagine that you would have put it in the paper. I don't know that it was discussed. The issue, of course, is that for a secondary analysis and for exploration you look at a zillion things. This would have been very reasonable for secondary analyses. That's what our group was talking about with considerable enthusiasm at the time. So it -- it -- I certainly can't make nothing out of the fact that I don't remember this one being discussed and it wasn't put in the paper. It wouldn't have belonged in the paper. 10:09:44 10:10:05
Q. I'm sorry. My question was: If you know who decided not to put it in the paper?

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MR. DAVIS: Object to the form. 10:10:16
BY THE WITNESS:
Q. The results of those four --
A. Right.
Q. -- variables? 10:10:18
A. Right. I do not know that this analysis was done by the time that the paper was written. I do not know that this analysis was ever presented to the investigators by the time the paper was written, and had it been done so it would have made little 10:10:28 sense in this paper because it really is a secondary examination of a fine -- a minute question rather than the primary hypothesis of this one main study.
Q. Well, let's see. We established yesterday that Jim McCafferty asked in August of 1997, a 10:10:39 couple months before the blind was broken, to add an efficacy variable, correct? Do you recall that?
A. Why don't you go back, because -- just go back and show me which one you're talking about, the efficacy variable, please? 10:10:58
Q. Well, I'm not going to have enough time to do that today. You don't recall that from yesterday?
MR. DAVIS: Object to the form.
BY MR. MURGATROYD: 10:11:05

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Q. Do you recall Jim McCafferty writing to 10:11:05 Rosemary Oakes saying, "Hey, I would like to analyze another efficacy variable"?
MR. DAVIS: Object to the form.
THE WITNESS: I need you to show me the 10:11:18 form if you want to discuss it, because I can't entirely count on your representation of things.
BY MR. MURGATROYD:
Q. I'm just asking you if you recall it? 10:11:24
A. I answered your question, sir.
Q. Okay. You don't recall it? Correct?
A. That's not my answer.
Q. All right. Fine.
A. My answer is show me and then I'll see if 10:11:26 we're on agreement of your characterization of it.
Q. Now, including Dr. Strober's four efficacy variables he asked to be analyzed, right, all of which failed to reach statistical significance using the last observation carried forward analysis, how 10:11:44 many efficacy variables that were analysed were not included in your paper in addition to the 11 we've already talked about?
MS. CONNELLY: Object to form.
THE WITNESS: He was not proposing these 10:11:59

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as -- I do not know the answer to your 10:11:59 question. I do not think these were efficacy variables that he was proposing as primary analyses.
BY MR. MURGATROYD: 10:12:13
Q. They were analyzed? You agree with that, right?
A. Yes.
Q. Okay. They were in the report?
A. Yes. 10:12:14
Q. And that report was prepared before your paper? Look at the report. What's the date of the report?
MS. CONNELLY: You haven't asked a question yet. 10:12:24
BY MR. MURGATROYD:
Q. Okay. What's the date of the report?
A. The date of the report is 24 November '98.
Q. Three years before your paper was published? Correct? 10:12:39
A. Yes.
Q. Now, would you agree that is three more efficacy variables that were not included in your paper?
MR. DAVIS: Object to the form. 10:12:52

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THE WITNESS: Yes. 10:12:52
BY MR. MURGATROYD:
Q. Okay. So now we have a total of 15? Correct?
MS. CONNELLY: Object to form. A total of 10:13:01 15 that were not included in a paper?
MR. MURGATROYD: No. 15 efficacy variables that he's aware of? Right? We're trying to get to the number.
MS. CONNELLY: I'm just trying to get a 10:13:05 clear question.
MR. MURGATROYD: I understand.
BY MR. MURGATROYD:
Q. Yesterday we established there was 11 efficacy variables in the paper? Right? 10:13:09
A. Yes.
Q. And now we have an additional four?
A. Your characterization of these as efficacy variables is dubious. Dr. Strober was -- you would not -- I -- in the treatment studies that I am 10:13:33 familiar with using these compounds or similar compounds through the lifespans you would not count these as a primary or a secondary efficacy measure. you would look at these subsequently to say, did it specifically change that? So I think your 10:13:52

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characterization of these four as efficacy variables is incorrect from the literature in psychiatry. 10:13:58

Q. Well, does GSK analyze them as secondary variables?

A. No. You said efficacy measures. As secondary variables, yes they're in analysis. As efficacy measures I don't think that characterization is completely correct. 10:14:13

Q. I'm using the word -- if I said measures excuse me -- I meant to say variables. 10:14:28

A. As efficacy variables? I don't think that characterizing these as efficacy variables for the treatment outcome is correct.

Q. That's your opinion?

A. I believe that's what I just expressed, sir. 10:14:28

Q. Okay. All right. And Dr. Strober obviously asked that they be analyzed, correct?

A. But not as outcome measures for the studies. 10:14:35

Q. Okay. Do you know that for a fact?

A. Let's see. What does it say? It is an expert informed opinion. I do not know it as a fact.

Q. Thank you. Again, you were here today to 10:14:59

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talk about what you know. If you don't know, please, don't testify to that. 10:14:59

MS. CONNELLY: Counsel, that's an interesting comment considering you've shown him multiple documents of which he has no first-hand knowledge of attempting to get him to testify about whether or not such documents say certain things or are authentic. So I suggest it be a two-way street. 10:15:11

MR. DAVIS: I join in that. 10:15:14

MR. MURGATROYD: And I will move to strike your comments from the record.

BY MR. MURGATROYD:

Q. And, Doctor, the purpose of this exercise is to try to determine how many efficacy variables were analyzed by GSK and not included in your paper? 10:15:26

A. In my expert opinion these are not efficacy variables and Mike Strober did not intend them as that.

Q. I'm sorry? You're testifying for Dr. Strober? 10:15:35

MS. CONNELLY: He testified in his expert opinion.

THE WITNESS: I'm giving you an expert opinion of what Dr. Strober intended, because 10:15:43

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of my knowledge of the psychiatric literature and my knowledge of Dr. Strober. 10:15:44

BY MR. MURGATROYD:

Q. I'm going to move to strike your answer. Thank you, sir. 10:15:59

I'm trying to get at the number of efficacy variables that you personally are aware of that failed to get into your paper and find out why they didn't get into your paper? Do you understand that? 10:16:14

A. Yes.

Q. We have determined that there are efficacy variables in which Paxil failed to reach statistical significance that didn't make it into your paper? Correct? 10:16:28

A. I don't know that we've determined that yet, sir.

Q. Well, I think you've already testified that that's true.

MS. CONNELLY: Object to form. I don't recall any such testimony. 10:16:28

THE WITNESS: I'm not recalling such testimony.

BY MR. MURGATROYD:

Q. Okay. When you give lectures such as the 10:16:39

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ones we've talked about, and we have a few more to go over, and you state in your slide presentation that Paxil is effective in treating adolescents with major depressive disorder, that is, in fact, you, stating to other physicians that it's okay to prescribe the drug to kids? Would you agree with that? 10:16:41 10:17:01

MR. DAVIS: Object to the form.

THE WITNESS: No, I would not.

BY MR. MURGATROYD: 10:17:14

Q. Would you agree that your colleagues who are listening to you and watching your slide presentation have the right to rely upon the accuracy of your information?

MS. CONNELLY: Object to form. He can't testify for his colleagues according to your recent instruction. 10:17:31

MR. DAVIS: I join in that objection.

BY MR. MURGATROYD:

Q. You can answer. 10:17:33

A. Okay. Repeat the question, please.

Q. Do you agree that your colleagues who listen to what you have to say and watch your slide presentation have the right to rely on the accuracy of your information? 10:17:58

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MS. CONNELLY: Same objection. 10:17:58
MR. DAVIS: Joined.
THE WITNESS: I agree that my colleagues have a right to rely that I've done my best to present the data, the important data as it was 10:18:11 known at the time, yes.
(Ryan Deposition Exhibit No. 51 was marked for identification.)
BY MR. MURGATROYD:
Q. If you would, please take a look at that 10:18:16 document.
A. Okay.
Q. Can you identify for the record what this document is, sir?
A. Yes. This was a talk I gave at the 10:18:37 American College of Psychoneuropharmacology also known as the ACNP in December of 2001.
Q. This is basically the same talk you gave a year earlier?
A. No. 10:18:50
Q. Okay. And in it do you include the slide that says Paxil is an effective treatment for MDD in adolescent outpatients?
A. Yes.
Q. Okay. Let's go to the next exhibit. 10:19:13

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MR. DAVIS: 50 was the e-mail from Dr. 10:19:16 Strober, is that right?
MR. MURGATROYD: No. The e-mail from Dr. Strober was 13.
MR. DAVIS: What is Exhibit 50? 10:19:16
MR. MURGATROYD: 50 is the Clinical Report. The full version.
MS. CONNELLY: Right. 1998, November 24.
MR. DAVIS: Oh, for study?
MS. CONNELLY: Final Clinical Report on 10:19:16 329.
MR. DAVIS: Thank you, ma'am.
(Ryan Deposition Exhibit No. 52 was marked for identification.)
BY MR. MURGATROYD: 10:20:01
Q. Okay. Let's go to what we've marked as Exhibit -- what number is that again?
A. 52.
Q. Great. And did you prepare this?
A. Yes. 10:20:03
Q. Is it authentic?
A. Yes.
Q. Okay. And you agree that all the information that you've provided today has been authentic, right, regarding these presentations? 10:20:14

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A. Yes. 10:20:16
Q. Okay. And in this -- well, why don't you tell us about this one? Who was this presented to?
A. Sure. This was the one that we discussed briefly yesterday. This was presented at the 10:20:18 American Psychiatric Association on May 2002 at an industry sponsored symposia sponsored by SKB or GSK.
Q. Okay. And so were there representatives from GSK present at that meeting?
A. I assume so. I didn't see them, any at 10:20:39 the meeting, but it seems likely.
Q. Okay. Because it was put on by them, right?
A. Yes.
Q. And in this presentation you talk about 10:20:50 the side effects of Paxil?
A. Yes.
Q. In adolescents, right?
A. Huh-huh.
Q. Did you tell the audience about the number 10:21:09 of suicide events that occurred during the clinical trial?
MR. DAVIS: Object to the form.
THE WITNESS: I do not have a slide on that. I believe something came up on that in 10:21:20

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the discussion. I'm not certain. I told them 10:21:20 only about the ones that had a statistically significant difference, and in the study there was no statistically significant difference on the suicidality. 10:21:33
BY MR. MURGATROYD:
Q. Actually, there was ultimately?
A. That's incorrect.
Q. Okay.
A. That's absolutely incorrect. 10:21:41
Q. After the complete analyses of study 329?
A. There's no analyses that I'm aware of where this study alone had a difference in the suicide rate. I'm sorry. I am aware of no such data, and certainly in all the data that I have seen 10:21:48 there was no significant difference in the two.
Q. And that was not a concern that you expressed along with Martin Keller when GSK told you about a manuscript they were going to publish about MMD? 10:22:13
MR. DAVIS: Object to form.
MS. CONNELLY: Object to form.
BY MR. MURGATROYD:
Q. Pediatric MDD? Do you know what I'm talking about? 10:22:22

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A. No, I don't. **10:22:22**
MS. CONNELLY: That was vague.
BY MR. MURGATROYD:
Q. Okay. Well, let's take a look at that. Before we get into that -- and we'll get into that 10:22:26 in a second -- do you agree that it was important in your presentation to inform the people present about the significant side effects that came up in your study?
A. Yes. I informed them of the significant **10:22:39**
side effects. I was trying to do what I thought was best there. On this one, like every presentation I've ever made, I prepared the slides. I decided what to put in and out. There was, to the best of my knowledge, no vetting by GSK on this. **10:22:41**
Q. All right.
VIDEOGRAPHER: Mr. Murgatroyd, we have two minutes.
MR. MURGATROYD: Okay. Let's switch them out. 10:23:20
VIDEOGRAPHER: At this time we're going off the record to change tapes. The time is 10:24 a.m. This is the end of Tape 1.
(Pause in Proceedings.)
VIDEOGRAPHER: We are now back on the 10:26:11

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record. This is the beginning of Tape Number 2 10:26:13 of Dr. Neal Ryan. The time is 10:27 a.m.
Please proceed.
BY MR. MURGATROYD:
Q. Doctor, before we took the break I asked 10:26:24 you whether or not you were aware of a manuscript that GSK was proposing to publish entitled "Efficacy and Safety of Paroxetine for Pediatric MDD"? Do you recall that?
MS. CONNELLY: Object to the form. You 10:26:48 didn't ask that question before the break.
MR. MURGATROYD: That's fine. Make your objection. Let's go on.
BY MR. MURGATROYD:
Q. Doctor, are you aware of a manuscript that 10:26:50 GSK proposed to publish entitled "Efficacy and Safety of Paroxetine for Pediatric MDD"?
A. Yes.
Q. Okay. And do you recall that you and Dr. Keller were dismayed about that article being 10:26:58 published?
MR. DAVIS: Object to the form.
THE WITNESS: I don't right now recall being dismayed to the extent that it was a duplication of what the FDA had done. Dismayed 10:27:11

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I don't recall. 10:27:14
BY MR. MURGATROYD:
Q. All right. Well, let's take a -- well, first of all let's -- let me mark this exhibit.
(Ryan Deposition Exhibit No. 53 10:28:05 was marked for identification.)
MR. DAVIS: Can I see it before it goes to the witness?
MS. CONNELLY: Exhibit 53 is an unbates-stamped document. It appears to be 10:28:13 from Dr. Keller.
BY MR. MURGATROYD:
Q. I'm going to show you a series of e-mails that we can have you read and then we can discuss them all at one time. 10:28:33
A. Okay.
VIDEOGRAPHER: At this time we're going off the record. The time is 10:31 a.m.
(Recess taken.)
VIDEOGRAPHER: We are now back on the 10:42:20 record. The time is approximately 10:43 a.m.
(Ryan Deposition Exhibit No. 54, 55, 56, 57, was marked for identification.)
BY MR. MURGATROYD:
Q. Doctor, while we were all off the record I 10:42:29

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showed you a number of exhibits; is that correct? 10:42:33
A. Yes.
Q. And what are the exhibit numbers?
A. 53 through 57.
Q. And did you get a chance to review those? 10:42:46
A. Yes.
Q. Do they help refresh your recollection as to the question I earlier asked you about being very dismayed about GSK publishing the MDD manuscript?
MR. DAVIS: Object to the form. 10:43:03
THE WITNESS: I now know what you were talking about, yes.
BY MR. MURGATROYD:
Q. And, in fact, those exact words were used in one of the e-mails by, I think, Dr. Keller that 10:43:01 the group of you were very dismayed? Correct?
A. Let's see. Dr. Keller used words like that. I think it was about a subissue and not about publication of the manuscript in general, however. I think it was one issue that he wanted to address **10:43:20**
and not the fact that the manuscript was to be published.
Q. Well, what was the dismay that the group of you all had?
A. Yes. Dr. Keller was the one who asserted **10:43:28**

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dismay for the group, and the issue was that in a reanalysis GSK had done in a paper aggregated the three depression treatment studies and looked at two things, one was efficacy and what they concluded in there was that none of the primary outcome measures came out significant in any of the three studies, but a meaningful number in the 329 Study of secondary measures indicated efficacy, and then they reported a reanalyses of the suicidal data. 10:43:29 10:43:52

In the reanalysis of that suicidal data on chart number 10 or Table 10 what they had is -- hold on a second -- that by reanalyses -- by reclassifying things they had significant P values in the 329 Study on several of the ways of looking at suicidality, specifically looking at things classified as self harm. Things classified as suicidal ideation and/or self harm -- I'm sorry -- self harm during the on-therapy period, and then on the 30 days post-treatment period suicidal ideation and/or self harm or self harm considered alone. 10:44:13 10:44:35 10:44:50

Q. And, Doctor -- I'm sorry.

A. I'm sorry. Dr. Keller, what he was concerned about was that this appeared to be different -- this was different than what Dr. Keller, myself and others had published in the 10:45:09

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original articles and in the letters and he wanted more explanation of why this was different than what we published before, because it was his assertion we acted in good faith with all data available to us, and so we wanted them to explain more clearly what the different methodology was that got these results. 10:45:11 10:45:18

Q. Okay. And a minute ago I asked you if -- and I think you testified, and correct me if I'm wrong, that you had never seen any document or any information that showed a -- that there was a significant -- statistically significant relationship of Paxil with suicidal ideation or suicide events? I think I used or suicidality ever? 10:45:28

A. Did I say that there was none or did I say that I didn't remember it? 10:45:48

Q. No. You said there was not. You said it didn't exist.

MS. CONNELLY: I thought he said he hadn't seen it. 10:46:01

THE WITNESS: I thought what I said was, to the best of my knowledge and that was the answer at that point.

I completely agree that this paper was in my files so I had seen it at some point, but 10:46:07

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I was also giving you a completely accurate answer that I certainly didn't remember at the time. 10:46:09

BY MR. MURGATROYD:

Q. Well, Table 10 is the discussion, the topic of discussion in the various e-mails that -- well, let's make sure the record is clear: How many of those documents that I marked and you just reviewed came from your files? 10:46:18

A. I don't know. Certainly the document -- the Table 10 came from my files. 10:46:35

Q. Okay.

A. The other documents I do not know whether -- one of the documents came from my files, the others are not indicated. I did not review the stuff I gave you from my files. 10:46:41

Q. Let's go through those documents one at a time. Pick one. Pick the earliest number.

A. 53.

Q. Okay. And can you please describe for the record what that document is? 10:46:59

A. This is a printout of e-mail from -- the containing e-mail is from Dr. Keller to Dr. Carpenter, myself, Dr. Wagner, Dr. Emslie, Dr. Strober, Mr. Perera, Mr. Liptschiz, and it says, 10:47:14

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"Please indicate where the points are in this paper", and then it contains a forward e-mail contained within it to basically the same individuals saying that he's concerned. 10:47:20

Q. And that is an e-mail that you are carbon copied on? 10:47:35

A. Yes.

Q. Or you were ccd on?

A. Yes.

Q. And do you have any belief that you didn't ever receive it? 10:47:41

A. No. I have no such belief.

Q. Do you believe you did receive it?

A. Yes.

Q. And do you recall the discussions with Dr. Keller about the concern of the statistical significant P value for suicidality that was expressed in the paper? 10:47:50

A. I recall them after looking at the paper. I did not before. 10:48:03

Q. Okay. Let's go to the next document.

MS. CONNELLY: I think -- I tried to put them in order.

THE WITNESS: I'm sorry. I am probably helping you in the wrong way then. 10:48:11

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BY MR. MURGATROYD: 10:48:11
Q. And before we go to the next one, the last one, does that document appear to be authentic to you? The first Exhibit 53?
A. I have no way to authentic this one. 10:48:18
Q. Okay. Do you have any reason to believe it's not authentic?
A. No.
Q. Okay. Let's take a look at the next one.
A. The one that we believe next is in 10:48:28 chronological order is Plaintiffs Exhibit 57. E-mail from Martin Keller to myself, Mike Strober, Karen Wagner and Graham Emslie. This one appears to be from my files. It says: David Carpenter and Alan Lipschitz just called me to say upper management was 10:48:28 told of our strong opinion that they write separate papers and they -- management rejected it.
Q. Okay. And is that document authentic?
A. It's from my files. I assume it's authentic. I can't further authentic it. 10:48:39
Q. Okay. It's from your files, correct?
A. By the notes here, yes.
Q. Okay. And do you recall receiving that?
A. I do not specifically recall receiving this e-mail. 10:48:59

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Q. Okay. But you know that you did? 10:49:01
A. Yes.
Q. Okay. Good. Let's go to the next one.
A. The next one is 56. The covering e-mail and manuscript, the draft manuscript. It's from 10:49:11 David Carpenter to Martin Keller, Graham Emslie, Karen Wagner, Mike Strober, myself. This one's also from my files.
Q. So that document's authentic?
A. To the best of my knowledge. 10:49:28
Q. And the next one, please?
A. The next one is dated 6-13-04. It says from Marty Keller to Ryan, Strober and Wagner, partial draft respond and it talks about dissatisfaction with the paper. 10:49:46
Q. And that had to do with regard to Table 10 and the P values that showed a statistical significant relationship between Paxil and suicidality idealization and/or self harm?
MR. DAVIS: Objection to form. 10:50:03
THE WITNESS: I think that's close, but not correct. What it had to do with is the fact that the paper didn't describe by this analysis why it came out different, and so my understanding of the reading of Dr. Keller's -- 10:50:14

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I mean my understanding of what Dr. Keller is saying to us here is that the authors had a much stronger obligation to be clear about why a subsequent analyses showed different results than what we published in good faith before. 10:50:18 10:50:24
Q. And that had to do with the suicide issue?
A. That's correct.
Q. Okay. And the next document, please.
A. Exhibit 54. It's e-mail from Dr. Keller to myself, Mike Strober and Karen Wagner. It says: 10:50:41 We're extremely concerned about major pieces of the draft, differences reported there from the 329 paper.
Q. And what were the differences that are expressed in this one? 10:50:59
A. It's again the question of what -- with the lack of explanation on why that data on suicidality is different.
Q. And the concern about the P value of the suicide events? 10:51:11
A. Right. It's not that -- it says, "what accounts for the differences and how to explain this." Not the fact that they came out. There was nothing in here to indicate Dr. Keller was concerned that there were P values. He was concerned that it 10:51:20

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was a different analyses and they didn't explain why 10:51:24 the different analyses.
Q. Well, he was concerned about the P values too, correct?
MR; DAVIS: Object to form. 10:51:29
MS. CONNELLY: Objection to the form.
BY MR. MURGATROYD:
Q. That's referenced in the documents I just gave you?
A. Okay. I don't think that characterization 10:51:33 is at all correct.
Q. Okay. Let me see the documents. Let me show you Exhibit 54, and I'm reading into the record under one and then I'll have you take a look at it to make sure I did this correctly. 10:52:01
It states "No where before (329 paper or responses to Jetter). Who is Jetter?
A. It was one of the letters to the editor that we responded to in the subsequent.
Q. Well, actually, Jetter's a reporter with 10:52:24 Health Magazine, isn't she?
A. You're right. I was wrong.
Q. And it says, "No where before (329 paper for responses to Jetter) did we report any of the 3 significant P values reported here." 10:52:39

Now, just make sure I read that correctly. 10:52:39

A. You read that correctly.

Q. Okay. And what is that referring to?

A. It's referring to the fact that this is a new analyses with P values on things that we had looked at before, and the best data we had before didn't have a significant P value there, and so the fact that you reanalyzed -- we analyzed statistically correctly before and didn't have a P value -- they had reclassified people and 10:52:52 10:53:09 reclassified and did have a P value, but they didn't explain the reclassification.

Q. And you were told -- do you remember being told at some point in time that there were more suicide events in your study than you had originally reported? Do you recall getting those e-mails from GSK? 10:53:24

A. I'm not recalling, but you can show me or I can take your word for it, but I'm not recalling it. 10:53:52

Q. All right. Let's take a look at it.

A. But that would be part and parcel of what's in here. I mean, the reanalyses finding more would certainly be consistent with what's in here, yes. 10:53:59

Q. Well, it isn't that new patients all of a sudden appeared and had adverse events? These were adverse events that the patients had during the clinical trial? Right? 10:53:59

A. Yes. They were adverse events when they were reclassified -- were being related to suicidality that were not so classified in the first place, yes, that's my understanding. 10:54:13

Q. And who made that error? Was that the investigator or GSK? 10:54:22

MR. DAVIS: Objection to the form; no foundation.

THE WITNESS: Yes. I think I would have no data -- let's see, error is not, I think, the correct way of classifying that. I think they did a good job of classifying it first to the best of knowledge and then they did more complete, more elaborate ways and it came out slightly different. 10:54:29

BY MR. MURGATROYD: 10:54:44

Q. Well, they were the same events? I mean, the events didn't change, right?

A. As we talked about yesterday it was vague in many cases, text descriptions of what happened, the classification of the events were open to 10:54:59

interpretation. 10:55:05

Q. Well, let me ask yo this: Whose job was it to properly classify the adverse events? Was it the investigators or was it GSK's?

MR. DAVIS: Object to form. 10:55:09

THE WITNESS: It was GSK's job. That's why we broke it down. GSK classified the events. It would have been their job to classify them properly.

(Ryan Deposition Exhibit No. 58 10:55:16 was marked for identification.)

BY MR. MURGATROYD:

Q. Okay. That's fine. Now, let me show you the next document that I've marked as Exhibit 58, and let me show you another document. 10:55:28

MS. CONNELLY: Exhibit 58 is one of Dr. Ryan's documents, but it's been marked with highlighting. Is this your highlighting?

MR. MURGATROYD: Oh, it may be. Here. Let's swap it out. Here. 10:55:37

MS. CONNELLY: It doesn't matter.

MR. MURGATROYD: No. It doesn't make any difference. It's my highlighting.

MS. CONNELLY: Just so you know that Counsel has highlighted that. 10:55:37

MR. DAVIS: May I see that? 10:55:46

(Ryan Deposition Exhibit No. 59 was marked for identification.)

BY MR. MURGATROYD:

Q. And let me show you what I'm marking as Exhibit 59 to go along with it. 10:55:48

A. Okay.

Q. Okay. Now, these are Exhibits 58 and 59, correct?

A. That's correct. 10:56:50

Q. And they both came from your files, correct?

A. Yes.

Q. Both documents are authentic?

A. To the best of my knowledge. 10:56:59

Q. Okay. And both of these are e-mails from you, right?

A. That's correct.

Q. So you prepared these?

A. Yes. 10:57:11

Q. And let's take 59 first.

A. Okay.

Q. 59. Can you please tell the jury what 59 is.

A. 59 is e-mail from me to Philip and Erica 10:57:16

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Wetherhold containing e-mail from me to David Carpenter, Jim McCafferty, Regan Fong, Philip Perera, Alan Lipschitz and ccd to Drs. Keller, Strober and Wagner entitled, "Study 329 update" referring to e-mail from the prior day from Regan Fong to Drs. Keller, Wagner and myself with ccs to the GSK people saying, "With your e-mail (appended below) about 4 additional 'events' in Study 329 on the Paxil arm, those of us involved in writing the recent letter to the reporter asking about details of our article need very very quickly to get absolutely as much information as you have and understand what part of this we need to pass on to her. Otherwise we are in the challenging position of sending her a good-faith effort at directly answering her questions that we find very shortly thereafter is no longer the most complete information available to us and which therefore might appear misleading. Can we get a much fuller explantation in e-mail? Should we quickly set up a conference phone call?" 10:57:22 10:57:33 10:57:59 10:58:09 10:58:18

The last containing one is the update. This is again from GSK, but it doesn't say who it was from on here -- I'm sorry -- from Regan Kong. Says, "Dear all, we want to update you, as 10:58:33

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investigators on Study 329, about additional potential pediatric suicidality cases that were recently discovered. In a manual review of all SAE narratives and 'trauma' cases, 10 additional events potentially suggestive of intentional self injury, suicidal ideation, or suicide attempt were identified. Four of the 10 events occurred in Study 329, all in the paroxetine group. Consequently, this could potentially change the number of paroxetine suicide-related adverse events for the study from 6 to 10. These cases are included among those undergoing blinded review by Dr. Wagner, Dr. Ryan, and Dr. Apter for the pediatric suicidality manuscript. Please feel free to contact us if you have any questions." 10:58:35 10:58:41 10:59:03 10:59:16

Q. Okay. Ms. Jetter with Health Magazine had actually sent a series of questions that you and your group responded to?

A. Yes. Dr. Keller took the lead in that, but yes she had. 10:59:28

Q. And one of the things she asks about are the suicide events that occurred in Study 329? Correct?

A. That would reflect both this document and my memory, yes. 10:59:50

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Q. Okay. And you responded and told her that none of the suicide events didn't reach statistical significance? Right? 10:59:50

MR. DAVIS: Object to form.

THE WITNESS: I didn't respond, but Dr. Keller did. I don't remember that e-mail correspondence, but it's likely that we would have done such, because by the best data they had they did not. 11:00:05

BY MR. MURGATROYD: 11:00:09

Q. And this e-mail talks about your problem with that? Right?

A. Yes. That we have to get her better information once we know it. Absolutely and

Q. Okay. 11:00:16

A. -- because there were P values that --

Q. Right.

A. -- that GSK had reclassified things from the process we had talked about before, and there were 4 more which would change the information we were giving her and we didn't want to give her incorrect information. 11:00:18

Q. Okay. And did you go back and correct the information?

A. I was never the one corresponding with 11:00:24

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her. I assume that Dr. Keller did. My memory is not sufficient to guarantee that he did. 11:00:28

Q. Now, in Exhibit 58, can you read the second paragraph in the record?

A. Sure. 11:00:41

Q. Just the first two sentences.

A. "FDA made each company go line by line through absolutely all documentation of all kids in all their studies. This is where 4 more subjects in our joint study fell out, unfortunately, all in the Paxil group." 11:00:50

This is an e-mail from me to Drs. Keller, Strober and Wagner and dated --

Q. That's fine. And my question was: Why was it unfortunate that they were all in the Paxil group? 11:01:05

A. Yes. Because then it meant that what we published in the paper was -- you know, if they come out in both cells then we simply have additional information that doesn't change the paper. If it comes out in one cell then we've got to go back and correct things, because we have more data. 11:01:16

Q. Okay. Did you go back and correct your paper?

A. GSK was getting the data out there so 11:01:26

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there was no erratum to the paper. This was a subsequent analyses. 11:01:28

Q. Okay. That's fine. So no erratum to your paper has been done to your knowledge?

A. To my knowledge, no. 11:01:41

Q. Okay.

A. That also wouldn't be the way you would handle a secondary analyses. That is the way you handle an error in the first one or something.

Q. Okay. Now, yesterday we talked about, and actually we have ... 11:01:48

MS. CONNELLY: Just for timing issues, it's a little after 11:00.

MR. MURGATROYD: Okay.

MS. CONNELLY: You had said you wanted to reserve an hour. Are you still going to do that or no? 11:02:20

MR. MURGATROYD: I'm going to continue in this for probably another half hour and then I'll reserve a half hour. 11:02:33

MS. CONNELLY: Okay.

BY MR. MURGATROYD:

Q. Do you remember yesterday when we talked about the document that said there was a 5.9 percent -- the risk ratio of a suicide event of an 11:02:37

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adolescent taking Paxil versus an adolescent taking placebo was 5.9? Do you remember us talking about that? 11:02:48

A. I remember talking about the risk ratio. I remember that it was approximately, but not exactly 5.9. 11:02:59

Q. Okay. And at some point you said, we'll get into whether or not that was the active drugs or the Paxil load?

A. I'm sorry. Say that again, please? 11:03:09

Q. I think, if I'm correct, you said, well, you didn't know because it said drug? Do you remember saying that?

A. I said, by that table the table didn't indicate whether it was imipramine plus the Paxil or the Paxil group alone. 11:03:16

MR. DAVIS: Object to form.

BY MR. MURGATROYD:

Q. Well, I mean, you would know that from your work on the case, right? 11:03:33

A. I would have to review the original table on imipramine to see if that could have been the combined two. You presented me one page out of a middle of a big document and asked me to comment on one table on one page. 11:03:43

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Q. Well, I wanted to know whether or not you knew that there was a five-plus -- almost six-fold? 11:03:48

A. That wasn't the question you asked me yesterday. Your implication on that question was I was being deliberately misleading. That's not an assertion I want to support. I was not being so. 11:04:03

Q. Well, let's take a look at the next document I'm going to mark here.

(Ryan Deposition Exhibit No. 60 was marked for identification.) 02:47:32

BY MR. MURGATROYD:

Q. Okay. And can you identify for the record what that document is, sir?

A. This appears to be an e-mail from myself to Drs. Keller, Strober, and Phil Perera at GSK. It says, "Please look at my draft answers. I hope I've got them right but you may have to tweak them since I don't know all the GSK internal stuff." 11:06:44

Q. Okay. And that's an authentic document?

A. It looks like it. 11:07:07

Q. It came from your files, correct?

A. Yes.

Q. Do you have any reason to think it's not authentic?

A. No. 11:07:09

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Q. And you prepared it, right? 11:07:11

A. Yes.

Q. And does it refresh your recollection as to whether or not the 5.9 risk ratio of a Paxil patient versus a placebo patient existed with regard to just Paxil? 11:07:16

A. Right. You're mischaracterizing ny prior answer.

Q. I'm just asking a question.

A. Ask the question again, please. 11:07:33

Q. Okay. Does that paper discuss a 5.9 risk ratio with regard to adolescents taking Paxil versus adolescents taking placebo?

A. Yes.

Q. Okay. Good. So the 5.9 risk ratio you would agree is not the combined imipramine and Paxil drugs, it's just Paxil? 11:07:59

A. I have no knowledge of what the combined imipramine plus Paxil one is. 5.9 is certainly the number to represent Paxil. 11:08:13

Q. Thank you, sir. Now, are you aware that study 329 was the reason the FDA looked into the issue of suicidality in kids taking antidepressants?

MS. CONNELLY: Object to form; that assumes a fact that is not in evidence. 11:08:26

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THE WITNESS: That's actually not the case. 11:08:22
MR. DAVIS: Join. And we all did discuss this yesterday.
BY MR. MURGATROYD: 11:09:01
Q. Well, let's take look at the next exhibit. I think you said you've seen this document before.
MS. CONNELLY: Had it been previously marked as an exhibit?
(Ryan Deposition ` No. 61 was marked for identification.) 11:09:16
MR. MURGATROYD: Yes. I think he testified he had read it before. Right? I have one section of the document -- obviously, you're free to read the entire document. 11:09:16
MS. CONNELLY: Plaintiffs Exhibit 61 is a memorandum from the Department of Health and Human Services, FDA, on February 5, 2004, and Counsel has directed the witness to page 7 of the document. 11:10:09
BY MR. MURGATROYD:
Q. And, actually, let me direct you to one other section too. Page 6. The bottom of page 6.
A. Okay.
Q. Are you familiar with that document? 11:11:22

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A. I'm sorry? 11:11:24
Q. Are you familiar with that document?
A. I sorry. Say that again.
Q. Are you familiar with that document?
A. I almost -- I read -- I reviewed most of the documents that were put on the FDA web site that were related to this particular pediatric advisory committee meeting at one time so almost certainly I looked at this document. I'm not -- I didn't spend much time on this particular one and obviously you gave me a chance to review it this morning. 11:11:29 11:11:50
Q. Okay. And I asked you to look at the bottom of Page 6; is that correct?
A. That's correct.
Q. And can you read that into the record, please, sir? 11:12:01
A. "Origins of Present Concern About the Emergence of Pediatric Suicidality in Association with Antidepressant Use; Initial Regulatory Response. Background to May 2003 Paroxetine Report." 11:12:03
Q. Okay. And paroxetine is Paxil, right?
A. That's correct.
Q. And can you read into the record the yellow -- the part I've marked at the bottom of Page 7? 11:12:22

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A. "This May 22, 2003 report suggested an increased risk (paroxetine vs. placebo) of various thoughts and behaviors coded as events considered 'possibly suicide related' and also for the subgroup of these events that met the sponsor's criteria for representing 'suicide attempts.' The signal for increased risk was clearest for 1 of the 3 trials involving pediatric patients with MDD. A summary of the sponsor's finding for the MDD trials in the Paxil program is included in Appendix 2. 11:12:31 11:12:31
Q. Okay. And so it talks about a signal, correct?
A. That's correct.
Q. Appearing in one of the 3 MDD trials? Right? 11:12:35
A. That's correct.
Q. And you would agree that one is Study 329?
A. Yes.
Q. Thank you. And yesterday you testified that you didn't think you had a signal regarding suicidality in your trial? Right. 11:12:41
A. That's correct.
Q. So if the FDA disagrees with you, would you agree with that? 11:13:20

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MR. DAVIS: Object to the form. 11:13:20
THE WITNESS: Let's see. The data that we had did not suggest a signal and we reported that accurately in the paper. The FDA talks about the subsequent analyses that GSK did and using that says that -- and said that there was a signal. 11:13:35
BY MR. MURGATROYD:
Q. Now, that document that you have was a preclude to a meeting that the FDA had in February of 2004, correct? 11:13:50
A. Yes.
Q. And you wanted to be a participate in that meeting, correct?
A. No. 11:14:07
Q. Well, weren't you on the -- didn't you want to be part of the Advisory Committee?
A. No. I in the most way wanted to be conflicted off, because I was fair and square conflicted. I was delighted when they told me -- the -- on that Advisory Committee which I was a member of they can ask for a variance for a member who has a conflict of interest. They do that frequently. It was my great hope that they would do that for me at that meeting. They decided I was in 11:14:20 11:14:29

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conflict. I was not there. That was a very good decision on their part and pleased me. 11:14:31

Q. And so if --

A. The last thing you want to do is appear to be impartial on a study you took part in. That would have been crazy. 11:14:43

Q. Okay. So if David Carpenter testified that the reason you dropped out of the after-suicide manuscript was because you wanted to be on that committee that would have been an inaccurate statement by Dr. Carpenter? 11:15:03

MS. CONNELLY: Object to form; again, it's based on a fact which is not in evidence in this case.

MR. MURGATROYD: And now it is. There is. 11:15:13

MS. CONNELLY: Then can you present to the witness the evidence upon which you're relying?

MR. DAVIS: That mischaracterizes Dr. Carpenter's testimony.

BY MR. MURGATROYD: 11:15:20

Q. Okay. You can answer the question.

A. I have no idea what was going on in Dr. Carpenter's mind. That would certainly not reflect anything that was going on in my mind. I definitely did not want to be there, and the reason for 11:15:28

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dropping out of that one is that it was non-contributory. 11:15:31

Q. And you agree that you through the University, for your efforts on 329, was paid a large sum of money? 11:15:43

MR. DAVIS: Object to the form. We went over this yesterday.

BY MR. MURGATROYD:

Q. I'm sorry?

A. I said no. 11:15:44

Q. Well --

A. Would you characterize a large sum in that I can you give you an answer to that more specific?

Q. Well, over a half million dollars?

MR. DAVIS: Object to the form. 11:15:59

THE WITNESS: I'm sorry. Then that's dramatically false.

BY MR. MURGATROYD:

Q. So if I got an interrogatory response from -- 11:16:05

A. You said that I was paid over a half million dollars?

MS. CONNELLY: Yes, you did. Yes, you did.

MR. MURGATROYD: I said the university for 11:16:13

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your efforts. 11:16:13

THE WITNESS: No. You did not say that.

MS. CONNELLY: Yes, you did.

MR. MURGATROYD: Well, let's make it very clear. 11:16:13

THE WITNESS: Fine.

BY MR. MURGATROYD:

Q. Would you agree that the university was paid by GSK a large sum of money for your efforts having to do with Study 329? 11:16:24

MR. DAVIS: Object to the form.

THE WITNESS: For my efforts on 329 they were paid a considerably more modest sum of money. The total amount was about $500,000 for their expenses in carrying out the studies, 11:16:43 including a little bit of my salary over that interval.

Q. And was --

A. That was total expenses for doing that. For hiring the staff to do it. For all the costs associated with the study. Not for my effort alone. 11:16:48

Q. Okay. So the information that I have from GSK is that they paid your university $541,017.60, does that approximately?

A. Yes. 11:17:03

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Q. Okay. And how much of that went into your pocket? 11:17:03

MR. DAVIS: Object to the form.

THE WITNESS: The best I can say -- I do not know what fraction of my salary was 11:17:13 covered, but whatever fraction of my salary was covered was no additional money to me over my salary. So there was -- so part of that covered my salary versus something else covering my salary was financially immaterial 11:17:22 to me.

I was a tenured full professor at the time so the university had an obligation to pay me and I would have simply done different work; in addition, my best estimate was I would have 11:17:31 gotten a bonus over that time of about $7000 and I would have gotten a bonus for doing different things had I done different things. So that's -- the most one could assert I got additional for this study was $7000 to me, and 11:17:43 realistically the number is probably zero.

BY MR. MURGATROYD:

Q. And are you aware that different entities have made assertions that you were paid by GSK to evaluate the data on Paxil and suicidality, the 11:18:05

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blinded review? 11:18:05
MR. DAVIS: Object to form.
MS. CONNELLY: Object to form; again, you're representing there's --
MR. MURGATROYD: I asked if he's aware that such assertions have been made? 11:18:07
MS. CONNELLY: I'm not aware that such a -- that's a fact that's not in evidence. You can ask him, are you aware that any have been made -- 11:18:16
MR. MURGATROYD: Fine. I'll take your question.
BY MR. MURGATROYD:
Q. Are you aware of any assertions that have been made publicly that you were paid by GSK to do the blinded review that ultimately ended up in the Apter paper? 11:18:20
A. Not to the best of my knowledge, but my review was blinded and so it's a little bit challenging to see how -- see how -- it's a little bit challenging to see how that influences the paper. 11:18:37
Q. I'm not asking whether it influenced the paper. I'm just want to know whether or not -- yesterday you testified you were not paid, and I'm 11:18:41

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just saying there's allegations -- 11:18:44
A. No. I think yesterday I said, to the best of my knowledge I wasn't paid. I'm not certain I wasn't. I don't think I was.
Q. Okay. Well, let's take a look at this document. Do you recall -- well, let's just take a look at the document. We're up to 62. 11:18:58
(Ryan Deposition Exhibit No. 62 was marked for identification.).
MR. DAVIS: May I see it? 11:19:28
MS. CONNELLY: Yes. Sure.
MR. DAVIS: This doesn't come close to what you're purporting to representant what you say it represents.
MR. MURGATROYD: I move to strike Counsel's comments. 11:19:33
MR. DAVIS: You can strike away.
MS. CONNELLY: Well, Plaintiffs Exhibit 62 is not bates numbered. It's a January 30, 2004 letter from an organization known as CSPI. 11:19:52
(Ryan Deposition Exhibit No. 62, 63 was marked for identification.)
BY MR. MURGATROYD:
Q. Let me show you what I've marked as Exhibit 63 also, which is from a web site. So you 11:20:03

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can take a look at the two combined. 11:20:03
MS. CONNELLY: So we've got some web site evidence here?
MR. MURGATROYD: Yes.
MS. CONNELLY: Okay. Plaintiff's Exhibit 63 -- 11:20:05
MR. MURGATROYD: I think it's -- yes, it's 63? Correct?
MS. CONNELLY: -- is an incomplete chart of unknown origin, not bates stamped numbered. Is this something that Counsel prepared? 11:20:16
MR. MURGATROYD: I didn't prepare it.
BY MR. MURGATROYD:
Q. Okay. Do you recognize or have you ever seen that document which we've marked as Exhibit 62? 11:20:58
A. Exhibit 62 I think got sent to me, yes.
Q. Okay. And can you identify for the record what it is?
A. It's a letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research -- I'm sorry -- it's directed to Dr. Janet Woodcock, I'm sorry, the director of the Center for Drug Evaluation and Research, FDA. It is from Merrill Goozner, G-O-O-Z-N-E-R, Director, Integrity in Science Project at the Center for Science in the 11:21:11 11:21:22

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Public Interest, and it's ccd to several other people. 11:21:22
Q. Okay. And is it requesting that you don't participate in the 2004 Advisory Committee meeting held by the FDA? 11:21:37
A. No.
Q. What is it? What is the purpose of that letter?
A. I'm sorry. This is different than a letter I had seen before. Yes. It is requesting that I not participate in that meeting. 11:21:50
Q. Okay. And what are the grounds that are alleged in the letter why you should not participate?
A. It's the -- it is -- of course, at this point I had already been adjudicated to be in conflict and so it was known I was not going to be participating there, and what it says the grounds I should not participate in there was that I was a consultant to GSK, maker of Paxil, paid by Glaxco to evaluate the data on Paxil suicidality and to design further studies on use of that drug. 11:22:09 11:22:14
I certainly evaluated -- I certainly did evaluate the data on Paxil and suicidality and I said yesterday I didn't think I was paid, but was 11:22:28

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not certain. You saw all my 1099s and if so it was a modest amount of money, and I certainly talked to you about designing prior studies; certainly, I have not been designing any further studies of that trial -- 11:22:29 11:22:31

Q. Okay. And --

A. -- so I was conflicted out at the time. I think I was not paid, but if so it was minimus and I hadn't designed any other things, and this is from a group that we don't know. 11:22:33

Q. Okay. What do you mean, we don't know?

A. A group that I don't know. I was using the word we I'm suppose. My mistake.

Q. Okay.

A. What is the group? 11:23:14

Q. What? It says right there what the group is.

A. Yes, but I mean it doesn't say what the group is. It says their name. What do they do?

Q. You know as well as I do, Doctor. I don't know. I was supplied the information. 11:23:16

MS. CONNELLY: Supplied to us.

BY MR. MURGATROYD:

Q. And now a minute ago we talked about the $541,000 that was paid to your university for 11:23:22

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conducting 329, correct? 11:23:28

A. Yes.

Q. And how much of that breaks down to per adolescent that participated in the study?

A. We weren't paid per adolescent so we'll have to do the calculations and get you those numbers. 11:23:39

Q. Okay. Remember yesterday you said you didn't know how many patients you had in Study 329?

A. Yes. I said my best estimate was about 30. 11:23:52

Q. Okay. Let me show you what I've marked as the next exhibit.

(Ryan Deposition Exhibit No. 64 was marked for identification.) 02:47:32

MS. CONNELLY: Are you not going to ask him any questions about the Internet chart?

MR. MURGATROYD: No. It's stupid. He answered my question.

MS. CONNELLY: Okay. 11:24:07

MR. MURGATROYD: We can strike exhibit -- what exhibit was it?

MS. CONNELLY: It must have been 63.

MR. MURGATROYD: We can strike Exhibit 63 from the record. I'm not going to ask him any 11:24:11

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questions about it. 11:24:16

MS. CONNELLY: Okay. Exhibit 64 looks like a progress report.

THE WITNESS: Okay.

BY MR. MURGATROYD: 11:24:35

Q. And can you identify for the record, sir, what that document is?

A. This is a progress report to the Institutional Review Board at the University of Pittsburgh talking about -- it would be a document you submit annually to the IRB talking about any recruitment and significant side effects dated November 14, 1995. 11:24:48

Q. Okay. And is that document authentic?

A. It appears to be so. 11:25:16

Q. Okay. And it was prepared by you or on your behalf?

A. Yes.

Q. And does it discuss how many subjects you had in your study? 11:25:22

A. It is just how many subjects we had enrolled as of November 14, 1995.

Q. Okay. And what was that number?

A. 25.

Q. And do you recall enrolling any subjects 11:25:31

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after that date? 11:25:35

A. I do not remember when enrollment ended; clearly, you have that information and it would be helpful if you would give it to me.

Q. No. I'm asking you? How would I know? 11:25:48

MS. CONNELLY: Asked and answered. He said he doesn't remember.

BY MR. MURGATROYD:

Q. Okay. And this document that you have talks about the number of adverse events that occurred to the adolescents who were participating in your trial? Right? 11:25:59

A. Yes.

Q. And it --

A. It actually talks not about the number, but also about the individual ones. 11:26:07

Q. Okay. And it talks about an individual who attempted suicide? Correct?

A. That's correct.

Q. And the IRB. Can you explain to the jury what an IRB is? 11:26:14

A. Sure. Studies conducted in the United States, and other countries have paralleled it, require an independent review board by an Institutional Review Board that looks at the 11:26:29

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scientific validity of the study, that you are informing patients correctly about the risks and benefits and that the risks and benefits have not materially changed, the best data of the risks and benefits haven't materially changed over the course of the study. 11:26:31 11:26:43

Q. And the risk level for your study was raised, correct, at some point during the study?

MR. DAVIS: Object to the form.

THE WITNESS: Again, this is more than a decade ago so I don't know the answer to your question. I'll have to refresh my memory, please. 11:27:01

(Ryan Deposition Exhibit No. 65 was marked for identification.) 02:47:32

MR. MURGATROYD: Okay. Let's look at Exhibit 65.

MS. CONNELLY: Counsel, for the record, it's 11:30. I don't care how you choose to spend you last half hour, but it's up to you. 11:27:24

MR. DAVIS: Can I see the document?

MS. CONNELLY: Oh, sorry.

MR. DAVIS: Thank you, Doctor.

BY MR. MURGATROYD:

Q. Okay. Can you identify for the record, 11:28:37

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sir, what that document is? 11:28:37

A. This is a memo from myself to the vice-chair at the IRB at the University of Pittsburgh dated January 4, 1996 referencing the same IRB. They had sent me back a memo and -- I'm sorry, I said that vice-versa -- a memo from the vice-chair of the Committee to me about the IRB submission, the annual IRB submission, and they had the following comments and they wanted to re-review it before final re-approval. 11:28:50 11:29:18

Their first one it says on the cover sheet. The level of risk should be moderate", and the second one it says in the progress report, "The subjects are not fully accounted for in the report: 25 entered the study, and 18 completed the acute phase. Please describe what happened to the 7 not completing the acute phase." 11:29:26

It asked me to address this with two copies. So this would have been something they considered straightforward, because the Full Board Review is anything they considered significant. This was reviewed by the chairman to see that that addressed those two points adequately. 11:29:39

Q. Okay. And --

A. And the rest of that is just my submission to do that. 11:29:52

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Q. Okay. And is that document authentic?

A. Yes. It appears so.

Q. Okay. And the question was whether or not the risk level for your study was raised to moderate? Do you recall that? 11:29:59

A. That was the question and the answer was yes.

Q. Okay. And what does that mean when you have a risk level of moderate? I mean, your study didn't start off as a risk level of moderate, correct? 11:30:11

A. Yes. That's correct.

Q. What did it start off as?

A. It would have started off as minimal risk. 11:30:16

Q. And then at some point it got raised to moderate?

A. Yes.

Q. Okay. And why does that occur?

A. Yes. It occurred because through this time the IRBs were redefining what they called mild, moderate and severe risks, and they decided that any study where you're giving medication to children was no longer considered minimal. 11:30:18

Q. Okay. Did it also have anything to do 11:30:41

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with the fact that a child -- an adolescent in your study tried to kill themselves on the drug? 11:30:43

A. My knowledge is the way I said it. I don't know whether the one suicide attempt was contributory to that change or not, but they were changing for all the studies through this interval. 11:30:52

Q. Okay. Thank you.

MR. MURGATROYD: I think I'll reserve the rest of my time and let Mr. Davis go forth. Are we going to 12:00 today or 12:30? 11:31:09

MS. CONNELLY: We had said 12:00, but that's a short time to start. Do you want to go to 12:00? Do you want a full hour before lunch?

MR. DAVIS: No. I would just assume to stop now. 11:31:09

MS. CONNELLY: Have lunch now?

MR. DAVIS: Do lunch now.

MR. MURGATROYD: Whatever you guys want works for me guys. 11:31:09

MS. CONNELLY: Okay. Let's do it.

VIDEOGRAPHER: We're going off the record. The time is approximately 11:32 a.m.

(Luncheon Recess taken.)

VIDEOGRAPHER: We're back on the record. 12:49:43

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This is the beginning of Tape 3, Day 2, of the deposition of Dr. Neal Ryan. The time is 12:51 p.m. Please proceed. 12:49:44

EXAMINATION

BY MR. DAVIS: 12:49:58

Q. Dr. Ryan, good afternoon, my name is Todd Davis. I represent GlaxoKlineSmith in the lawsuit that Mr. Murgatroyd's law firm has filed and I'm here today to ask you some questions about your involvement with Study 329 and also about the topics that Plaintiffs Counsel covered. 12:50:09

A. Okay.

Q. And if you don't understand one of my questions, will you let me know?

A. Yes. **12:50:24**

Q. And if you answer my question I'll assume you understood the question that I asked, is that acceptable to you?

A. Yes.

Q. Thank you, sir. Have we ever met before today? 12:50:24

A. Yesterday.

Q. Have we ever met before the deposition started?

A. No. **12:50:29**

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Q. Have you ever spoken with any GlaxoSmithKline lawyer or employee about the substance of your testimony? 12:50:31

A. No.

Q. Let me hand you what is going to be marked as -- 12:50:43

MR. DAVIS: May I have some exhibit stickers here, please?

MR. MURGATROYD: Here you go.

(Ryan Defendants Deposition Exhibit No. 1 was marked for identification.) 02:47:32

BY MR. DAVIS:

Q. I'm going to hand you what's been marked as Defendants Exhibit 1 and ask you if you recognize that document? 12:51:13

MS. CONNELLY: This is a document definitely with some highlighting on it. Is that yours?

MR. DAVIS: Yes. I put the highlighting on it. I'm going to go over that with Dr. Ryan just to try to focus our discussion on the topics of interests. 12:51:58

THE WITNESS: Yes. I recognize that document.

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BY MR. DAVIS: 12:52:05

Q. What is that document, Dr. Ryan?

A. It's a review article -- it's a review that was solicited from the editor of the journal -- by the editor of the Journal of Child and Adolescent Psychiatry in -- published in 1996 December reviewing the prior ten years research on child and adolescent depression. This is part two of the article. There were two parts. **12:52:11**

Q. Yes, sir. And who are the authors of the article? 12:52:24

A. The authors are Dr. Boris Birmaher, myself, Doug Williamson, Dr. David Brent and Dr. Joan Kaufman.

Q. What year was the article published? 12:52:35

A. In 1996.

Q. And what journal was it published in?

A. The Journal of The American Academy of Child and Adolescent Psychiatry.

Q. I've highlighted some portions of that article that I would like to talk about. On page 1 of the article -- can you read the first highlighted part of Defendants Exhibit 1? 12:52:46

A. "Early-onset major depressive disorder (MDD) and dysthymic disorder (DD) are recurrent or **12:53:05**

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chronic illnesses with significant morbidity and mortality requiring precise assessment, prompt treatment, and preventive interventions." **12:53:09**

Q. Did you agree with that statement both in 1996 when the article was published and also today? 12:53:22

A. Yes.

Q. And why do you believe that early onset of major depressive disorder and dysthymic disorder are recurrent or chronic illnesses with significant morbidity and mortality? 12:53:35

A. Right. At the time the study had been done there was several other studies, which are not necessarily all referenced here. This one references another Birmaher review, but there was several longitudinal studies showing that these disorders recurred and that on average they lasted something like nine months. More than half of them recurred within five years and that there was significant hazard for completed suicide with major depression in kids, in children and adolescents, and that they had impairment in their home functioning and their functioning with friends and their functioning at school. **12:53:46** **12:54:05**

MR. MURGATROYD: Before we go on any further I want to make sure the record is clear 12:54:20

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that I object to this line of questioning because it exceeds the scope of direct examination, and I think we've agreed for the record that those objections are -- it's going to be a continuing objection to the degree it occurs. I don't have to make it each time. 12:54:20 12:54:20

MR. DAVIS: All objections except to the form of the question or the responsiveness of the answer are reserved until such further use at deposition or until time of trial. And for the record there is no limit on what I get to ask the witness even though you've noticed the deposition. I'm not limited to your direct examination in any respect. 12:54:31

MR. MURGATROYD: We'll take that up with the judge. 12:54:48

MR. DAVIS: Well, there's been no agreement to that certainly.

MR. MURGATROYD: Well, I think --

BY MR. DAVIS: 12:54:58

Q. Dr. Ryan. Dr. Ryan, are pediatric -- let me start again.

In 1996 were pediatric patients with depression and other psychiatric disorders over treated or under treated in the United States? 12:55:07

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MR. MURGATROYD: Objection; calls for speculation. 12:55:13

THE WITNESS: There were several published data sets at the time strongly demonstrating that they were under treated. About one in five got treatment. 12:55:14

BY MR. DAVIS:

Q. And were you aware of those data sets at the time that you published this --

A. Yes, I was. **12:55:24**

Q. -- article?

A. Yes, I was.

Q. Okay. And --

MS. CONNELLY: Be careful to wait until he finishes. 12:55:26

THE WITNESS: My apologies.

BY MR. DAVIS:

Q. Are pediatric patients with depression and other psychiatric disorders over treated or under treated today, ten years later? 12:55:39

MR. MURGATROYD: Object; calls for speculation.

THE WITNESS: The published literature strongly supports the contention that on average they're under treated. 12:55:46

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BY MR. DAVIS: 12:55:52

Q. And have you kept -- are you familiar with that scientific literature that addresses that issue?

A. I'm familiar with much of it; clearly, there were papers I don't know. **12:56:05**

Q. Let's look on page 1579 at the second highlight. Can you read that highlight into the record, please?

A. "The reports that SSRIs are efficacious for the treatment of adults with MDD (e.g., Greenberg et al., 1994,) together with the findings that SSRIs have a relatively benign side effect profile, low lethality after an overdose, and easy administration (once a day) have facilitated the use of SSRIs in children and adolescents. In fact, from 1989 to 1994 SSRI prescriptions for these populations by physicians has increased fourfold (data obtained from the National Disease and Therapeutic Index, 1994)." **12:56:20** **12:56:33** **12:56:50**

Q. Why do SSRIs have low lethality in overdose?

MR. MURGATROYD: Objection; calls for speculation.

THE WITNESS: The statement there was both 12:57:13

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in absolute terms, but it was also referring to lethality in overdose of tricyclic antidepressants, which was the treatment available before this. 12:57:13

I had published papers on this as had many of my colleagues that tricyclic overdoses had -- are remarkably lethal even in relatively small fold overdoses from primarily cardiovascular deaths. Those were hard to treat even if the kid got to the hospital -- even if the child got to the hospital. 12:57:14 12:57:26

BY MR. DAVIS:

Q. Are -- in terms of comparing SSRIs including Paxil to tricyclic antidepressants or TCAs, how do the two compare in terms of which one is more or less lethal in overdose? 12:57:43

A. In animal models and in experience with overdose kids, children who come to the emergency room with overdose, the SSRIs are very much less lethal than tricyclics in overdose. **12:58:05**

Q. In your experience as a psychiatrist who has done research in depressive -- in psychiatric disorders in children and adolescents, what is it of concern to you in terms of giving a tricyclic or a TCA to a depressed pediatric patient? 12:58:24

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MR. MURGATROYD: Objection; leading. 12:58:29
THE WITNESS: There are now -- after the Keller et al., article, two concerns. After the Keller et al., article and after the Med Analyses of Agnell two concerns; one of 12:58:41 which is the data suggested tricyclic antidepressants aren't effective. At -- during the time this paper was written in 1996 that would not have been my assessment of the literature. That's just with more results 12:58:59 coming in.
So the first one is there's just no evidence that the tricyclics treat antidepressants -- I'm sorry -- treat depression. The second one is that the risk of 12:59:09 death in kids taking tricyclics was so much higher.
BY MR. DAVIS:
Q. Is that risk of death and overdose?
A. Risk of death and overdose, yes. **12:59:22**
Q. Is this a concern that the physician is placed in the situation -- in terms of trying to treat the depression actually giving the pediatric patient a medication which they, in fact, they may use to harm themselves in overdose? 12:59:35

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A. Yes. There's even a week -- even a week's worth of tricyclic antidepressants could be lethal in overdose. **12:59:41**
Q. Okay. Let me ask you a question concerning the statement that you have here that 12:59:48 says, "In fact from 1989 until 1994 SSRI prescriptions for these populations by physicians have increased by fourfold." What's the basis of that statement?
A. That was -- there are registraries. There are commercial registraries that accumulate the usage data of how many prescriptions for different age groups are given for different compounds, and that was from that sort of a source. **01:00:05**
Q. And the patient population that's being 01:00:26 discussed is children and adolescents?
A. I do not remember. We would have to look at the original citation.
Q. It's in the preview section.
A. I'm sorry. I assume it's children and adolescents. I do not remember that particular citation so presumably so, but I don't remember it enough and we would have to go and check the citation to see if it's referring to both or just to adolescents. **01:00:37** **01:00:48**

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Q. So was it your assessment in 1996 that 01:00:52 prescriptions of SSRIs in children and adolescents were, in fact, increasing because of the fact that there's relatively -- they have a relatively benign side effect, low lethality in overdose, and the fact 01:01:05 that they were shown to be efficacious for the treatments of adults with major depressive disorder?
A. I think yes, yes, and sort of. It was my assessment they were increasing because of the low lethality. That was a very big deal. It was my **01:01:24** **assessment, the sort of one, is that tricyclics has also been shown to be effective in adults, and so I don't know -- I don't know that the effectiveness was nearly a push as the safety issues. That was a big deal.** **01:01:43**
Q. Okay. Now, was this increase in the prescription rate of SSRIs for treatment of children and adolescents with major depressive disorders occurring before Study 329 was ever commenced?
A. Yes. Before it was commenced? Yes. **01:02:05**
Q. And was it occurring before the data had ever come in on Study 329?
A. Yes.
Q. And was it occurring before you and your colleagues had ever analyzed the data for the first 01:02:16

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time in November of 1997 when you had the clinical 01:02:22 investigator meeting?
A. Yes.
Q. And so is it fair to say that regardless of what was happening at that time with the study 01:02:31 called 329 that physicians were using SSRIs to treat children and adolescents with major depressive disorders irrespective of any publications concerning -- or completed studies concerning use of SSRIs in children and adolescents? 01:02:48
A. Yes.
MR. MURGATROYD: Objection; calls for speculation.
THE WITNESS: I'm sorry.
BY MR. DAVIS: 01:03:05
Q. You mentioned that -- just for the jury's benefit -- you mentioned that SSRIs have low lethality in overdose. What do you mean by that?
A. Yes. If you take a big overdose of any of the compounds in this class of Serotonin Reuptake **01:03:24** **Inhibitors almost everybody who does that, unless they take it with other compounds, lives.**
Q. Let me turn your attention to page 1580 where I've highlighted the next portion, and then if I could, if I could just ask you to read the very 01:03:39

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first sentence that's highlighted? 01:03:43
A. "Prevention of depression for children and adolescents at high risk of developing depression, such as the offspring of depressed parents and children with depressive symptomatology, but not 01:03:52 clinical depression is of prime importance."
Q. Why is that of prime importance?
A. The argument saying it's of prime importance is because depression was then and is now known to be strongly recurrent, and then as now 01:04:14 there was reasonable, but not overwhelming data that each future episode made it easier to get a subsequent episode; in addition, obviously people are at more risk for a completed suicide -- a child who has depressions in their life is at more risk 01:04:31 for completed suicide during the depression and about 60 percent of suicides in youth seem -- appear to be secondary to a depressive episode.
(Ryan Defendants Deposition Exhibit No. 2, 3,4 were marked for identification.) 01:04:46
Q. Doctor, I'm going to hand you what has been marked as Defendants Exhibits 2, 3, and 4, and ask you if those are fair and accurate representations of the highlighted portions of your article that you just read into the record in 01:05:11

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response to my questions? 01:05:14
A. Yes, they are.
Q. Thank you.
MS. CONNELLY: Do you want one?
THE WITNESS: No. I've got one. 01:06:18
MS. CONNELLY: Okay.
THE WITNESS: I've got one. It just takes a while to stop.
MR. DAVIS: Ms. Connelly, could you find Exhibit 42? It's the grand rounds presentation 01:06:18 that Dr. Ryan provided?
MS. CONNELLY: Yes.
MR. DAVIS: Thank you.
BY MR. DAVIS:
Q. Doctor, I'm going to hand you what has 01:05:14 been marked as Exhibit 42 to your deposition. Is this a copy of a presentation that you provided at grand rounds at the University of Texas in Galveston in July of 1999?
A. Yes, it is. 01:06:31
Q. All right. Let me ask you just a few questions about some of the slides that are presented here.
MS. CONNELLY: I'm going to have a late objection. Object to the form, because it's 01:06:39

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not your presentation, it's your slides? 01:06:39 Right?
MR. DAVIS: I'll rephrase.
THE WITNESS: I'm very sorry, guys.
MR. DAVIS: Are you okay? 01:06:46
THE WITNESS: I'm as good as I'm going to be. Go for it.
BY MR. DAVIS:
Q. Is Exhibit 42 a copy of the slides that you prepared for grand rounds at the University of 01:07:01 Texas in Galveston, Department of Psychiatry, in July of 1999?
A. Yes.
Q. All right. Let me ask you a few -- and when you presented these slides, how did you do 01:07:11 that?
A. Yes. Like I would always do. You present the slides and then use those as prompts to discuss the question in more detail.
Q. Let me ask you some questions. The slide 01:07:26 on the first page down at the bottom left-hand corner?
A. Yes.
Q. What's the title of that slide?
A. It say, "The important bits." 01:07:33

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Q. And, please, if you could for the jury, 01:07:33 read in there what are the important bits that you had on that slide?
A. It says, "An episode of depression is bad; suffering, psychosocial impairment and suicide." 01:07:33
Q. Let me stop you right there: Do you know what the suicide rates are in children or adolescents?
A. The suicide rate in young children is quite small. The suicide rate in adolescents has 01:07:59 gone down in the past decade.
Q. Do you know why? Have there been any studies looking at how prescription medications have affected the suicide rates?
MR. MURGATROYD: Objection; lack of 01:08:14 foundation and calls for speculation.
THE WITNESS: I am aware of several studies on the matter.
BY MR. DAVIS:
Q. What studies are you aware of? 01:08:24
A. Yes. There is on the FDA web site pointing to an original article who -- I'm forgetting the author of -- there's the correlation between -- there's the temporal correlation suggesting that overall in this country completed 01:08:33

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suicide in youth dropped about the time of introduction of SSRIs. 01:08:37

There's a second study that looked over a 10-year period, from 1991 to 2001, at the interrelationship within ZIP codes of the uptake of SSRIs and the rate of completed suicide finding a correlation between the time of uptake of SSRIs and a decrease in hazard for suicide. 01:08:50

Q. To summarize. Do those studies essentially show that as prescriptions of selective serotonin Reuptake inhibitors have increased that the suicide rate has decreased? 01:09:16

MR. MURGATROYD: Let me object on the grounds that those studies has been proven to be -- have shown to be false and that any statement based on those studies would be equally false. 01:09:35

BY MR. DAVIS:

Q. You may answer.

A. Yes. The studies are evidence in that direction, but like all studies considered separately they're just evidence in that direction. I don't know that they definitely show -- I don't know that they reached a level of proof. 01:09:37

Q. But do they show a trend? 01:09:48

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A. Yes, they do. 01:09:52

Q. And is it --

A. They show a significant P value. That's different than saying they definitively prove the question, in my mind. 01:09:59

Q. Yes. But do they provide evidence --

A. They do indeed.

Q. Let me -- do they provide evidence that with the increase of prescriptions of SSRIs that suicide rates have decreased in both youth and adult patients? 01:10:09

A. I'm aware of the youth ones. I'm aware of the youth studies that do provide that evidence. I'm not as familiar with the adult studies.

Q. Now, back to my talking about suicide rates in adolescents, are you aware of what the suicide rates are now? 01:10:26

A. Yes. The blended male/female rate in the most recent decade is approximately 10 per 100,000 per year for later adolescents. It's smaller -- it's less for younger children. 01:10:33

Q. Are you aware of any studies that have looked at how often teenagers or -- let me strike my question.

Are you aware of any studies or analyses that have been done looking at how often teenagers or youth think about suicide? 01:10:52

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A. The data suggests that about 20 percent of adolescents think about suicide each year. 01:10:59

Q. What type of analyses are you referring to? 01:11:20

A. I know the secondary parts on that so I can't answer that question about it.

Q. Now, let's look at "Important Bits" number two. Can you read that bullet point, please? 01:11:33

A. Sure. It says "Depression is recurrent and the more one has the more one gets in the future."

Q. Can you explain that to the jury if you would, please? 01:11:46

A. Yes. Again, this is for a slide so it's informal language, but what it's is that there's evidence in children and adolescents that each depressive episode makes the next one easier to get, and it was also emphasizing again the really important majority of children, approximately 70 percent, will get another depression within five years. 01:12:05

Q. There's a slide that's right next to that, just to the right of it that's called "Epidemiology of Child Depression", do you see it? 01:12:20

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01:12:22

A. Yes.

Q. And there's a bullet there. The second bullet. Can you read that for the jury, please?

A. Yes. It says "Lifetime prevalence in adolescents 15 to 20 percent." 01:12:24

Q. What type of information are you trying to convey?

A. I'm trying to convey that the data at the time would suggest that by someone who was reaching age 18 or 20 approximately 1 in 5 would have had one or more life-time depressions. 01:12:39

Q. Is there any new data out that changes those figures?

A. The National Co-morbidity Survey data of Dr. Kessler and colleagues got a number that was slightly higher than that I believe. 01:12:50

Q. Do you know what the slightly number is?

A. I think it was 25 percent.

MR. MURGATROYD: I want to make sure it's clear. GSK didn't Cross-Notice Dr. Ryan's deposition, did it? 01:12:50

MR. DAVIS: It doesn't matter. I don't care.

MS. CONNELLY: Counsel, yesterday you said 01:13:09

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on the record that this wasn't a deposition for use at trial. 01:13:09

MR. MURGATROYD: I'm just asking whether or not GSK Cross-Noticed it.

MS. CONNELLY: I'm just confused, because yesterday you said that it wasn't, and so it sounds like today you're trying to say it is. 01:13:28

MR. MURGATROYD: No. I'm just asking whether or not GSK Cross-Noticed Dr. Ryan's deposition? 01:13:35

MR. DAVIS: It's not necessary to Cross-Notice it. Just like it's not necessary for your firm to Cross-Notice depositions that we Notice in order for you to use those depositions. Otherwise -- 01:13:37

MR. MURGATROYD: I'm just questioning? Do you agree that you did not?

MR. DAVIS: I want to ask a question.

BY MR. DAVIS:

Q. Look at the next slide, Dr. Ryan. There's a slide that talks about "Age of Onset Unipolar and Bipolar Depression." 01:13:39

A. Yes.

Q. What information are you trying to convey in that slide? 01:13:59

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A. Yes. This slide is just a schematic. It is not trying to convey precise numbers. The issue it's trying to convey is that bipolar disorder typically has its first onset somewhere between 15 and 25. It can start sooner. It can start later, and unipolar depression, which is more common overall, can start at any decade of life. 01:13:52 01:14:09

Q. At the bottom of that is a slide that's called "Clinical Picture."

A. Yes. 01:14:22

Q. Can you read for the jury the two bullets that you have there?

A. Bullet Number one: "Dysthymic disorders go on to major depression and 'double depression', which is associated with a more morbid course than MDD alone." 01:14:24

Q. What is double depression?

A. Double depression is children who have dysthymia, which is persistent depression, not severe enough to make a major depression and then getting major depression on top. Those children in the Study Covax had the worse course. 01:14:37

Q. And then the next bullet point, can you read that?

A. "Increase in suicidal ideation, plans and attempts with longer, multi-year duration of depressive episode(s)." 01:14:52 01:14:52

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Q. By that, are you saying that as -- that patients who are adolescents or children who have dysthymic disorders or major depressive disorders have an even more increased risk of suicidality with each episode? 01:15:13

A. That wasn't --

MR. MURGATROYD: Objection; leading.

BY MR. DAVIS: 01:15:24

Q. Let me ask it again: What are you trying to convey by that?

A. I was referring to a study that I had done with my colleagues at Columbia looking at 192 children where most of the suicide attempts were children who had a depression for two years or longer, so talking about the data that suggests the suicide attempts are from the children who don't get better rather than the short duration depressions. 01:15:35

Q. If a child or adolescent has one or -- has more than one -- strike that. 01:15:50

A child or adolescent who has more than one depressive episode, are they at increased -- more increased risk of suicidality with each depressive episode? 01:16:11

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A. I -- the data may well be done -- known. I do not know if there's data to confirm or disconfirm that. 01:16:16

Q. Okay. At the top of the "Clinical Picture" let me ask you a few questions about the bullets there. What's the first bullet you have there? 01:16:22

A. The first bullet says the "Clinical picture in child, adolescent and adult depression is very similar." 01:16:31

Q. Why do you mean by that?

A. Yes. That was also referring to the same study that I did while at Columbia University in saying that if you look at all the symptoms in depression in children and adolescents and look at the same symptoms in adults the symptom picture is very similar from children to adolescents to adults. 01:16:43

Q. And in the next bullet, would you read that for the jury, please?

A. Yes. The next bullet says, "Endogenecity/melancholic, suicide attempts, lethality of suicide attempts, and impairment of functioning increase with age." 01:16:52

Q. What information are you trying to convey with that bullet? 01:17:07

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A. Again, it's results of the same study saying that adolescents had more of a few things than children do. The things they had more of included the so-called endogenous or melancholic subtype, and that's typically having to do with psychomotor retardation, slowed thinking, several other symptoms, and that adolescents had more suicide attempts than children with major depression. That the suicide attempts were more lethal in adolescents than the attempts that existed in children and that they had more psychosocial functioning in adolescents than those with depression compared to depressed children. 01:17:07 01:17:16 01:17:37

Q. On the next page you have a slide entitled, "What were adult major depressive disorders like as children." 01:17:46

A. Yes.

Q. And can you read what that bullet says?

A. Says, "Higher rates of many personality disorders including avoidant, histrionic, narcissistic, and borderline in adults whose depression started in children or adolescence." 01:17:46

Q. Based upon your research that you have done in child and adolescent literature, in your review of the literature, what happens to children 01:18:14

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and adolescents who are not adequately treated for depression when they move into adulthood? 01:18:16

MR. MURGATROYD: Objection; leading.

THE WITNESS: There are not separate studies to say what happens to the ones who are not adequately treated. There are a number of studies to say what happens in general to them. The data of persistence from adolescents to adulthood is found in every study that is looked at to the best of my knowledge so it's -- it's essentially incontrovertible that adolescents with depression grow up to be adults with depression. The data on school-aged children, pre-adolescents with a major depression in our studies and in several others is they've grown up to be depressed adults. In two other studies they've had more psychopathology in general, but not depression, per se, at least in adult. 01:18:29 01:18:46 01:18:58

BY MR. DAVIS: 01:19:11

Q. What level of impairment have you seen for a child or adolescent who has major depressive disorder?

MR. MURGATROYD: Objection; lack of foundation. 01:19:26

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THE WITNESS: If you look on -- the worst impairment that you see in an individual may -- is not terribly useful so let me talk about some group averages. 01:19:26

BY MR. DAVIS: 01:19:35

Q. Yes. That would be helpful if you could talk about some group averages of those things.

MR. MURGATROYD: Same objection.

THE WITNESS: Which is that during a major depression they have worse school functioning, worse home functioning and worse functioning with friends on average and that lasts after the end of the depression. Also, from our work and work of others they have a higher rate of pregnancy. They have more smoking and they have more substance abuse and they have a higher rate of attempted suicide and completed suicide. 01:19:44 01:20:07

BY MR. DAVIS:

Q. Thank you. Are you aware of the literature on where suicide ranks in terms of cause of death for adolescents? 01:20:26

A. Yes.

Q. And where does suicide rank in cause of death of adolescents? 01:20:46

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A. Number three. 01:20:48

Q. And do you recall from the data what's number one and what's number two?

A. I should. Accidents and homicide. That was a rising inflection. I'm not certain that I recall. 01:21:03

Q. Now, for suicides, you said suicides are the third leading cause of death, and are you aware they have more combined deaths from suicides -- strike that -- 01:21:28

Are you aware that suicides in adolescents is greater than the combined deaths from cancer, heart disease, chronic respiratory disease, birth defects, strokes, influenza and pneumonia and blood poisoning? 01:21:50

MR. MURGATROYD: Objection; calls for speculation.

THE WITNESS: I have seen what I assume you're referring to before, but could I have listed all of those? So was I aware of that before you asked me. Not entirely, no. 01:22:01

BY MR. DAVIS:

Q. Are you aware of some of those?

A. Yes, I was.

Q. Which ones are you aware of? 01:22:11

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A. The first three or four medical conditions you suggested. I am aware that in general that suicide is a bigger cause of death than essentially all medical conditions put together. 01:22:11

Q. Thank you. Have studies -- have clinical studies been done to try to establish efficacy of tricyclic antidepressants in patients under 18? 01:22:18

A. Yes.

Q. And what have the results of those studies been? 01:22:59

A. The results considered separately study by study and considered in med analyses have been negative.

Q. Before the introduction of serotonin Reuptake inhibitors, in your opinion, were there any effective medications available to treat children and adolescents who suffer from depression? 01:23:07

A. In my opinion, no there were not.

Q. What about the use of cognitive behavior therapy or psychotherapy? 01:23:29

A. Can I go back to your prior question?

Q. Yes, sir.

A. I answered it incorrectly. I believe I answered it incorrectly by mistake. There was no pharmacology treatments with efficacy before. 01:23:39

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Q. No. I did ask you -- I asked you whether or not there were any effective medications? 01:23:43

A. Oh, did I answer that question correctly? Okay. So I answered the question correct before correctly. I'm sorry. Could you tell me your last question? 01:23:58

Q. Yes. What about the use of cognitive therapy or behavioral therapy? Has that proven to be an effective treatment for adolescents or children with depressive disorders? 01:24:16

MR. MURGATROYD: Objection; calls for speculation.

THE WITNESS: The studies on that, the proponents of those have showed that it's effective. One recent study, the so-called TADS, T-A-D-S, Study led by John Marsh did not find cognitive behavioral therapy to be effective. Those studies are somewhat limited. The TADS Study was well designed compared to a realistic control. Many of the other studies showing efficacy for -- or, you know, presenting efficacy for CTB have not used a realistic control compared to weightless control or no treatment, which is a less strong evidence approach. 01:24:22 01:24:35 01:24:50

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BY MR. DAVIS: 01:24:52

Q. Are there any limitations which prevent patients from -- pediatric patients from undergoing cognitive behavior therapy or psychotherapy?

MR. MURGATROYD: Objection; calls for speculation. 01:25:16

THE WITNESS: The cognitive behavioral therapy is not well studied in younger children. It's well studied in adolescents. There's only a few studies in younger children, and there is a question of the cognitive maturity for that to work. So I think that's an open question. On any one individual case they may be willing to do psychotherapy and not medications, willing to do medications and not psychotherapy, not willing to do either, but there are not major limitations that prevent children or adolescents from doing psychotherapies. 01:25:29 01:25:43

BY MR. DAVIS: 01:25:59

Q. Are there enough qualified child and adolescent psychiatrists or therapists available if every child or adolescent went and used psychotherapy as opposed through seeking treatment through medication? 01:26:09

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MR. MURGATROYD: Objection; calls for speculation. 01:26:18

MS. CONNELLY: I join that one.

THE WITNESS: There has been considerable literature saying that there are insufficient child therapists, including by the people who train -- who've done the studies in cognitive behavioral therapy saying that there are massively insufficient therapists of any kind trained in cognitive behavioral therapy to treat patients. 01:26:26 01:26:37

MR. MURGATROYD: I'm just going to move -- I'm going to move to strike his answer just on a lack of foundation. Actually, the last series of -- the last 20 questions no foundation has been laid. No articles have been identified; therefore, his last 20 questions and therefore they are improper testimony. 01:26:50

MR. DAVIS: I believe your objections are untimely. 01:27:07

BY MR. DAVIS:

Q. Let me hand you what's been previously marked as Exhibit 1 -- excuse me -- Exhibit 60. Dr. Ryan, do you see that Exhibit 61 is a copy of 01:27:28

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Dr. Thomas Laughren's January 5, 2004 memo? 01:27:44
A. Yes.
Q. And is Dr. Laughren an employee of FDA?
A. Yes.
Q. I want you to turn to page -- I think it's 01:28:01
6 on yours where it says that -- there should be a paragraph that reads -- that begins with "The point I am making"?
A. Yes.
Q. All right. Look at the second sentence in 01:28:11
that paragraph, and could you read that -- excuse me -- the third sentence in that paragraph and will you please read it into the record?
A. "We at the FDA, however, do not view negative studies as proof of no benefit." 01:28:28
Q. Do you view negative studies as proof of no benefit?
A. No.
Q. And do you agree that the fact that a particular study is negative and is not able to 01:28:37
establish efficacy under primary end-points set forth in the study means that particular drug is ineffective in treating children or adolescents with depression?
MR. MURGATROYD: Objection; lack of 01:29:01

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foundation. He can answer that question, calls 01:29:01
for speculation.
THE WITNESS: No.
BY MR. DAVIS:
Q. And do you hold the opinion also for -- 01:29:09
with respect to Paxil in the studies that have been conducted on Paxil to treat pediatric patients with major depressive disorders?
MR. MURGATROYD: Same objection.
THE WITNESS: I hold that opinion in 01:29:16
general about studies that a single negative study -- because of the way science is designed, because of the way statistics are done it provides relatively little evidence against efficacy. 01:29:28
BY MR. DAVIS:
Q. And does the absence of evidence of effectiveness mean that there is a absence of lack of benefit caused by Paxil?
A. No. 01:29:41
Q. Is it unusual for one or more depression studies to not meet the primary end-points and yet later on efficacy is established in later studies?
A. No. Dr. Pace and others have written that in reviewing FDA studies in recent decades that more 01:29:58

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than half of studies of antidepressants in adults 01:29:59 for depression failed to show efficacy on compounds that are subsequently shown to be efficacious.
Q. And even though a medication does not meet the primary end-points in a clinical study, can a 01:30:14
medication still provide meaningful, clinical benefits to patients?
MR. MURGATROYD: Objection; it's vague, ambiguous, lack of foundation and calls for speculation. 01:30:26
THE WITNESS: It certainly could in theory.
BY MR. DAVIS:
Q. Okay. And based upon the results of Study 329, did you believe that Paxil could provide 01:30:29
meaningful, clinical benefits to patients notwithstanding the fact that the two primary end-points in that clinical study were not met?
A. Yes.
Q. And based upon the results of Study of 01:30:46
329, did you believe that Paxil could provide clinical benefit to patients -- strike that.
Based upon results of Study 329, did you believe that even though Study 329 would not be sufficient to pass regulatory requirements of 01:31:13

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efficacy that it still could provide a significant 01:31:13
improvement to pediatric patients with major depressive disorder?
MR. MURGATROYD: Objection; calls for speculation, lack of foundation. It's a 01:31:29
compound question.
THE WITNESS: Yes.
BY MR. DAVIS:
Q. I want to talk to you about the process by which you and the other clinical investigators 01:31:44
approached GlaxoSmithKline, then SmithKline Beecham about conducting Study 329. All right? And if I use the words GSK or SmithKline Beecham I mean GlaxoSmithKline, is that acceptable to you?
A. Yes. 01:32:11
Q. All right. Do you recall the -- do you recall the genesis of the idea to do a study of SSRI and adolescents with depression?
A. At a child depression consortium meeting Drs. Keller, Strober, myself, and I believe 01:32:24 Gittleman-Klein were talking and we all sort of looked at each another and said, we should do a study. We, from the beginning, wanted to do a three-arm study. We wanted to do a study of tricyclic versus SSRI versus placebo, because we 01:32:41

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anticipated that both active compounds would work compared to placebos, but the SSRIs would be safer. 01:32:44

Q. And why did you believe them to be safe?

A. For the reasons we've discussed, because of the cardiotoxic effects of tricyclic antidepressants. 01:32:58

Q. Do you recall either you or any member of the principle investigators approaching GlaxoSmithKline about conducting the study?

A. The investigators discussed and agreed for Dr. Keller to approach the company. 01:33:13

Q. And why did the investigators believe it was important to conduct this study?

A. Because there was at the time no published studies on these compounds. They were being used a lot. We did not have good treatments for depression, because the tricyclic antidepressants in all the studies were small so we actually wanted to look at both together because we thought that society needed good treatment in children. 01:33:28 01:33:33

Q. Do you believe that before Study 329 was initiated that Paxil was being used by physicians to treat child and adolescent depression?

A. I certainly knew of children being treated with Paxil. I did not have and do not have data on 01:34:09

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the compound -- how many different SSRIs were used. 01:34:09

Q. Were you involved in the design of Study 329?

A. Yes.

Q. And what was your level of involvement in the design? 01:34:24

A. I was involved as anybody in the design of that. It was the subgroup of us that I've discussed, including also Dr. Birmaher.

Q. How would you describe the amount of effort that you put into trying to design Study 329 so we can properly assess efficacy of Paxil and imipramine in treating adolescents with major depressive disorders? 01:34:39

A. It was a long weekend retreat plus considerable work, you know, on the phone and revising things, so presumably two to three weeks of full-time work equivalent perhaps. 01:34:58

Q. And after the initial proposal was made to GlaxoSmithKline, did GlaxoSmithKline agree to proceed and to fund the study? 01:35:11

A. Yes.

Q. And did you and the other clinical investigators continue to work on the design of that study even after the -- GlaxoSmithKline had agreed 01:35:26

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to fund it? 01:35:29

MR. MURGATROYD: Objection; compound question.

THE WITNESS: I do not remember that we were making fundamental design. I don't remember whether the fundamental design was essentially completed at the time they decided to fund it or we were still doing design issue. This would not have been a large design issue, you know, in terms of -- there would not have been large design issues at that point. I don't remember. 01:35:39 01:35:50

BY MR. DAVIS:

Q. Now, did you and the other principle investigators participate in any meetings or conference calls about how the study would be designed and what efficacy variables would be analyzed and looked at? 01:35:59

A. Yes.

MR. MURGATROYD: Objection; compound. 01:36:16

THE WITNESS: Yes. We certainly discussed efficacy measures as a group.

BY MR. DAVIS:

Q. Dr. Boris Birmaher works with you at the University of Pittsburgh? 01:36:43

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A. He's a colleague with me. We work together on some studies; separately on some studies. 01:36:44

Q. Is he a psychiatrist?

A. He's a child psychiatrist as am I. 01:36:48

Q. And was he co-principle investigator in Study 329?

A. I don't remember whether he was listed as co-investigator or principle investigator. Probably co-principal, but I would have to review my notes. 01:36:59

Q. Before the study began, had you and Dr. Birmaher worked on other clinical studies together?

A. We had worked on other studies. Yes, we had worked on other clinical studies.

Q. And how would you describe the level of involvement that you and he had together with respect to implementing Study 329 in enrolling patients and making sure that the procedures were followed? 01:37:20

A. Yes. I had a larger role in the design of the study. He had a larger role in the implementation. 01:37:29

Q. Did you and he at any time discuss how -- well -- strike that.

Did you and he at any time during the 01:37:43

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course of the study discuss how patients were during on the medication with the understanding that it was blinded and you did not know which patient was on placebo and patient on Paxil? 01:37:44

A. We would of at the time discussed SAEs, severe adverse effects, and other, you know, or things that seemed problematic or otherwise -- otherwise we would not have, and it would have been disadvantages to have large discussions about how patients seem to be doing in a study that you are trying to keep blind, because you don't want to successfully guess. 01:37:58 01:38:13

Q. Let me hand you what's been marked as Plaintiff's Exhibit 3, which is an article that you co-authored with Dr. Martin Keller about the results of Study 329. 01:38:26

MR. MURGATROYD: There were other authors than just Dr. Martin Keller.

MR. DAVIS: I said Dr. Keller and others.

MS. CONNELLY: I missed that. 01:38:29

BY MR. DAVIS:

Q. Is this the article Dr. Keller, yourself, and others authored about the results of Study 329?

A. Yes.

Q. Now, if you could, would you please turn 01:38:50

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to the section entitled "Patient Eligibility." 01:38:59

A. Yes, I have it.

Q. Now, looking at the bottom part of that paragraph, do you see that it says, "In addition to fulfilling the DSM-4 criteria for major depression, 01:39:20 subjects were required to have a total score of at least 12 on the 17-Item Hamilton Rating Scale for Depression"?

A. Yes.

Q. And were they also required to have other 01:39:33 scores on other rating scales?

A. Yes. They were required in addition to have a score of less than 60 on the Child's Global Assessment Scale and a score of at least 80 on Picture Peabody Vocabulary Test, which is a rough proxy for an IQ. 01:39:44

Q. Now, Plaintiffs Counsel asked you questions about the -- whether children -- strike that.

Plaintiffs Counsel asked you questions 01:40:03 about the HAM-D score for eligible patients who were enrolled in Study 329.

A. Yes.

Q. And was the average HAM-D score 12, which was the entry criteria? 01:40:18

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A. No. The average HAM-D score can be extracted from Table two if you look at the means across; for paroxetine was 18.99, for imipramine was 18.11, and placebo was 18.97. So mathematically since the cells were about the same the overall mean would be approximately 18.6 for the average Hamilton Score of Admission. 01:40:20 01:40:37

Q. Now, would you characterize an average Hamilton Depression Rating Score of around 18 to be just mild depression? 01:40:52

A. No.

Q. Would you characterize it's just as an ordinary case of the blues for any of the adolescents who were enrolled in Study 329?

A. No. 01:41:07

Q. What does the mean Hamilton Depression Score in Table one tell you concerning the severity of the depression of the patients that were enrolled in Study 329?

A. It tells me that on average they were of moderate depression since that's the mean and the least was 12, you know, that some were considerably higher than 18 and some were lower. 01:41:26

(Defendants Deposition Exhibit No. 5, 6 was marked for identification.) 02:47:32

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MS. CONNELLY: Exhibit 5 looks like an extract of the article at issue. Have you done that?

MR. DAVIS: Yes. I've done that.

BY MR. DAVIS: 01:42:29

Q. Dr. Ryan, you have been handed what's been marked Exhibits 5 and 6.

MR. MURGATROYD: I'm sorry. Which is which?

MR. DAVIS: The first one, which is from 01:42:43 the abstract is 5 and the other is 6. Okay?

MR. MURGATROYD: Okay. Thank you.

BY MR. DAVIS:

Q. And let me ask you this. Look at the abstract that's in the Keller article that you were 01:42:59 a coauthor on.

A. Yes.

Q. And in that abstract, does this article identify the primary end-points?

A. Yes. 01:43:20

Q. What does it say about the primary end-points?

A. It's about the second or third sentence into the abstract. It says, "The two outcome measures were endpoint response (Hamilton Rating 01:43:28

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Scale for Depression [HAM-D] score less than or equal to 8 or greater than or equal to 50 percent of reduction in baseline HAM-D) and change from baseline HAM-D score." 01:43:31

Q. Now, does Defendants Exhibit 5 accurately and fairly represent what you just read out of the abstract? 01:43:46

A. Yes.

Q. Okay. Now, does the Keller article, again, identify the primary end-points in the section describing the efficacy and safety evaluations that's on page 764? 01:44:03

A. Yes.

Q. And would you please read what is stated in the section entitled "Safety and efficacy about the primary end-points"? 01:44:24

A. "The protocol described two primary outcomes measures: (1) response, which was defined as HAM-D sore of less than or equal to 8 or a greater than or equal to 50 percent reduction in baseline HAM-D score at the end of treatment; and (2) change from baseline in HAM-D total score." 01:44:33

Q. Now, does Defendants Exhibit 6 fairly and accurately represent what you just read from the article that you coauthored? 01:45:01

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A. Yes. 01:45:05

Q. Okay. Now, I'll hand you what I'm marking as Exhibit 7.

A. Okay.

(Ryan Defendants Exhibit No. 7 was marked for identification.) 01:45:24

BY MR. DAVIS:

Q. Dr. Ryan, can you take a look at Defendants 7 and tell me whether that is a fair and accurate representation of Table two that's in the article that you coauthored on the results of Study 329? 01:46:01

A. Yes, it is.

Q. What's the title of that table, please, sir? 01:46:41

A. "Mean scores of Depression-Related Variables in Adolescents who were treated with Paroxetine, Imipramine or Placebo."

Q. Is that table entitled "All efficacy outcomes measures or variables that were analyzed in Study 329"? 01:46:50

MR. MURGATROYD: Objection; the document speaks for itself.

THE WITNESS: No.

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BY MR. DAVIS: 01:47:07

Q. Would it be possible to include all the efficacy variables or outcome measures that were analyzed in a journal article of this nature?

MR. MURGATROYD: Objection; calls for speculation. 01:47:14

THE WITNESS: It would not be possible.

BY MR. DAVIS:

Q. And why don't you think would that would be possible? 01:47:24

A. Because there's a space limitation.

Q. Now, does the Table two -- the article which you coauthored -- strike that.

What does Table two outline in the article in which you coauthored on the results of Study 329? 01:47:39

A. Table two looks at the difference between paroxetine and placebo and the difference between imipramine and placebo on variables related to depression and what the mean differences are and whether they're statistically significant or not. 01:47:58

Q. And what depression related variables are analysed in Table two?

A. Whether the Hamilton-D Score was less than 8 at end-point. The combination criteria, which was a primary outcome measure of whether either the 01:48:18

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Hamilton-D was less than 8 or there was a 50 percent reduction in HAM-D or not or both. The depression alone from Hamilton-D at end-point. The K-SADS-L depression mood item alone at end-point, whether the CGI score was 1 or 2 at end-point versus 3 or higher. The K-SADS-L 9-item depression subscale, mean clinical global score and the mean Hamilton-D total Score. 01:48:18 01:48:20

Q. Now, are the depression related variables, which are outlined in Table two also identified in the abstract which you coauthored and in the efficacy and safety evaluation section of that paper? 01:48:52

A. I'm sorry. Let's see? Yes.

Q. Now, does Table two set forth for any person who reads the article what the results were for the 8 depression related variables which you just described? 01:49:26

A. Yes.

Q. And are the statistical percentages revealed for anyone who reads the article, which you coauthored on the results of Study 329, to see how Paxil performed against a sugar pill or a placebo and whether or not Paxil performed better than the sugar pill? 01:49:41 01:49:50

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MR. MURGATROYD: Objection; compound question. 01:50:09

THE WITNESS: The statistics that are provided in the table allow the reader a fair comparison of the magnitude of the effect and whether or not it was statistically significant or not. 01:50:16

MR. DAVIS: Okay. Let's stop.

VIDEOGRAPHER: At this time we are going off the record. The time is approximately 1:51 p.m. 01:50:24

(Recess taken.)

VIDEOGRAPHER: We are now back on the record. The time is approximately 1:57 p.m. This is the beginning of Tape 4, Day Two, of the deposition of Dr. Ryan. Please proceed. 01:56:35

BY MR. DAVIS:

Q. Dr. Ryan, does Table two in the article you coauthored on the results of Study 329 set forth how Paxil performed on the two primary end-points? 01:56:48

A. Yes.

Q. Okay. And does it -- what does it say about how Paxil performed on the two primary end-points?

A. On the end-point of a Hamilton-D less than 01:57:11

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8 and/or a 50 percent reduction in the baseline HAM-D it shows that there was a 66.7 percent of the people on paroxetine met the criteria of 55.2 percent. The ones on placebo met the criteria and the P value was .11 so that was greater than .05 so 01:57:13 01:57:26 it was not significant on the HAM-D total score. The mean on those treated on paroxetine was 18 -- I'm sorry -- the mean post-treatment on those treated with paroxetine was 18.24 compared with a mean of 9 point -- I said that wrong -- let me try 01:57:52 it again.

Mean on paroxetine 8.24. Mean of those treated on placebo 9.88. So the paroxetine -- the difference on that was a P value of .13, which was not significant. 01:58:05

Q. Does Table two show that Paxil did not meet statistical significance on both of the primary end-points?

A. Yes.

Q. Okay. And with respect to the P values that you stated or set forth in Table two for the two primary end-points, did they tell you anything about whether there is a trend on whether or not Paxil is or it is not effective in treating adolescent depression? 01:58:22 01:58:37

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A. By convention and by plan on this study as you do on many studies we required a 0.5 to declare something significant. The means -- and the P values show you that there was a possibly, quote, "trend" in that direction, but it's not at the level you would declare significant, and so you have to say we don't know whether they're better on those measures or not. 01:58:39 01:58:58

Q. Now, does the table set forth and identify how Paxil performed on the other depression related variables, which were the secondary end-points? 01:59:11

A. Yes.

Q. And do you believe that the article, which you coauthored on the results of Study 329 clearly distinguishes between the efficacy results of the primary and the secondary end-points? 01:59:20

A. Yes.

Q. Now, was there ever any attempt to hide or confuse readers about what was a primary or secondary end-point in the article which you coauthored on the results of Study 329? 01:59:39

A. No.

Q. Now, was this article reviewed, analyzed and commented on by multiple reviewers at the journal where it was ultimately published? 01:59:48

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A. Yes. 01:59:58

Q. And what's the process by which articles like this go through a review before they're published?

MR. MURGATROYD: Objection; calls for speculation. 02:00:01

BY MR. DAVIS:

Q. Let me back up. Are you familiar with the review process for articles which are submitted to the Journal of the American Medical Academy Association and the Journal for American Academy of Child and Adolescent Psychiatry? 02:00:13

A. I have submitted articles to the Journal of American Academy -- sorry -- I've submitted articles to the American Academy Journal. I've been a reviewer for them and I've been on their editorial board. Yes. I'm familiar with the process. 02:00:31

Q. Based upon your time on their review board, do you believe that the reviewers who are asked to review articles at the Journal of the American Academy of Child and Adolescent Psychiatry have high standards in terms of the quality and the clarity of the articles to be published in that journal? 02:00:52

A. Yes. 02:01:07

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Q. Okay. Was this article reviewed by reviewers at the Journal of the American Academy of Child and Adolescent Psychiatry? 02:01:07

A. Yes.

Q. Okay. Do you believe the reviewers and the editors of the Journal of the American Academy of Child and Adolescent Psychiatry would have allowed this article to be published if they believed it would misinform readers about what was a primary or a secondary end-point? 02:01:20 02:01:35

MR. MURGATROYD: Objection; lack of foundation and it's compound. There's no foundation that a reviewer can prevent an article from being published.

THE WITNESS: No. I do not believe that they would. 02:01:52

BY MR. DAVIS:

Q. Let's talk just about the four secondary end-points that showed that Paxil performed better than sugar pill in Study 329. Keep the Table Two in front of you there and also the article there. 02:02:01

What were the four secondary end-points that were statistically significant and showed that Paxil performed better than the sugar pill or placebo? 02:02:18

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A. Sure. Hamilton-D score less than or equal to 8 was the first. The second was the single item about depressed mood from the Hamilton-D. The third was the item about mood from the K-SADS-L mood interview, and the last one was a clinical global score of 1 or 2 at endpoint. 02:02:20 02:02:31

Q. And why did you and the other investigators believe that these were important secondary end-points to evaluate and assess in terms of this study? 02:02:58

MR. MURGATROYD: Objection; lack of foundation.

THE WITNESS: The problems that we faced in designing this study was that there had been no published studies of any antidepressant agents in children or adolescents showing efficacy at the time we designed this study. Absolutely not. 02:03:07

All the tricyclics studies were negative and Dr. Giles (phonetic) was underway and had not been published so we had to go with very little data -- with no data -- make good choices on our primary outcomes measures, clearly given that we had to say what are other ways of measuring depression that might also be sensitive to different changes in depression between active compounds and placebo. 02:03:20 02:03:35

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BY MR. DAVIS:

Q. And why were these four measures determined to be of importance to evaluate and analyze on that question? 02:03:58

A. Well, these four plus another couple secondary ones, because they were capturing the essence of the depression in different ways. They were core of the essence of depression and they were sort of -- they were questions that were known to be assessed reliably by the instruments and they made sense. 02:04:05

Q. And what was it about the HAM-D Depressed Item and the K-SADS-L mood item -- so the jury can understands this -- so the jury can understand this -- let me start my question again. So the jury can understand this, what was it about the Hamilton-D depressed mood item and K-SADS-L mood item that helped you and the other clinical investigators assess whether or not Paxil and imipramine would or may perform better than a sugar pill to treat depression? 02:04:20 02:04:29

A. Yes. The Hamilton scale that we used contained 17 items. The K-SADS-L depression item 02:04:52

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contained 9 items, and so they contained items that go along with the syndrome of major depression and we looked at them in aggregate, but we also thought it would be informative to look simply at the question of how depressed you are, because that's the core symptom of major depressive disorder. That's the criteria symptom to get in there and then you're required to have so many other symptoms. 02:04:52 02:05:11

Q. How was it that the Hamilton-D less than or equal to 8 was viewed as a core variable for assessing whether or not Paxil and imipramine was effective in treating adolescent depression? 02:05:24

A. The question we were trying to address with that was, what fraction of the people get like a whole lot better, get to the point where you say they're not so bad. Not completely free of symptoms perhaps, but really to the point where you say it's subclinical, and that was that approximation for that. 02:05:41

Q. And why was the CGI or Clinical Global Improvement score of 1 or 2 determined to be a core variable in terms of assessing whether or not Paxil or imipramine was effective in treating adolescents depression? 02:06:01

A. Donald Klein at Columbia University and 02:06:14

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others who are experts on adult depression had been for sometime saying that Clinical Global Improvement, which is a clinician's aggregate of everything put together, using the clinician's judgement unblinded was a really important thing to look at in studies like this. A CGI of 1 or 2 would be the kids where a clinician was saying these kids are all better or almost all better. 02:06:18 02:06:26

Q. And just so the jury can understand, what ends up getting categorized as a CGI score of 1 or 2? 02:06:41

A. That's much better or very much better.

Q. You told the Plaintiffs Counsel that it would be wrong -- excuse me -- you told the Plaintiffs Counsel that it would be wrong not to look at the study -- strike that. I'm sorry. I'll start again. 02:07:09

You told the Plaintiffs Counsel that it would be wrong not to look at these core features of efficacy. You also told him that it would be unethical not to look at these core features for assessing efficacy? Why do you believe that? 02:07:22

MR. MURGATROYD: Objection; compound question.

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BY MR. DAVIS: 02:07:37

Q. I'll rephrase it. Do you believe it would be wrong not to the look at those four efficacy variables in the study?

A. Yes. 02:07:46

Q. Why do you believe that?

A. At the time the study was done and the study was published we had a number of studies showing the tricyclics -- we had the aggregate of the studies on tricyclics and was enough to say that they were unlikely to work very well, and we had no studies showing they worked and we had -- when it was published -- when it was designed we had nothing, but when it was published we had one study of the study of Dr. Emslie's, the first study of Dr. Emslie finding efficacy for Prozac, for fluoxetine, and this study then was the second study to provide any control data for the world in the treatment of a disorder associated with a lot of morbidity and mortality, a lot of impairment and death and suffering. 02:08:01 02:08:13 02:08:31

If you look only at the things that the FDA -- for example, the primary outcomes as the FDA would look at them for approval to say that this compound is approved for that you are missing most 02:08:43

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of the data. You're saying that we're not going to look at the rest of this data. We won't find out more that's important to the world. 02:08:50

So in all of medicine there is the question of how much to look at in addition to the primary outcome measures to really understand the deep questions about what -- we had an obligation to say what's the best evidence that this does work or doesn't work in addition to report that our primary outcome measures didn't come out significant, because, you know, the world has to -- you have to treat these kids. You have a kid -- and without really great data for how to treat them with a bad disorder, and so simply saying we refuse to look at anything more because the primary outcome measures didn't come out better -- so we're not going to say, did the other data look like it works and the other data not look like it works is throwing away critical information that the world needed. 02:09:05 02:09:16 02:09:33

Q. Let me ask you questions about the K-SADS-L 9 item depression subscore and the mean CGI. Did any of those show a statistically significant improvement on Paxil or Imipramine? 02:09:48

A. The K-SADS-L 9 on depression subscore was better on paroxetine than placebo. It did not reach 02:10:09

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statistical significance. It had a P value of .07. The CGI was better on paroxetine, but not at a statistically significant level. It had a P value of .09. 02:10:09

Q. And did that give you any information in terms of a trend in either direction about whether or not Paxil was effective in treating adolescent depression? 02:10:22

A. Yes and no. It certainly said -- the good things it said was the directionally was the same and it sort of said it kind of came close to making it. One can make a little of that. The thing I think you can make something of it is the fact that everything was in the same direction and it came close. Alone, simply if you have something that simply that reached your P value one doesn't want to over interpret that single fact in isolation. I think it's weak support, but probably a squidge of support for the question of efficacy. 02:10:35 02:10:50

Q. But when you look at the trend for the primary end-points and two of the secondary end-points that don't meet statistical significance and you match those up with the four end-points that did meet statistical significance, do you interpret that to mean that things were heading in the right 02:11:11 02:11:29

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direction towards showing effectiveness of Paxil in treating pediatric depression? 02:11:35

A. The fact that you had significance on core items here that were planned, plus the other ones all went in the same direction, yes, I think add some support. 02:11:46

Q. At the time of your findings on Study 329, was it new information that was important to tell clinicians who were faced with the difficult task of treating adolescent depression? 02:12:07

A. I did this study to find out for everybody, and my goal was to get this data out to the field to everybody including clinicians.

Q. Why did you want to get this information out to everybody including clinicians? 02:12:37

A. Yes. Children and adolescents were being treated with this compound and there was evidence that this compound was helpful in adolescents, and the only data on SSRIs at the time we published this was the study by Dr. Emslie and that just was not very much information for people to make decisions. 02:12:58

Q. Let me turn your attention to page 766 of the article that you coauthored on the results of Study 329. If you could look at the column on the right-hand side, can you tell whether there is a 02:13:28

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discussion on whether or not Paxil separated physically from the sugar pill, the non-symptom measures of functioning, health and behavior? 02:13:31

A. It says that "Although neither paroxetine nor imipramine separated statistically from placebo across the non-symptom measures of functioning, health, and behaviors, improvements over baseline were achieved for each active treatment group. Placebo-treated subjects also improved along behavior measures, but to a lesser extent." 02:13:44 02:13:48

Q. Is this paragraph discussing quality of life measures that had been assessed during Study 329?

A. Yes, it is. It's saying that the directional comparisons were in the same direction. That the kids on placebo directionally speaking did worse, but that we did not achieve a statistically significant difference. 02:14:11

Q. Are the quality of life measures that are being assessed and being discussed there, are the Sickness Impact Profile, the Autonomous Functioning Checklist, and the Self-Perception Profile that's described in the Efficacy and Safety Evaluation section of the paper? 02:14:24

A. That's correct. 02:14:46

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Q. Now, were those not core variables for answering the question of whether or not Paxil is effective in treating adolescent depression? 02:14:48

MR. MURGATROYD: Objection; assumes facts not in evidence, lacks foundation. 02:15:07

THE WITNESS: We know that from prior studies I collaborated with and studies that others had done that during a depression functioning deteriorates, as we've talked about. We also know from studies -- that I don't know if we've discussed so far -- that as the clinical symptoms of depression improves there is a lag in the improvement of the psychosocial impairment. 02:15:37

When we designed the study we thought as was -- there was a lot of excitement, appropriately so, in adult studies for depression at looking how people function in their life, not just looking at how sad they were. It was a topic of a lot of scientists interest at the time and we felt it important to include those in this study. 02:15:44 02:15:50

We did not have prior studies to say, which are the ones that are going to be the most responsive to treatment so we had to pick, 02:16:05

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and we thought it was scientifically important. It was clearly not the heart of interest, was -- does it get the depression better, but we thought this was an important question too. 02:16:13

My reading of how it turned out is that we didn't show over the length of the study that these things improved significantly more with the Paxil than with the placebo. The fact that they went in a good direction of slightly more than the placebo is, I think, that one can't interpret very much. It indicates you may want to look at it in the future. It may or may not indicate that they get better over this period of time in terms of their functioning. 02:16:24 02:16:43 02:16:44

BY MR. DAVIS:

Q. Are you aware of any other clinical studies which were placebo controlled that assessed depression and used either the Sickness Impact Profile, the Autonomous Functioning Checklist, or the Self-perception Profile as core variables in assessing whether or not a medication was effective in treating depression? 02:17:03

A. In children I'm not aware of it. It could be there. It's not something that I would 02:17:26

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necessarily known had been one. 02:17:26
Q. Have you ever been involved in a clinical trial involving pediatric patients where those three assessments were utilized either individually or in combination as core variables to assess whether or 02:17:37
not a medication was effective in treating pediatric depression?
A. No.
Q. I'm handing you what was marked as Plaintiffs Exhibit 13. Just to refresh the jury's 02:18:16
recollection, is this an e-mail that Dr. Michael Strober sent concerning some analyses on Study 329?
A. Not precisely.
Q. Can you tell the jury what that is, Doctor? 02:18:33
A. Yes.
MS. CONNELLY: Also I have an objection. I -- unless I'm wrong. This is not your document, is it?
THE WITNESS: That's correct. It is not 02:18:39
my document. This appears to be an e-mail from Mr. McCafferty to other GSK folks, Rosemary Oakes and William Bushnell, saying that Dr. Strober had suggested some things with what appears to be a cut and paste probably from 02:18:58

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other e-mail of Dr. Strober's suggestions. 02:18:58
BY MR. DAVIS:
Q. What suggestions is Dr. Strober making concerning some analysis for Study 329?
A. This e-mail suggests he's making the 02:19:11
following: One, that the Hamilton-D four factor scores, which are composite scores of some, but not all of the questions assessing four different domains; anxiety/somatization, sleep, cognitive disturbance and psychomotor be analyzed, and then 02:19:24
secondly if there is evidence for treatment effect to look at subgroups and the effect over time and time interactions showing different patterns of improvement across treatment.
Q. Do you believe that those proposed 02:19:44
analysis would be core variables for assessing whether or not Paxil or imipramine was effective in treating adolescents with depression?
A. This, to me, looks like something that you would put in a secondary paper trying to explore 02:20:11
stuff more.
Q. And why do you believe those proposed analyses are not core or central to the question of whether or not Paxil or imipramine was effective in treating pediatric depression? 02:20:24

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A. For two reasons. One, the second one is 02:20:26
clearly talking about secondary analysis you would do if the primary one came out to sort of delineate it further, and the two of them are together so that makes it more likely the first one is also intended 02:20:33
in that manner.
The second reason is that cognitive disturbance, second -- motor slowing is very rare in children so it would not be a primary, it wouldn't be something that you would look at first, and 02:20:50
Dr. Strober -- we had conversations about that -- it says very rare in children so you wouldn't look at that as a primary measure.
Cognitive disturbance is also relatively rare in children with depression, and 02:21:05
anxiety/somatization are symptoms of different though related disorders. So it wouldn't be a primary measure on a study of depression. It would be very interesting as secondary analysis.
Q. When you say a secondary analysis, are you 02:21:24
suggesting that it would be a core secondary variable to assess whether or not Paxil was effective in treating pediatric patients?
A. No, I am not. I'm sorry that I used technical jargon. I'm suggesting that once you have 02:21:41

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the main analysis of a study like this done you want 02:21:43
to say, how much more information can you get from it to make hypothesis for future studies? So for example, you could do a lot of different comparisons without producing for multiple comparisons, because 02:21:59
you want to say what's all the things that are different here and then make specific hypothesis on your next study. That's what I'm suggesting that would be appropriate for.
Q. Let me turn your attention to the 02:22:11
conclusion section of the article that you coauthored on the results of Study 329.
I'm going to ask you to read the very first sentence under the conclusion section for us.
A. "The findings of the study provide 02:22:26
evidence of the efficacy and safety of the SSRI, paroxetine, in the treatment of adolescent depression."
Q. Do you believe that to be a true statement? 02:22:41
A. I believe that to be a true statement.
(Defendants Deposition Exhibit No. 8 was marked for identification.)
Q. Now, do you believe -- what I've marked as Defendants Exhibit 8 a fair and accurate 02:22:46

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representation of the statement that you read to the jury concerning the conclusion? What was in the conclusion in the study you coauthored? 02:22:52

A. Yes.

Q. Okay. Now, do you believe that the -- excuse me -- do you believe that the article that you coauthored on the results of Study 329 properly describe and disclose the efficacy results of that study? 02:23:05

A. Yes. **02:23:22**

Q. And at any time did any GlaxoSmithKline employee try to influence you on how you should interpret the efficacy results on Study 329?

A. Not to my memory.

Q. Do you believe that you would recall something like that if some GlaxoSmithKline employee was trying to improperly influence you in terms of how the data should be presented in this article? 02:23:33

A. Yes.

Q. Now, in terms of -- if this study had been funded -- strike that. 02:23:41

Have you conducted studies for the National Institute of Mental Health?

A. Yes.

Q. What is the National Institute of Mental 02:24:07

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Health? 02:24:11

A. The National Institute of Mental Health is one of approximately 20 institutes under the National Institute of Health. It funds the large majority of medical research in this country. **02:24:20**

Q. How many studies have you conducted from funding from the National Institute of Mental Health?

A. I don't know. A number. I've been PI on, principle investigator, on six, seven maybe and co-investigator on a larger number than that. **02:24:33**

Q. If this study had been funded by the National Institute of Mental Health, would you have described the efficacy and safety findings of the study in the exact same way that you reported in the article that was published? 02:25:03

A. Yes.

Q. Now, in the conclusion section of the article that you coauthored of the results of Study 329, did you state that it had been conclusively established that paroxetine or Paxil is effective in treating adolescent depression? 02:25:35

A. I do not believe that we did.

Q. Did you instead say this study provided evidence of the efficacy and safety of the SSRI, 02:26:03

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paroxetine, in the treatment of adolescent depression? 02:26:07

A. Yes.

MR. MURGATROYD: Objection; one, it's leading; two, it misstates the evidence. 02:26:13

BY MR. DAVIS:

Q. Okay. Well, just to fix that. What did you say -- again, Dr. Ryan, what did you say in the conclusion section?

MR. MURGATROYD: Objection; asked and answered. You already done that. 02:26:22

MS. CONNELLY: You can answer.

THE WITNESS: We said the findings of this study provide evidence of the efficacy and safety of the SSRI, paroxetine, in the treatment of adolescents depression. We said it that way because a single study no matter how positive doesn't mean conclusively. Science to man's replication. 02:26:31

BY MR. DAVIS: 02:26:48

Q. And do you believe that's a general known principle in the scientific field?

A. Yes.

Q. Do you believe that other physicians who treat psychiatric disorders understand that 02:26:59

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principle? 02:27:07

A. Yes.

Q. Do your conclusion there say other medications prove to be more efficacious in treating children and adolescents? 02:27:37

A. No.

MR. MURGATROYD: Objection; calls for speculation.

BY MR. DAVIS:

Q. To your knowledge, are there any other medications that have proven to be more efficacious than SSRIs in treating depression in children and adolescents? 02:27:46

A. No.

MR. MURGATROYD: Objection; calls for speculation. 02:27:48

BY MR. DAVIS:

Q. Sorry?

A. No.

Q. Do you recall whether there were any letters to the editor that were about the conclusions that you and the other coauthors reached about the efficacy results in Study 329? 02:27:50

A. I believe there was four published letters to the editor with three responses. My colleagues **02:28:05**

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and I would not necessarily have seen letters sent to the editor that the editor did not ask us to comment on. 02:28:07

(Defendants Deposition Exhibit No. 9 was marked for identification.) 02:47:32

BY MR. DAVIS:

Q. Okay. Doctor, I'm going to hand you what's been marked as Defendants Exhibit 9 and ask you if that is one of the letters that were sent into the Journal of the American Academy of Child and Adolescent Psychiatry about the efficacy results of Study 329 as well as the reply by you and other coauthors? 02:28:39

A. Yes.

Q. Did you draft this reply letter? 02:29:07

A. I made the first draft on this reply letter.

(Defendants Deposition Exhibit No. 10 was marked for identification.)

Q. Okay. I'm going to hand you what's been marked as Exhibit 10 and ask you if that is a copy of the first draft of this reply letter that you prepared and circulated to other coauthors? 02:29:18

A. This is e-mail from me to Dr. Keller, Ms. Laden, Dr. Strober, Mr. McCafferty, and it says 02:29:48

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Draft 01. It's from my files. I assume that it's the first draft from what it says. 02:30:01

MR. MURGATROYD: What Exhibit number is this?

MR. DAVIS: Ten. 02:30:14

MR. MURGATROYD: And it's an authentic document?

THE WITNESS: As far as I can tell, yes.

BY MR. DAVIS:

Q. What is the date of the e-mail that you sent circulating the draft 1? 02:30:22

A. November 6, 2002.

Q. Okay. And which physicians were you replying to in this that had sent in a letter to the Journal of the American Academy of Child and Adolescent Psychiatry? 02:30:35

A. This is in reply to the Jureidini and Tonkin letter.

Q. And where are Dr. Jureidini and Dr. Tonkin located? 02:30:43

A. I believe they're in Europe, but I don't remember more detail than that.

Q. Could you look on the first page where it's marked on Exhibit 9?

A. I could. I'm sorry. Dr. Jureidini at the 02:30:52

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time of his writing this letter was in the department -- he's a B.M. Ph.D in the department of psychological medicine, Women's and Children Hospital, Department of philosophy, Finders University, Adelaide, Australia. Dr. Tonkin is a B.M. Ph.D in the department of clinical and experimental pharmacology, University of Adelaide, Royal Adelaide Hospital, Adelaide, Australia, 02:30:59 02:31:05

Q. So those are letters that had come in from two individuals in Australia? 02:31:28

A. That's correct.

Q. And did you agree with the comments that Dr. Jureidini and Dr. Tonkin sent in concerning the article that you and others coauthored about the results of Study 329? 02:31:44

A. No.

MR. MURGATROYD: Objection; vague and ambiguous.

BY MR. DAVIS:

Q. Why don't we for the jury's benefit, could you read the second paragraph to the reply letter and I'll stop you when I have a question? 06:59:58

A. In my draft or the final published reply?

Q. The final published reply.

A. "It seems that they argue that (1) we were 02:32:14

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insufficiently clear in distinguishing between our primary and secondary outcome measures and (2) our assessment that this study found paroxetine effective is incorrect. We feel that we were quite clear about which were primary outcome measures and which were secondary; this is explicitly and clearly elucidated in the abstract of the article; Moreover, the manuscript explicitly addressed the various limitations of the study design and discussed in detail these limitations with regard to the clinical implications of the research results. Within this context, because our two outcome measures did not reach a P level of less than .05 level of statistical significance, the more complex question that remains is whether or not we fairly interpreted the pattern of significant P values across the range of secondary endpoints as indicating that paroxetine is better than placebo for treating adolescent depression." 02:32:14 02:32:24 02:32:37 02:32:58

Q. Let me stop you there. Dr. Ryan, what was the date which you coauthored on the results of Study 329 was published? What was the publication date? 02:33:13

A. The publication date on the Keller et. al, article was July 2001. 02:33:20

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Q. And what's the date of when the letter and the reply letter from you and the coauthors? 02:33:35

MR. MURGATROYD: Object; compound question.

THE WITNESS: The date appears to be May 2003. 02:33:43

BY MR. DAVIS:

Q. Is that the date that the letter from Dr. Jureidini and Tonkin and the reply letter that you and the other coauthors sent was published? 02:33:50

A. Was published? That's correct.

Q. It was published in the same journal where the Keller et. al, article was published?

A. Yes.

Q. All right. You read a section of the reply letter. Do you believe that to be a truthful and accurate statement? 02:34:20

A. Yes.

Q. Why did you write that, "The more complex question that remains is whether or not we fairly interpreted the pattern of significant P values across the range of secondary endpoints as indicating that paroxetine is better than placebo for treating adolescent depression"? 02:34:37

A. Yes. Again, if we had simply stopped with 02:34:48

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the primary outcome measures we would have said that that's -- we refuse to look more at this even though there's -- there's no other data in the world right now to help us answer this question and we're simply going to say the primary outcome measures were sort 02:34:52 02:35:05 of in the right direction, didn't reach statistical significance, and we're not going to find out anything more to see if we can help children or to find out where the science lies or the truth lies.

As one would, I think essentially always do, we tried to say how do you find out more of the truth in this matter, and we looked at what seemed to be useful to find that out and published it. 02:35:14

Q. Okay. Now, if you could read the second paragraph. I'll stop you when I have a question. 02:35:35

A. "This study was designed at a time when there was no randomized control trials showing antidepressant (tricyclic antidepressant or SSRI) superiority to placebo, so we had no prior data from which to astutely pick our outcome measures." 02:35:43

Q. And that's a true statement?

A. Yes.

Q. Go ahead.

A. "The field has moved strongly away from using the Hamilton Rating Scale for depression, 02:36:03

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(HAM-D) in adolescent treatment studies and has gone virtually uniformly to using the Children's Depression Rating Scale-Revised because the latter better and more reliably captures aspects of depression in youth. Surely a national regulatory body charged with approving or not approving a medication for a particular use might well simply say that if a study does not show efficacy on the primary endpoint(s), it is a failed study and secondary outcome measures cannot then be used for approval. However, as scientists and clinicians we must adjudge whether or not the study overall found evidence of efficacy, and we didn't have the convenience of falling back on such a simple rule. If we choose wrongly (in whichever direction), we don't treat depressed children as well as the data would permit. Because we found a clear pattern of significant P values across multiple secondary analyses (recovery is assessed by the HAM-D less than 8, HAM-D depressed mood item, the scheduled -- 02:36:07 02:36:16 02:36:31 02:36:35 02:37:01

Q. Let me stop you there. You say: If we choose wrongly in whichever direction we don't treat depressed children as well as the data would permit. Why did you believe that?

A. Yes. If the compound works and we say we 02:37:16

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looked only at this and it doesn't work we discourage use. If it truly does work and we simply fail to find it on our two primary outcome measures and we discourage use that's a bad thing. If -- in the either direction part is if we get too excited about parts of it and say this compound works and it turns out in subsequent studies it doesn't we also encourage more use that otherwise they should have been treated with different things. So both ways of -- we had limited data. We had to -- you know, you have to say what does the data say, and both ways of being wrong are wrong and have disadvantageous. 02:37:20 02:37:22 02:37:41

Q. Okay. And you made reference that a regulatory body charged with approving or not approving a medication for a particular use might well simply say that a study that does not show efficacy on the primary end-points it's a failed study. Do you believe that in terms of assessing, you know, clinical benefit of Paxil in this study that was the right way to go just in terms of looking at the primary endpoints? 02:37:59 02:38:16

A. Can you hit me with the last part of your question again, please? I apologize.

Q. Sure. You say here a national regulatory 02:38:28

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body in charge with approving or not approving a medication for a particular use might well simply say that if a study does not show efficacy on the primary endpoints it is a failed study, and I'm asking you, do you believe that was the right way to go with respect to Study 329. 02:38:33 02:38:48

A. I believe that the FDA does a good job and that sort of rule has served it well, because it is accomplishing one task. I believe it's not the only thing you want to do on a study like -- which is the first one, because you're trying to bring all the juice from it that you have either in favor or against, not simply say, does it reach FDA regulatory requirements. **02:39:09**

Q. The last sentence of that paragraph reads that "Without established reliable measures that distinguish medication responders from nonresponders at the time the study was designed, it is not surprising that the primary measures did not reach significance while other measures did." 02:39:18 02:39:35

What are you trying to explain in that sentence?

A. Right. I'm trying to say that a very reasonable and even likely hypothesis as we picked was okay, but not great measures and so we found **02:39:52**

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less of an indication for efficacy than we would had we picked better measures. **02:39:59**

Q. Was there a high placebo response rate for Study 329?

A. There was a relatively high placebo response rate. **02:40:09**

Q. What does that tell you about trying to assess efficacy in Study 329?

MR. MURGATROYD: Objection; leading.

THE WITNESS: A number of studies. 02:40:16

MR. DAVIS: Let me back up. Let me respond to the objection.

BY MR. DAVIS:

Q. Does the fact that there was a high placebo response rate tell you anything in terms of trying to assess efficacy in Study 329? 02:40:28

A. A high placebo response rate mathematically makes it much harder to find efficacy from a mathematical statistical standpoint even if it's there. **02:40:39**

Q. And in terms of studies that have been done in pediatric patients with SSRIs, have there been other studies which have shown a high placebo response rate?

A. A number of the studies have had high **02:40:58**

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placebo response rates. That's not unique to pediatric studies or adolescent studies; however, a number of adult studies also show that. **02:40:59**

Q. In terms of the pediatric studies that have been done on SSRIs which have showed a high placebo response rate, what do you take away from that in terms of trying to assess what the difficulty is in conducting studies? 02:41:07

A. I take away two separate things. One of which is that children seem to get better to a greater rate than adults for at least a while just from all the encouraging parts of treatment, just from the nonspecific good stuff of coming in and meeting with somebody nice and expecting to get better and getting more attention and so forth. **02:41:09 02:41:11**

That's part of all treatments in medicine, but in some disorders that's sort of a larger impedance. It's larger pushed towards getting better than for other disorders and there's considerable anecdotal and a little bit of clinical data that children sort of get more of that than adults do. **02:41:11**

The second thing is that it may also indicate instruments that aren't as specific as you like, assessment instruments.

Q. Assessment instruments for determining 02:42:11

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whether or not a medication is effective in treating the pediatric population? 02:42:11

A. For determining whether or not the depression is improved, yes.

Q. Okay. And in terms of the reply letter that you coauthored to Drs. Jureidini and Tonkin's letter, do you stand by the statements that you made in that letter? 02:42:18

A. Yes.

(Defendants Deposition Exhibit No. 11 was marked for identification.) **02:42:37**

Q. Okay. I'm going to hand you what has been marked as Exhibit 11 and ask you if you could look through that document and recognize it as a summary of the reviewer comments that came in from the Journal of the American Medical Association about the draft manuscript on the results of Study 329? 02:44:22

A. That is certainly what that appears to be. I don't have any way of authenticating it separately. **02:44:48**

Q. What I want to do is turn your attention to reviewer's No. 2 comments, and can you read -- do you remember receiving comments back from the Journal of the American Medical Association?

A. Not before -- no, I do not remember the **02:45:13**

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details on these or anything about them. 02:45:14

Q. Okay.

A. I do remember that after discussions yesterday that we submitted several places, including first in the Journal of American Medical Association, otherwise, no, I don't remember the details of that. 02:45:22

Q. Let me turn your attention to -- Plaintiffs have asserted that the authors of -- you know, the authors of this -- of the -- of the Keller et. al, article -- this interpreted an overstatement in their results of Study 329, and I want to walk you through some of the comments that the reviewers made about those results. Okay? If you can turn to Reviewer's No. 2 comment. 02:45:31 02:45:48

MR. MURGATROYD: First of all, let me object if you are going to cherry pick the reviewer's comments that it's -- you are using the partial document and not a complete document, therefore, it's inadmissible. 02:46:05

MR. DAVIS: You can ask the doctor whatever question you like and show him any document you like.

BY MR. DAVIS:

Q. Look at Reviewer's No. 2 comments. Do you see -- if you could, could you read the second -- first sentence in the second paragraph? 02:46:11 02:46:11

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A. "The strength of the study is that it is the first replication of the efficacy of antidepressants in treatment of adolescent depression and the first report of efficacy of paroxetine." 02:46:18

Q. Okay. And could you read the second sentence please?

A. "The introduction does an excellent job of discussing the past studies of adolescent depression and in describing the limitations of all but one of those studies." 02:46:29

Q. All right. And do you believe that the strength of this study is it's the first replication of evidence of efficacy of antidepressants in the treatment of adolescent depression? 02:46:41

A. Yes.

(Defendants Deposition Exhibit No. 12 was marked for identification.) 02:47:24

Q. I'm going to hand you what's been marked as Defendants Exhibit 12 and ask you if you recognize this as the reviewer's comments that came back from the Journal of the American Academy of Child and Adolescent Psychiatry? 02:47:46

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A. It appears to be as you represent it, certainly it's on their letterhead and Dr. Dulcan who signed it was the editor then. I can't separately authentic it. 02:47:52

Q. And can you turn to the second of the last page, Dr. Ryan? 02:48:16

A. Yes.

Q. And if you could just read to yourself the second paragraph and let me know when you're done?

A. I am done. 02:48:28

Q. Do you recall -- let me strike that.

Did you get feed -- did you and other authors get feedback from the editor of the American Academy of Child and Adolescent Psychiatry of what they believe to be the merits of the study? 02:48:44

A. Reviewers are encouraged to include the strengths of the paper to help the editor judge the importance of the paper. Sometimes they do. Sometimes they do not. It appears that they did in this case. 02:49:07

Q. What feedback did you and the other coauthors get about the strengths of this study and reflected in this document?

A. I only had time to read the one paragraph. That's clearly a feedback about the strengths. I do 02:49:14

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not know on the rest of this, because I do not remember it. 02:49:14

Q. Okay. Well, if you could read what that second paragraph reads.

MR. MURGATROYD: I need to object. Again, that if you are going to read the document -- well -- go ahead read it. 02:49:24

THE WITNESS: "This study has multiple strengths, including large sample size, randomized controlled design, and the use of standardized measures addressing multiple domains. Moreover, the study addresses an important area of clinical child psychiatry, the efficacy of antidepressant therapy in depressed youth. The results are clearly presented. Documenting that paroxetine has efficacy in adolescent depression is an important finding." 02:49:31 02:49:43

BY MR. DAVIS:

Q. Does this reviewer's comments suggest anything that the efficacy results were somehow hidden or not clearly set forth in the manuscript that was submitted? 02:49:58

A. No. This reviewers comments in its entirety -- this reviewer in the entirety in the 02:50:18

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feedback does not suggest that. 02:50:18
Q. Now, you testified that earlier that there was a meeting in November of 1997 of the clinical investigators and GSK employees to discuss the results of Study 329; is that right? 02:50:48
A. Yes.
Q. And at that meeting, do you recall who was present?
A. There were maybe 20. I would estimate that there was about 25 people present to the best of my memory. All of the PIs of the site were there. Dr. Birmaher from the Pittsburgh site was there. There were a number of GSK or SKB people there. I do not remember all who was there. 02:51:03
Q. Do you remember whether or not Mr. McCafferty was there? 02:51:24
A. Mr. McCafferty was there.
Q. Do you remember whether or not Dr. Ivan Gergel was present?
A. I believe he was. I'm not certain. 02:51:43
Q. Do you remember the names of any of the GlaxoSmithKline employees that --
A. No. I apologize. I do not.
Q. Now, were there efficacy findings of Study 329 discussed at this November 1997 meeting? 02:51:58

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A. Yes. 02:52:03
Q. And were the adverse events discussed at this November 1997 meeting?
A. Yes.
Q. Did those adverse events include adverse events of suicidal thoughts or behaviors and conduct disorders? 02:52:07
A. Yes.
Q. Based on the data that you saw then, was there a statistically significant and increased risk of suicidal thoughts and behaviors in the adolescent patients taking Paxil compared to those taking the sugar pill or placebo? 02:52:18
A. No.
Q. Did you and the other authors discuss adverse events in the published article about the results of Study 329? 02:52:37
A. Yes.
Q. Okay. Let's talk about those. Looking on page 769 is there a discussion there about the serious adverse events that were discussed in the published article on Study 329? 02:53:01
A. On the top of 769?
Q. Yes.
A. The first full paragraph? 02:53:22

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Q. And in that first full paragraph, is there a description about what is meant by the term emotional lability? 02:53:26
A. There is an example of some of the things that were included under emotional lability, yes. 02:53:43
Q. Will you tell the jury what is described there in terms of examples of emotional lability?
A. Suicide with ideation/gestures.
Q. Okay.
A. Conduct problems or hostility. 02:54:01
Q. Let me stop you there. The example of emotional lability is --
A. You're right. I misread that.
Q. Could you read that again?
A. So they have emotional lability and they give the example; suicidal ideation/gestures. 02:54:01
Q. Okay. And then does the paper then report within the descriptive term of emotional lability that it does include suicidal ideation or gestures?
A. Yes. 02:54:20
Q. And is there also a discussion of adverse events in Table three on the proceeding page which also discusses the adverse events which fell under the term of emotional lability?
A. Table three includes the numbers and 02:54:46

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percentages and the three different treatment arms that experienced emotional lability, yes. 02:54:46
Q. Okay. And in the article itself, do you and the other authors discuss an assessment of what was believed to be occurring with the patients with the adverse events? 02:55:05
A. To some extreme, yes.
Q. Now, was there also ...
VIDEOGRAPHER: We need to change tapes in two minutes. 02:56:14
MR. DAVIS: Let's go ahead and change the tape.
VIDEOGRAPHER: At this time we're going off the record at 2:57 p.m to change videotapes. This is the end of Tape Number 4. 02:56:18
(Recess taken.)
VIDEOGRAPHER: This is the beginning of the videotape of Dr. Ryan. The time is 3:04 p.m. Tape 5. Please proceed.
(Ryan Defendant's Deposition Exhibit No. 13 was marked for identification.) 02:47:32
BY MR. DAVIS:
Q. Dr. Ryan, I'm going to hand you what's been marked as Defendants No. 13, and it's got underline on it by -- that I'm going to need to 03:02:59

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substitute out. That's not probably the original letter, but I'm going to ask you, is Defendants Exhibit 13 a copy of a reply that was sent to the Journal of the American Academy Child and Adolescent Psychiatry which was published in April of 2002? 03:03:13

A. It's a copy of a letter to the editor from Mitch Parsons of Alberta, Canada. A letter to the editor about our -- the Keller et. al, letter and the response of Dr. Keller and myself to that letter. 03:03:31

Q. And are these series of articles discussing adverse events that were reported in the Keller article including those that -- concerning emotional lability?

A. Yes. 03:03:48

Q. All right. And who are the -- in terms of the reply letter back to Dr. Parsons, who was the individuals who responded?

A. The authors of the reply letter were Dr. Keller, myself and Dr. Wagner. 03:04:05

Q. And do you remember assisting in the preparation of this reply letter?

A. Yes.

Q. And did you have input into the content?

A. Yes. 03:04:20

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Q. Can you read the first two sentences of the reply letter, please? 03:04:20

A. "We thank Drs. Parsons and Weintrob for their words of encouragement and for their questions about adverse effects associated with paroxetine in our study of adolescents with major depression (Keller et al., 2001). In particular, Dr. Parsons was interested in our decision-making process for determining that adverse effects in the paroxetine treated group were not attributable to the selective Serotonin Reuptake Inhibitor." 03:04:28

Q. And can you also read the next sentence, please?

A. "In the 11 paroxetine-treated patients with serious adverse effects, 1 experienced headache and 10 experienced psychiatric symptoms, including emotional lability, suicidal ideation, conduct problems and behavioral disturbance." 03:05:01

Q. And can you read the next sentence, please? 03:05:14

A. "The psychiatric symptoms were chronologically related to a variety of situational factors."

Q. And can you please read the last -- through that paragraph? 03:05:24

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A. The rest of the paragraph? 03:05:26

Q. Yes, sir.

A. "Acute psychosocial stressors, for example arguments with boyfriend and parents, torment by peers, medication non-compliance, and/or untreated Comolli disorders. For example conduct disorder were judged by the investigators to account for the adverse effects in all 10 patients. Only headache in the one patient was judged to be related paroxetine." 03:05:31 03:05:46

Q. When the authors of the Keller's et. al, article received the letter from Dr. Parsons concerning his questions about adverse events, did the clinical investigators involved in Study 329 discuss the adverse events that he had questions about? 03:06:13

A. Yes.

Q. All right. Can you tell me about what was done?

A. I don't remember the details. Dr. Keller took the lead on this one. As I remember it as best I can we looked at the available data, the clinical data around that time to see what more was documented. 03:06:20

Q. And do you remember what it is in terms of 03:06:31

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available clinical data that you looked at? 03:06:31

A. No.

Q. And did you -- you and the other clinical investigators coordinate with GlaxoSmithKline to look at analysis in this data about the adverse events? 03:06:46

A. We coordinated with GlaxoSmithKline to look at the data. I don't think -- this was not a statistical analysis. It was not a, you know, lining them up and saying what's most likely one by one on this by simply looking at the descriptions. 03:07:07

Q. And when you say descriptions, are you describing case report narrative?

A. That's correct. That's what I should have said. 03:07:22

Q. And for the jury's benefit, what's a case report narrative?

A. As the research subjects -- as the adolescents with MDD would come in and they would have an adverse event there was a free text narrative written describing the adverse event. 03:07:22

Q. Let me hand you what's been marked as Plaintiffs Exhibit 33. Doctor, is that a copy of the paper that was coauthored by Dr. Alan Apter and others and is entitled "Evaluation of Suicidal 03:07:46

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Thoughts and Behaviors in Children and Adolescents taking Paroxetine"? 03:07:46

A. Yes.

Q. Did you assist in the analysis of the adverse events described in this study by doing a blinded review? 03:08:09

A. Yes.

Q. And let's turn to the -- did this analysis include additional adverse effects in Study 329 that might be possible suicidal thoughts or behaviors experienced by the adolescent patients in Study 329? 03:08:35

A. Yes.

Q. Look at Table Five that appears on page 85, Doctor.

A. I have it in front of me. 03:08:58

Q. What's the title of that table?

A. Incidence Density for Self Harm by Treatment Group and Indication For On-Therapy plus 30 Days Post Treatment."

Q. And is this analysis that's described in that table, does it breakdown each of the three depression studies that were conducted by and funded by GlaxoSmithKline? 03:09:16

A. Yes.

Q. And does that include Study 329, Study 377 and Study 701? 03:09:33

A. Yes.

Q. And does it with respect to Study 329, which you were involved in as a principle investigator, does it show for the analysis of suicide-related events which happened on-therapy which were analyzed in this paper? Is there a statistically significant increased risk of suicidal related behavior for patients taking Paxil versus those taking placebo? 03:09:50 03:10:07

A. No.

Q. Okay. Let's turn to table number six and can you tell us -- that's on page 87, can you tell us what the title of the table is?

A. "Incidence of Emergent and Worsening Ideation." 03:10:18

Q. Again, does this table include an analyses of the three pediatric depression studies that were funded by GlaxoSmithKline, which include Study 329, Study 377 and Study 701? 03:10:29

A. Yes.

Q. And with respect to Study 329 that you worked on, does that show a statistically significant increased risk of emergent or worsening ideation? 03:10:58

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A. No. 03:11:01

Q. And what is emergent ideation?

A. Suicidal ideation. Suicidal thoughts that come out during the treatment for the first time.

Q. And is that also true in worsening ideation in terms of what comes out after the treatment starts? 03:11:14

A. Worsening would be presumably worsening after the beginning of treatment.

Q. Okay. Were there any deaths in pediatric patients in Study 329? 03:11:29

A. No.

Q. Are you aware of any deaths that occurred in any pediatric study and conducted by GlaxoSmithKline? 03:11:43

A. The FDA reported that there were no deaths in any of the studies it had including those from GSK.

Q. So for either of these different analyses that were carried out at a later date, which included additional adverse events that were analyzed from Study 329 and which you were involved, did either of them show a statistically significant increased risk of suicidal behavior with taking Paxil versus placebo? 03:12:03 03:12:20

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A. No. 03:12:24

Q. This study -- this analyses that was published by Dr. Aptner and others, did that look at the -- did it conduct these analysis in the context of the on-drug period versus looking at on-drug plus 30 day period? 03:12:41

MR. MURGATROYD: Are you talking about the drafts or the final article?

MR. DAVIS: Talking about the article that was published. 03:13:05

THE WITNESS: I'm going through this quickly. We discussed yesterday while this was published in January of this year I missed it until yesterday and today. It does not appear to include -- it appears to only include the on-drug interval, but if you have other data point me to the pages and I will look at that and then give you a different answer -- give you an appropriate answer. 03:13:22

BY MR. DAVIS: 03:13:37

Q. Okay. Turn back to Dr. Laughren's memo that is dated January 5, 1994.

MS. CONNELLY: Wait. Is this one of your exhibits?

MR. DAVIS: It's one of Plaintiffs 03:13:46

Exhibit. 03:13:48
MS. CONNELLY: We don't have any of them.
MR. MURGATROYD: Oh, I have some, which one are you looking for?
MR. DAVIS: I'm not sure of the number. 03:14:11
THE WITNESS: We discussed it today.
MR. MURGATROYD: I don't have it, Todd.
MS. CONNELLY: There's a bunch right here.
MR. MURGATROYD: And we're looking for the Laughren memo? 07:59:58
MS. CONNELLY: If it's from today it should be in the smaller pile.
MR. MURGATROYD: It should be in here. Here it is. I got it.
BY MR. DAVIS: 03:14:46
Q. If you could look at page 15 that I opened that -- that document to and down at the bottom of that page, Dr. Ryan, is there a discussion by Dr. Laughren where the FDA has focused its attention in terms of looking on-drug versus on-drug plus a 30 03:15:52 day period?
A. Yes, it does.
Q. And what does Dr. Laughren say about what the period the FDA will be looking at?
A. This document says. "While we've been 03:16:11

provided data both for 'on-therapy' and for 03:16:14 "on-therapy plus 30 days" events, I have focussed on the "on-therapy" data, since these are the least problematic from the standpoint of interpretation. While we do sometimes utilize them "on-therapy plus 03:16:31 30 days" time frame for capturing events of interests, this analysis is problematic in this case for two reasons. First it may be confounded by discontinuation symptoms occurring following withdrawal of medication, and second, different 03:16:41 sponsors used different rules in deciding what events to include and exclude the 30 days plus period in their analyses. For simplicity, I have provided the data for all ages combined, rather than breaking it out by age group." 03:17:05
BY MR. DAVIS:
Q. Do you agree that the more appropriate suicide related events would be looking at the on-drug therapy versus the on-drug therapy plus 30 days? 03:17:20
MR. MURGATROYD: Objection; calls for speculation; lack of foundation and lack of expertise.
THE WITNESS: I agree that if one had to choose between the two that Dr. Laughren makes 03:17:24

a cogent argument why the on-therapy would be 03:17:24 the first one to examine. It seems that the on-therapy plus 30 days, you know, may also be deserving of examination.
(Defendants Deposition Exhibit No. 14 03:17:41 was marked for identification.).
BY MR. DAVIS:
Q. Let me hand you what has been marked as Defendants Exhibit 14. Dr. Ryan, you mentioned that you had reviewed the analysis conducted by FDA on 03:18:03 the pediatric studies which were performed by Dr. Hammond? Did I understand that correctly?
A. That's correct.
Q. And who is -- that's Dr. Terry Hammond?
A. That's correct. 03:18:24
Q. Who is Dr. Hammond at FDA?
A. I don't know the answer to your question.
Q. Is he a scientist at the FDA?
A. Yes.
Q. Let me turn your attention to page 45, 03:18:35 which I've dog-eared to get you right to the section.
A. I have that page.
Q. Now, under "Reviewer's Conclusion", can you read the third bullet please? 03:18:46

A. "No individual trial showed a 03:18:46 statistically significant signal for suicidality. However, many had a RR, risk ratio, of 2 or more and some of the overall estimates, across various trial groupings, were statistically significant." 03:18:59
Q. Was Dr. Hammad's analysis of the suicidality events in the Paxil pediatric trial that were part of his analysis find a statistically significant increased risk for Study 329?
MR. MURGATROYD: Objection; calls for 03:19:22 speculation.
THE WITNESS: The data is clear in here that it did not.
BY MR. DAVIS:
Q. And do you recall looking at the data on 03:19:33 Study 329 when this data became available?
A. I looked at the data on all the studies including that study when this data became available.
Q. Now, you mentioned to Plaintiffs Counsel 03:19:44 that one of the reasons you were no longer involved in the Aptner papers is because Dr. Hammand's analyses was more thorough? Do you recall that testimony?
A. If I said more thorough that is not what I 03:20:03

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intended to say. **03:20:07**
Q. What did you intend to say?
A. Well, a better way of expressing it, it's more comprehensive, because adding data from all the compounds and putting it together that's of much more value to the field than looking at a single compound. **03:20:18**
Q. Okay. I think you answered my question. Thanks. Let me have you look at Exhibit 60, if you would? 03:20:46
MS. CONNELLY: It should be in that pile, if you could please help me out.
MR. MURGATROYD: Absolutely. I won't ask you to get paper clips.
MR. DAVIS: It's right here. 03:20:46
BY MR. DAVIS:
Q. Dr. Ryan, Plaintiffs Counsel mentioned to you that you had received an inquiry from a reporter at Health Magazine, do you recall that?
A. I think Dr. Keller received the inquiry and he asked me to help work on some of this. **03:21:11**
Q. And what was the time that inquiry was received by Dr. Keller?
A. All I have is the notes from here, because otherwise I don't know. The first e-mail from here **03:21:28**

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is dated March 16, 2004 from me to Dr. Keller. **03:21:29**
Q. Okay. And was that date after GlaxoSmithKline had submitted to FDA its analyses of pediatric suicidality events in the pediatric studies? 03:21:52
A. If you can help me out on the date on that one I can tell you if that was before or after.
MR. MURGATROYD: Let me object to lack of foundation.
BY MR. DAVIS: 03:22:01
Q. Are you aware GSK submitted to FDA analysis of suicide -- possible suicide related events in pediatric studies in May of 2003?
MR. MURGATROYD: Objection; leading, and it misstates the evidence. Now, wait a minute. 03:22:13
You can't do that, Todd. He submitted that in 2002.
MR. DAVIS: Excuse me?
MR. MURGATROYD: The original was submitted in 2002. 03:22:24
MR. DAVIS: The pediatric analyses were submitted in May of 2003.
MR. MURGATROYD: I'll object for lack of foundation, and it's a leading question, and you're assuming facts not in evidence. 03:22:33

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THE WITNESS: I'm sorry. Can you repeat your question? 03:22:37
MS. CONNELLY: How about ask him if he has any knowledge of the date.
BY MR. DAVIS: 03:23:22
Q. Let me show you what has been marked as Plaintiffs Exhibit 27. Do you see that's a copy of the FDA Talk Paper dated June 19, 2003?
A. Yes.
Q. Thank you. And does it discuss anything 03:23:35
about submissions that GlaxoSmithKline has made to the FDA in the first paragraph?
A. It says that "It's reviewing the reports of a possible increased risk." Let's see. It says, "New safety information is currently under review that was derived from trials of Paxil." **03:23:58**
And was there something that you would like me to comment on?
Q. Yes. I was going to say, is that based upon the FDA Talk Paper dated June 2003? Does that 03:24:20
refresh your recollection about the time that GlaxoSmithKline had submitted some analysis of adverse events, possible suicidal-related behavior in pediatrics?
MR. MURGATROYD: Objection; misstates the 03:24:33

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evidence. I don't think the Doctor ever said 03:24:33
he knew at any time what the date was.
THE WITNESS: I -- I -- even after looking at this I don't -- I don't know the date.
BY MR. DAVIS: 03:24:48
Q. Okay. How many months after the date, according to the e-mail that's been marked as Plaintiffs 60, was the Terry Hammond analyses published?
A. The Terry Hammond analyses was published relatively recently. I haven't actually seen the published version just that one today, have I? **03:25:07**
Q. I'm sorry. I mean, what's been marked as Defendants Exhibit --
A. I'm sorry. You meant published on the web? **03:25:18**
Q. Yes.
A. Okay. Perfectly fair. It was published also in the journal, so this is ...
Q. If you look at the very last page. 03:25:26
A. That would be a help. So this is 4-16-04 and this is --
Q. This -- I'm sorry. I think it's August 16, '04, Doctor.
A. You're completely right. August 16, '04, **03:25:44**

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and this is March 16, '04. **03:25:44**

Q. And were you aware that there was a Pediatric Advisory meeting on the use of SSRIs in treating pediatric patients in February of 2004?

MR. MURGATROYD: Objection; leading. 03:26:11

THE WITNESS: I am aware that there was a meeting in February 2004, yes.

BY MR. DAVIS:

Q. And I'll hand you what's been marked as Plaintiffs Exhibit 38, which is a copy of the 03:26:13 article dealing with Study 511 that was published by Dr. Braconnier. Doctor, is this a placebo controlled study?

A. No.

Q. What type of study is it? 03:26:37

A. This was compared to another active compound.

Q. Okay. And can one -- with respect to the suicide attempts that occurred with placebo, paroxetine and tricyclic antidepressants, can one 03:26:44 calculate an incidence rate of possible suicide attempts in this study that it is not placebo controlled?

MR. MURGATROYD: Objection; leading.

THE WITNESS: Well, you have an incident 03:27:09

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rate for each compound, but you do not have a 03:27:11 ratio. You have a ratio between the two, but you have no way to judge what that would be over, you know, you have no way to attribute that to medication or happenstance because 03:27:22 there's no control

BY MR. DAVIS:

Q. Let me ask you another question. Based upon the fact that this is not a placebo based trial, can one determine whether or not those events 03:27:39 occurred as a result by study medication or by chance?

A. No.

(Defendants Deposition Exhibit No. 15 was marked for identification.) **03:28:16**

Q. I'm going to hand you what's been marked as Exhibit 15. Doctor, can you read that article for us, please?

A. Yes. This was an article that was published in 2002 in the Society -- the Journal of the Society of Biological Psychiatry entitled "Skating to where the Puck is Going to Be: A Plan for Clinical Trials and Translation Research in Mood Disorders". It was the result of a consensus conference I coauthored with along 30 other authors. **03:28:50**

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Q. And there's a page there that's dog-eared 03:29:01 and highlighted, can you turn to that page?

A. Yes.

Q. And can you read that into the record, please, what you and your coauthors state in this 03:29:11 article?

A. "Selective serotonin Reuptake Inhibitors appear to be efficacious in pediatric major depressive disorder. Three randomized controlled trials report superiority of SSRI to placebo in **03:29:22**
Emslie et al.1997); Keller 2001; however, two failed to find SSRI superiority, one of fluoxetine, (et al 1990) which had a high placebo response rate, and an industry-sponsored study of paroxetine (Milen et al 1990)." **03:29:35**

Q. And is the reference to the Milan et. al, is that reference to a poster presentation that was made by Dr. Milan about the results of Study 377?

A. Yes.

Q. And was this article published in a 03:30:03 peer-reviewed journal I think that was read by that physician?

A. Yes.

Q. And what year was this article published?

A. 2002. **03:30:13**

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Q. Is that a year after the Keller et. al 03:30:14 article was published?

A. Yes.

Q. And in this article, did you and the other authors disclose the efficacy results of Study 377 03:30:24 in terms of whether or not Study 377 failed to find SS of SSRI superiority?

A. Yes.

Q. Now, was there ever any effort on your part to not disclose the results of Study 377 which 03:30:50 you were aware of?

A. No.

Q. And by the that fact you published this information in a peer-reviewed journal, what did you try to inform physicians about the results of Study 03:31:05 377?

A. We were trying to give physicians the results of all studies that we knew the results of, because it's important to get all the data.

Q. Now, did any one at GlaxoSmithKline try to 03:31:14 prevent you from disclosing this information about Study 377?

A. No.

Q. Did any one at GlaxoSmithKline try to persuade you to present this data in some other way 03:31:22

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in which it wouldn't describe the fact that Study 377 was not effective in showing superiority over placebo in that study? 03:31:28

A. No.

Q. Plaintiffs Counsel questioned you about a number of your slides that you brought today and shared with us in which you discussed the results of Study 329 and other clinical studies on pediatric patients. Did Plaintiffs Counsel ever tell you when Study 701 was completed? 03:31:58

A. Not to my memory. 03:32:20

Q. Okay. I want to hand you what was marked as Plaintiffs Exhibit 36. Turn to page 3, which is a report synopsis, and I'll ask if you can read into the record what was the treatment date excluding the paper phase for Study 701 and what was the date of the final Study Report for 701? 03:32:43

A. The last -- the last dose of study medication excluding taper was admitted on 24, January 2001, and you asked me something -- a second thing to do and I've forgotten that. 03:33:05

Q. Yes, sir. What was the date of the final study report?

A. Final Clinical Report was dated 30, July 2001. 03:33:26

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Q. Okay. For the presentations that have been marked as exhibits here and for other presentations that you gave, could you have put any data about Study 701 in those slides presentations or discussed the results if the study had not been completed when you did those slides? 03:33:28 03:33:39

A. No.

Q. Okay. And so how many slide sets could you have -- that the vast majority of the slide sets that you discussed with Plaintiffs Counsel predated January 2001 when Study 701 -- excuse me, thank you -- do you agree that the vast majority of the slide sets that you discussed with Plaintiffs Counsel predated July 2001 when the final study report was done for 701? 03:33:58 03:34:20

MR. MURGATROYD: Objection misstates the evidence. I think -- I mean, do you know that for a fact?

MS. CONNELLY: I have the University's -- the nine slides presentations. 03:34:35

THE WITNESS: Okay. So the majority or the vast majority. Okay. 1, 2, 3, 4, 5, 6 --

MS. CONNELLY: What's the critical date again?

MR. MURGATROYD: July 2001. 03:34:39

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THE WITNESS: So I'm getting a December 2001 and a July 2001. 03:34:48

MR. MURGATROYD: There's another one right in front of you.

THE WITNESS: Is there another one? 03:34:48

MS. CONNELLY: Oh, okay.

THE WITNESS: May 2002. So I'm getting six of nine. The majority.

MS. CONNELLY: One is the same month.

THE WITNESS: One is the same month and I don't know -- let's see if I can figure out when it was in it. I don't know. I think it was towards the end of the month so I think you've got either six of nine or seven of nine. 03:34:48

BY MR. DAVIS: 03:35:20

Q. And the final study report of 701 was finished -- I believe was finished on July 30, 2001.

A. Then you've got seven of nine.

Q. Okay. Dr. Ryan, do you recall when you first learned of the study results of 701? 03:35:37

A. To the best of my knowledge that was 2004 on the FDA web site.

Q. Do you remember any discussions that you had with GlaxoSmithKline employees before April of 2002 about the results of study 701 before GSK 03:36:26

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submitted an indication -- for an indication to treat pediatric obsessive compulsive disorder? 03:36:33

A. I do not remember this.

Q. There's also this Pediatric advisory committee Meeting -- 03:36:44

A. I'm sorry. I'm sorry. My apologies. About the depression study or about the OCD study?

Q. The depression study.

A. I do not remember discussing the depression study related to the OCD. 03:36:58

Q. Okay. And on what's been marked as Plaintiffs Exhibit 2.

A. Right.

Q. Do you recall participating in person or by phone about a discussion about the results, the efficacy and safety results about the pediatric studies that had been conducted to date? 03:37:13

MR. MURGATROYD: Wait a minute. Correct me if I'm wrong, but I think the Doctor testified he wasn't part of that. 03:37:14

BY MR. DAVIS:

Q. I'm just asking, does he recall participating in person or by phone in the Pediatric Advisory Committee Meeting?

A. I'm not remembering it. Let me look at 03:37:35

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the slides and see if that refreshes my memory. I cannot say that for sure that I have seen this before. I remember it. There certainly was sometime through this interval -- I can't pinpoint -- some discussion with GSK employees about suicidality issues and what they're doing. I just can't remember more. 03:37:48 03:38:52

(Ryan Deposition Exhibit No. 16 was marked for identification.).

BY MR. DAVIS: 03:39:09

Q. Let me hand you what's been marked as Defendants Exhibit 16 and ask you if you can identify that as an article that Dr. Karen Wagner published in the Psychopharmacology Bulletin?

A. This appears to be as stated. A Psychopharmacology Bulletin article in the spring 2003 by Karen Dineen Wagner so authored entitled "Paroxetine and Treatment of Mood and Anxiety Disorders in Children and adolescents." 03:39:28

Q. And was Dr. Wagner a principal investigator in Study 329? 03:39:41

A. Yes.

Q. And was she a coauthor of the article known as the Keller et. al article that published the results of Study 329? 03:39:52

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A. Yes. 03:39:59

Q. Okay. Turn to page 169 to that dog-eared, if you will. Actually, if you turn to page 170 -- I'm sorry -- in the third paragraph that is down from the top. 03:40:18

A. Yes.

Q. Do you see where it says "In another multicenter, double-blind placebo-controlled trial of paroxetine treatment of children and adolescents with major depression, there was no statistically significant difference in the response rates between the paroxetine and placebo groups"? 03:40:29

A. I do.

Q. And do you understand that study refers to Study 701? 03:40:46

A. Yes.

Q. And do you see that Dr. Wagner is disclosing that trial did not reach statistical significance in terns of the efficacy parameters?

A. Yes. 03:41:05

MR. MURGATROYD: What's the date on that?

THE WITNESS: It says Spring 2003.

MR. MURGATROYD: And did you establish that the doctor read it?

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BY MR. DAVIS: 03:41:13

Q. Doctor, do you recall reading this article when it came out?

A. No.

Q. Do you recall one way or the other if you read it? 03:41:20

A. I don't remember one way or the other.

Q. Okay.

A. Certainly somewhere through here I think that Dr. Wagner there had a -- I think there may be other references to Dr. Wagner to this study that was not at the time published or presented at a meeting. 03:41:29

Q. Let me ask you: Plaintiffs have made the claim in this litigation that Sally Laden or STI, who she was employed with, ghost-wrote the article that you coauthored which reported the results of Study 329? Is that claim true? 03:41:43

A. I certainly -- I do not think it to be true. I certainly do not have evidence that would support it. 03:42:11

Q. Did you have input into the contents of the Keller et. al article of which you were named coauthor?

A. Yes. 03:42:22

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Q. Okay. Did Sally Laden or STI control the content of the Keller et al, article? 03:42:24

A. No. In no sense did they control it.

Q. Who controlled the content of the article?

A. The authors. 03:42:37

Q. The named authors?

A. The named authors.

Q. Okay. And do you know how many drafts were circulated -- commented on by the outside investigators? 03:42:48

A. I do not. It would be multiple drafts, and I do not know the total number.

(Defendants Deposition Exhibit 17, 18, 19, 20, 21 was marked for identification.)

Q. Doctor, I have given you Exhibit 18 and 19 -- 03:44:22

MS. CONNELLY: Actually I only see 17 in his hand.

THE WITNESS: I have 17 here. I'm sorry. I should actually be responding to your questions rather than ignoring you. 17 and 19 are duplicated here. 03:45:46

MR. DAVIS: I don't think so. I'll walk you through those.

THE WITNESS: I have four distinct 03:45:50

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documents instead of five. 03:45:50
MR. DAVIS: That's different. That's different. That's different. The thing on this is 18. I'll fix that in a second.
THE WITNESS: Okay. There's no 18 exhibit right now. 03:45:50
BY MR. DAVIS:
Q. Okay. So we've got our Exhibits 17, 19, 20 and 21. Is that right, Doctor?
A. Yes. That's correct. **03:46:43**
Q. And in reviewing those documents, do you see on them -- particularly on Exhibit 17, what's the date of Exhibit 17?
A. It appears to be December 18, 1998.
Q. And do you recognize Dr. Martin Keller's handwriting down at the bottom? 03:47:07
A. It's similar to Dr. Keller's handwriting. I can't authentic it.
Q. Okay. And do you see that article -- that draft has multiple revisions on it? 03:47:28
A. Yes.
Q. And let's look at what's marked as Exhibit 19.
A. Yes.
Q. What's the date of that letter? 03:47:28

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A. The date of that letter is February 11, 1995. **03:47:29**
Q. And does it have a memorandum that is attached to it?
A. Yes. **03:47:41**
Q. And what's the date of that memorandum?
A. The memorandum is February 22, 1999.
Q. Who is the memorandum addressed to and who is it from?
A. It's from Dr. Martin Keller. It's addressed to the co-authors on Paxil, Imipramine Adolescent Research, and it says, enclosed is draft number three of the acute phase manuscript. **03:47:46**
Q. What does it say in the next sentence?
A. It says: Neal, Mike and Jim, meaning myself, Mike Strober and Jim McCafferty, have edited the first two drafts with me. **03:47:59**
Q. And does that refresh your recollection that you edited the first two drafts of that article? 03:48:13
A. Yes.
Q. And is -- what's the purpose of Dr. Keller in sending this out to the other coauthors of the article?
A. So that every coauthor on the article has fair and square inputs on all aspects. **03:48:20**

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Q. No let's look at the next marked exhibit, which I think is 20.
A. It's Exhibit 20. Has a handwritten date of 4-14-99 saying it's related to -- it says -- I'm sorry -- it looks like -- it's 4-24-99 is the date on it. **03:48:29**
Q. So is that another version of the draft?
A. It's a later version and it's got further edits on it. **03:48:46**
Q. Okay. What does it say on the top left-hand corner of that?
A. Says, "Edits made by Keller Incorporated. All feedback received as of 4-14-99."
Q. Okay. And what's the last document that's been marked? 03:49:09
A. The last document is e-mail that's not produced by my office from me to Barbara Ryan and Brown, which was the way to get stuff to Marty then, because he didn't have his own e-mail so it was sent to this administrator with some more feedback on the draft. **03:49:22**
Q. Is that feedback from other authors of the Keller et al. article?
A. Some of it's from Greg Clarke. More of **03:49:37**

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it's from Greg Clarke. It may all be from Dr. Greg Clarke. I cannot tell if it's multiple authors or just Dr. Clarke. **03:49:43**
Q. Okay. Now, did -- based upon your review of those drafts of the Keller et al. article, do you believe that you had substantial input into the content of that article? 03:49:58
A. Yes.
Q. Has Paxil or Paxil -- my next series of questions when I say Paxil I mean Paxil and Paxil CR. Okay, Doctor, just to speed this up? Is that agreeable to you? 03:50:18
A. Yes.
Q. All right. Now, has Paxil been approved by FDA for use in pediatric patients? 03:50:41
A. I do not believe so.
Q. And are you aware that pharmaceutical companies do not promote or market their medications for other uses?
A. Yes, I am. **03:50:48**
Q. And when you have a professional association such as the APA, which is the American Psychiatric Association or the Journal of the American Academy of Child and Adolescent Psychiatry or the new drug clinical evaluation unit that holds 03:51:01

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a conference or a symposium or the rules and guidelines about what a pharmaceutical company can and cannot do in promoting its product? 03:51:07

MR. MURGATROYD: Objection; leading.

THE WITNESS: Each organization has its own rules, but they all have a great deal in common, which is that anything targeted or developed by a company would have to be so identified and the rest -- any conflicts of interest or any potential conflict with authors would have to be disclosed in the program, and at the beginning of the talks, and they all work really hard to make sure that people aren't biased. 03:51:20 03:51:33

Q. Now, are there also rules about what pharmaceutical company employees can do in terms of interactions with the attendees at the conference? 03:51:50

A. Yes.

Q. And are there rules that -- concerning whether or not there are certain areas that are off limits for marketing or promotion? 03:52:07

A. Yes.

Q. And are those places that are off limits where the scientific presentations or/and posters are presented for review? 03:52:18

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MR. MURGATROYD: Let me just object on the ground of lack of foundation. We haven't seen anything that establishes what you're saying. 03:52:22

THE WITNESS: Yes.

BY MR. DAVIS: 03:52:35

Q. Do you have any evidence that GlaxoSmithKline did not comply with those rules and guidelines with respect to Paxil?

A. No.

Q. And do you have any evidence that GlaxoSmithKline tried to market or promote Paxil for pediatric use at any scientific conference or symposium? 03:52:44

A. No.

Q. And when you answered Plaintiffs Counsel questions earlier in the deposition about what happens at scientific conferences or presentations or through the publication of articles, did you mean to suggest in any way that GlaxoSmithKline intended to or did, in fact, promote Paxil for use in pediatric patients? 03:52:58 03:53:11

MR. MURGATROYD: Objection; leading, misstates the evidence.

THE WITNESS: That was not my intention. My intention in answering that question, which 03:53:28

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I may have answered incompletely, was that it's important for researchers to get the data out there, and the part that I answered that wasn't a complete answer is that this has an unintended consequence of being a good mention of being something that does likely increase the use of the compound even for unapproved uses. 03:53:28 03:53:39

BY MR. DAVIS:

Q. When you presented findings on Study 329, were you ever trying to increase Paxil sales in the pediatric population? 03:53:48

A. No.

Q. And when you presented findings on Study 329 whether at scientific conferences or symposium or by way of a published article, were you trying to promote or market Paxil in the pediatric population? 03:54:07

A. Absolutely not.

Q. And when you were invited -- let's leave that go. 03:54:22

At any time did any GlaxoKlineSmith employee ever ask you or suggest to you that he or she wanted you to present scientific data about Study 329 for purposes of increasing Paxil sales in the pediatric population? 03:54:33

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A. No. **03:54:35**

Q. At any time, did any GlaxoSmithKline employee ever ask you or suggest to you that you should present data on the safety and efficacy findings of Study 329 for the purpose of promoting or marketing Paxil in the pediatric population? 03:54:58

A. No.

Q. When you were invited to speak at any professional organization about the results of Study 329, at any time did anyone at GlaxoSmithKline ask you or suggest to you that you ought to do so for the purpose of marketing or promoting Paxil for use in pediatric patients? 03:55:16

A. No.

Q. And at any time that you presented data to professional organizations or physicians about the results of Study 329, did anyone at GlaxoSmithKline ask you or suggest to you that they wanted you to do that for the purpose of increasing sales of Paxil to pediatric patients? 03:55:33 03:55:48

A. No.

Q. At any time, did anyone at GlaxoSmithKline ask you to present data on pediatric data on pediatric studies involving Paxil that was not scientifically accurate and reliable? 03:56:09

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A. No. **03:56:14**
Q. Did you ever do so?
A. No.
Q. Did any one at GlaxoSmithKline ask or suggest to you to do anything along the lines of 03:56:18 only presenting Paxil's positive data in Study 329?
A. No.
Q. At any time did any one at GlaxcoSmithKline ever ask you or suggest to you that you should downplay or hide what may be viewed as 03:56:29 negative safety or efficacy data in pediatric studies including Study 329?
A. Absolutely not.
Q. When you gave talks or presentations about the results of Study 329 even at scientific 03:56:44 conferences or meetings of physicians, who prepared those presentations?
A. Absolutely in all -- I prepared all my slides. In two cases, both presented to your industry, put their own backgrounds on them **03:56:59** **subsequently.**
Q. Did GlaxoSmithKline control the contents of any --
A. No. They did not control the content in any way. They did not suggest any modifications of **03:57:11**

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any slides. They did not change the content of any slides. **03:57:11**
Q. When you presented data on the safety and efficacy of Study 329 to physicians, whether it be in scientific conferences or meetings with 03:57:24 physicians or published literature, were you trying to present that data in a balanced view?
A. All cases, yes.
Q. At any time did any other clinical investigator in Study 329 or coauthor of the Keller 03:57:44 article suggest or say to you that the authors should present data about the results of Study 329 for the purposes of promoting Paxil or increasing sales of Paxil in pediatric patients?
MR. MURGATROYD: Objection; compound, 03:58:13 asked and answered.
BY MR. DAVIS:
Q. Well, I'll break it down. At any time, Dr. Ryan, did any other of the clinical investigators of Study 329 who were also coauthors 03:58:18 of the Keller et. al article ever suggest or ask you to present data on Study 329 for the purpose of increasing sales in pediatric patients?
MR. MURGATROYD: Objection; compound question. 03:58:37

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THE WITNESS: None of the 03:58:41 co-investigators. None of the authors of the article ever suggested such a thing.
BY MR. DAVIS:
Q. Did any clinical investigator in Study 329 03:58:44 or any author of the Keller et. al, article ever say to you that they had been asked by GlaxoSmithKline to present data on Study 329 either for the purpose of promoting or marketing Paxil in the pediatric population or for increasing sales of Paxil in the 03:59:01 pediatric population?
A. No.
MR. DAVIS: Thank you, Dr. Ryan. No further questions at this time.
MR. MURGATROYD: I think we're going to 04:07:16 change the tape.
VIDEOGRAPHER: At this time we're going off the record. The time is 4:00 p.m.)
(Recess taken)
VIDEOGRAPHER: We are now back on the 04:07:50 record. This is the beginning of Tape No. 6, the deposition of Dr. Ryan. The time is approximately 4:09 p.m. Please proceed.
BY MR. MURGATROYD:
Q. Doctor, you were shown a number of 04:08:07

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exhibits by Mr. Davis that you stated accurately 04:08:11 reflected the information in your article, in the 329 article?
A. Yes.
Q. Do you recall these Exhibits 6 and 7? 04:08:14
A. Yes.
Q. Okay. Let's take a look at Exhibit -- which is the one with the table?
THE WITNESS: 7.
MS. CONNELLY: 7. 04:08:24
BY MR. MURGATROYD:
Q. 7. okay. And that lists the -- lists eight efficacy variables, right?
A. Yes.
Q. Four of which you testified were 04:08:37 statistically significant, correct?
A. Yes.
Q. And how many of the four that were statistically significant relate to the HAM-D?
A. Two. **04:08:50**
Q. Okay. And have you ever been involved in a conversation with Dr. Keller in which either you or he trashed using the HAM-D in studies involving adolescents?
MR. DAVIS: Object to form. 04:09:16

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THE WITNESS: I think that Dr. Keller, Dr. Emslie, myself, the entire field after this study had said that the HAM-D was not as good as the CDSRR. 04:09:16

MR. MURGATROYD: I think we're up to 62, Todd? 04:09:50

MR. DAVIS: I think you're up to 65.

MR. MURGATROYD: Oh, good.

(Ryan Deposition Exhibit No. 65 was marked for identification.) 02:47:32

BY MR. MURGATROYD:

Q. Okay. Let's see. let's take a look at 65.

A. Yes.

Q. And can you identify for the record, sir, what that documents is? 04:10:18

A. It's a letter -- I'm sorry -- it's an e-mail from me to Dr. Martin Keller, re: "in response to the Jureidini -- entitled "Paxil Response to the Jureidini Article", dated November 8, 2002 produced by my office. 04:10:37

Q. Okay. And in it, do you discuss the HAM-D scales that were used in Study 329?

A. Yes.

Q. Sir, I'm not quite sure how to read them. What -- do me a favor. It seems -- if you could, 04:10:58

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would you read the paragraph that starts with, "Heh Neal." 04:10:58

A. "Heh Neal. Talked to Karen Wagner and Boris Birhamer about this today and showed them earlier draft. Boris suggested we say that our 04:11:01 measures that are positive." And then there is some asterisks and all caps, "Careful we just trashed the HAM-D and 2 of our positive measures are the H-D less than 8 and the D depressed mood item. Have a long tradition of use in other studies." I forgot 04:11:09 to put in the K-SADS depression item was also positive. I don't have the reference in the AACAP format (trivial change in text and format of reference, just see recent article.) Can your office do that since I don't get home until Saturday and 04:11:33 can't really do from road."

Q. Okay. And let's stop right there. And was this you writing this or was this Dr. Keller writing this?

A. No. This was Dr. Keller writing this. 04:11:39

Q. Okay. Writing that to you?

A. That's correct and to -- with cc's to Dr. Birmaher and to Kelly MacNell who is someone at Brown.

Q. And why did you trash the two of the 04:11:46

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positive -- or did Dr. Keller trash two of the positive efficacy variables from Study 329? 04:11:50

A. Yes. This goes -- the issue is, was the HAM-D a less sensitive measure of differences, and so actually finding a statistically significant 04:12:07 difference on the HAM-D is harder to do and so it's a little bit more impressive that we found it on some of the measures from that. So the argument where they're saying they've trashed it is that it's not a sensitive change as the CDSRR. 04:12:22

Q. Okay.

A. And so that would go against your order -- against the directional you're trying to argue?

Q. Well, I'm sorry. He said he trashed the HAM-D. What's that again? 04:12:31

A. Right. That he -- and the rest of child psychiatry is saying it's a less sensitive measure.

Q. Okay.

A. That we found a P value on this on a less sensitive measure doesn't say we shouldn't report 04:12:44 it. It just says it's not a good choice for future studies.

Q. Okay. And what did you decide -- or what you stated in the reply to Dr. Jureidini was a better instrument of measurement? 04:12:52

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A. The field has moved strongly away from 04:13:01 using the Hamilton Depression Scale for depression and is using the Child Depression Rating Scale Revised.

Q. Okay. is that considered a better -- a better scale? 04:13:11

A. Yes, because it's more sensitive to changes that you see with medications.

Q. Okay. And did GSK perform a MDD study in adolescents utilizing that scale, to your knowledge? 04:13:16

A. Yes. I think -- I think that every study funded by industry since than, to my knowledge, that's used a measure has used the CDSRR.

Q. Okay. And so you're aware that 701 used that instrument, correct? 04:13:35

A. Yes.

Q. Okay. And in 701 did that instrument reach statistical significance in favor of Paxil?

A. No.

Q. Okay. And the reason you didn't point that out in this article is because you had not read 701 at the time you wrote this -- I mean, wrote this reply to Dr. Jureidini? 04:13:43

A. That would be not the only reason, not the most so substantive reasons, but one of the reasons. 04:13:58

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If I hadn't read it I can't point out that we used it in that one; but again, you're getting the direction wrong. That we used a less sensitive instrument to the change and found a significant P value, and that the whole field had moved away from that because the CDSRR looked better doesn't say that -- I mean, doesn't say anything bad about the Hamilton. It just said that you should move away from it. That a study using the CDSRR didn't find a difference doesn't say why the study didn't find a statistically significant difference. 04:13:58 04:14:18 04:14:28

Q. I think you say in your reply to Dr. Jureidini. "The field has moved strongly away from using the Hamilton rating scale for depression in adolescent treatment studies", correct? 04:14:41

A. The emphasis on the strongly was yours. It's not italicized; but yes, otherwise that was a correct quote.

Q. Okay. And Dr. Jureidini criticized you for writing an article that confused the reader as to what response was, correct? 04:14:50

A. That's correct.

Q. Okay. And one of the -- I think the -- Exhibit 6 that Mr. Davis gave you defines response, do you see that? 04:15:09

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A. Exhibit 6, yes. 04:15:09

Q. Okay. And what is response?

A. The protocol described two primary measures, one either Hamilton-D less than 8 and/or 50 percent reduction in baseline HAM-D or two change in the HAM-D total score. 04:15:18

Q. Okay. And you agree that Paxil failed to reach statistical significance with regard to either of those efficacy variables?

A. Yes. 04:15:31

Q. Okay. Now, if you return to your article, sir.

MS. CONNELLY: Do you have your article?

THE WITNESS: I think the Keller article is right there. 04:15:39

MR. MURGATROYD: That's the disappearing act article.

BY MR. MURGATROYD:

Q. And if you would, turn to page 765 at the bottom. 04:15:58

A. Yes.

Q. And do you see under that section it says "Efficacy Results"?

A. Yes.

Q. And can you read the first sentence through the parenthesis, please? 04:16:03 04:16:14

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A. "Of the depression-related variables, paroxetine separated statistically from placebo at endpoint among four of the parameters: Response.

Q. Keep reading. 04:16:29

A. I.e, primary outcome measure).

Q. Okay. Let's there. That's not a true statement, is it?

MR. DAVIS: Object to the form; it mischaracterizes the article. 04:16:31

THE WITNESS: I think that's misstated.

BY MR. MURGATROYD:

Q. Okay. So you would agree what Dr. Jureidini criticized your article about in number one of his criticism in the letter to the editors, do you see that? "The definition of response is changed." 04:17:31

A. That's a fair question. Let's go through it again. Perfectly fair question. You could read responses the first half of that in which case it makes it or the whole thing. 04:18:13

Q. Sop it's confusing, correct?

MR. DAVIS: Object to the form.

THE WITNESS: Yes.

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BY MR. MURGATROYD: 04:18:28

Q. So Dr. Jureidini's criticism is well taken? Would you agree with that?

MR. DAVIS: Object to form.

THE WITNESS: It could be. It's confusing. I do not know that it was deliberately changed. 04:18:33

BY MR. MURGATROYD:

Q. Okay. Well --

A. You know, I don't know whether you say it's changed. It is ambiguous in the way where it says where the response is just the HAM-D less than 8 or response is both of those put together. 04:19:05

Q. Well, what do we know response is? What was response? 04:19:09

A. I think that was the point that I was agreeing with you on. It is confusing here.

Q. Okay. Now, I asked you yesterday with regard to this article whether or not the secondary end-points had been defined what it called -- is it A-priority? 04:19:31

A. Yes.

Q. And I think you said that you did not believe that was true or you didn't recall?

MR. DAVIS: Objection; mischaracterizes 04:19:41

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the testimony. It stands as it is. If you want to ask another question and see if it's already been answered. 04:19:44

BY MR. MURGATROYD:

Q. Okay. That's fine. Were the secondary end-points, particularly the four that found in favor of Paxil to a statistical significance predefined? 04:19:48

MR. DAVIS: Objection; asked and answered.

THE WITNESS: They were not to the best of my knowledge predefined at the very beginning of the study. They certainly were predefined before we looked at the data. 04:20:22

BY MR. MURGATROYD:

Q. Would that fall under the category of A-priority? 04:20:33

A. Yes.

MR; DAVIS: Asked and answered.

THE WITNESS: Yes.

BY MR. MURGATROYD: 04:20:39

Q. In fact, two of the efficacy were not decided to be used until after the breaking of the blind. A statement saying that they were predefined would be incorrect? Is that correct?

MR. DAVIS: Object to the form. 04:20:46

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THE WITNESS: No. The question is you planned that analysis before you dredged the data, and that's certainly one of perfectly fair meanings of that priority. 04:20:48

If you go do a bunch of analysis and say these come out that's not A Priority. If you say I hypothesis in this area. Here's what we need to look at. You don't know what the data looks like. That's A priority. 04:21:03

BY MR. MURGATROYD: 04:21:16

Q. Okay. So if you don't even analyze the data until after the study is concluded and the blind is broken, what is that called?

MR. DAVIS: Objection to form.

THE WITNESS: Say it again. 04:22:01

MR. MURGATROYD: Can you read that one back, please.

(Record read.)

THE WITNESS: Well, but I'm sorry. The question still makes no sense, because you can't analyse the data until the blind is broken, and certainly there was no analysis of any data related to treatment assignment until the study was over. 04:22:01

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BY MR. MURGATROYD: 04:22:16

Q. Well, let me ask you this. In terms of -- what is the scientific definition of A priority?

A. Before the thing.

Q. And does that mean before the study is started? 04:22:26

A. No. I don't think so. I mean, my best understanding of the definition is no, that doesn't mean that at all.

Q. Have you heard it used that that's the proper way to use that term? It's before the study's started and not before the blind is broken? 04:22:39

MR. DAVIS: Object to form.

THE WITNESS: I have not heard it used that way. 04:22:46

BY MR. MURGATROYD:

Q. Would you agree that it would be improper to add an efficacy variable after the blind was broken without so disclosing it in the paper?

A. It seems like there's two parts to that. If you -- it would be improper? It would not necessarily be improper. 04:23:03

Q. You would have to disclose it though, correct? Isn't that called a post hoc analysis?

A. No. A post hoc -- you can make a few A priority hypothesis -- a post hoc analysis -- I do not think you're using -- I don't think that's what you're saying. Say it again. 04:23:18

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Q. Okay. Let's go back to the original question. 04:23:20

If you decide to use a secondary variable after the blind is broken for the first time, what is that called? 04:23:31

A. In general that would be called post hoc.

Q. Okay. And is it scientifically proper then to -- if you're going to use that in a paper to disclose that it was post hoc? 04:23:48

A. Yes.

Q. And would you agree that post hoc variables are less scientific than those that are predefined because you already know the answer when you declare it's a variable? 04:24:03

A. No.

Q. Okay. When -- let me ask you this: Do you still -- you know all the slides we talked about today in which you state that -- the slide states that Paxil is effective in the treatment of adolescents with major depressive disorder? Do you still give that lecture? 04:24:22

A. No. 04:24:26

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Q. Do you still use that slide? 04:24:35
A. No.
Q. Do you agree that if you would use that slide today knowing what you know now it would not by truthful? 04:24:50
MR. DAVIS: Object to the form.
THE WITNESS: I guess it depends on what you would say with the slide since the slide is just a prompt for discussion, but certainly I think that once you aggregate three studies up 04:24:52 the evidence for Paxil being efficacious is relatively weak.
BY MR. MURGATROYD:
Q. Okay. And Mr. Davis had you read reviewer comments from the JAMA reviewers, do you remember 04:25:13 that?
A. Yes.
Q. Okay. Do you recall the reviewers from JAMA -- actually, before we discuss that, JAMA is the Journal of? 04:27:03
A. The American Medical Association.
Q. And you originally submitted your article on 329 to that publication?
A. Yes.
Q. And that was rejected, correct? 04:27:13

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A. That's correct. 04:27:14
Q. And there were reviewer comments, correct?
A. Yes.
Q. Okay. Do you recall the comment, and I'll quote this. "This study could do more harm than 04:27:20 good unless the authors devote much more attention in their discussion to the fact that the bulk of the effect in this study was the result of good clinical management and not the medication"? Do you recall reading that, sir? 04:27:39
A. Yes.
Q. Okay. What does that criticism mean to you?
A. What it means is the people on placebo got quite a bit better and the people on medication in 04:27:46 this study by some, but not all of the measures, got statistically significantly even better than that.
Q. Do you agree that your study could do more damage than good?
A. No. That same criticism would apply to 04:28:07 every study that I'm aware of basically of antidepressant treatment certainly in children and most in adults that the response of people to placebo in terms of their clinical improvement is greater than -- is more than half of the response of 04:28:18

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the people on active medication. 04:28:20
Q. Well, actually this talks -- it doesn't talk about placebo. It says: Good clinical management.
A. That's what they were talking about, the 04:28:29 placebo group got good -- all of the groups including the placebo group got good clinical management.
Q. And what's good clinical management mean?
A. It's described in the paper. It's 04:28:33 basically more medication management. They were talked to my a human being who cared about them. They were asked how they were doing. They were given general non-specific advise.
Q. And do you agree, sir, that the majority 04:28:43 of cases of mild depression spontaneously resolve?
A. The majority of all cases of depression spontaneously resolve, but it's just that people suffer and have suicide and have bad functioning during the cases. 04:28:59
Q. I'm sorry? I never heard that before. All cases of depression? Does severe depression spontaneously resolve?
A. If you don't treat it for long enough other than the other chronic dysthymia, but you're 04:29:09

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talking about major depression so over time they all 04:29:11 have remissions and they all get better to the point where they all -- essentially all -- where they no longer meet major depression and then they get -- most all of them -- 70 percent plus get worse again. 04:29:20
Q. Okay. I'm talking about mild depression?
A. But that's the case for all depression. That would include mild depression. They all over time get better.
Q. Okay. Well, I'm just asking. I'm just 04:29:33 talking about mild depression. Do you agree that cases of mild depression spontaneously resolve?
A. I agree the cases of severe depression spontaneously resolve. Cases of moderate depression spontaneously resolve. Cases of psychotic 04:29:46 depression spontaneously resolve, and cases of mild depression.
Q. Okay. Now you were talking before about a -- like a relapse in depression and severely depressed, they get better and then get worse? 04:29:59
A. We know that for most depressions, 70 percent of -- in kids -- in children and adolescents have a recurrence over a five-year period.
Q. And is that for kids who are mildly depressed? 04:30:11

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A. There's no separate data that I'm aware of that would pull that out. 04:30:16

Q. Now, you're aware that kids that have killed themselves on Paxil, right.

MR. DAVIS: Object to the form. 04:30:35

THE WITNESS: I am aware that adolescents have -- who are depressed have killed themselves while being treated with Paxil.

BY MR. MURGATROYD:

Q. Okay. Are you aware of kids who were given Paxil for other reasons than depression who have killed themselves? 04:30:46

A. I'm not aware of it.

Q. Okay. Is that information that would be important to you? 04:31:01

A. Individual cases of -- the question of suicidal risks with all these compounds is overly important. Individual cases don't let you assess anything more about that risk, unfortunately. That's why it's been so hard to study. So as a human being, of course, it would be interesting to me. As a scientist, unfortunately, those are not informative as to whether Paxil was causable that. 04:31:13

Q. Well, do you agree that -- well, in your study you looked at whether or not -- or you were 04:31:16

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asked to determine whether or not a serious adverse event that you observed in your patient was related to the drug either possible, probably, definitely or not at all, correct? 04:31:16

A. Right. 04:31:39

Q. And is that something that there's criteria that's set up that you try to use to determine that?

A. No, unfortunately not.

Q. Well, actually, you've listed those in e-mails, haven't you? Different criteria for determining that? Didn't it list it in the protocol on how to do that? 04:31:50

A. Not to my knowledge.

Q. Well, is that because you didn't have any relationship with the patients in your study? 04:32:05

A. No.

Q. Well, are you aware of what an audit is to install a study by a drug company?

A. Yes. 04:32:16

Q. Are you aware that an audit was done on your site?

A. Yes.

Q. Have you seen the results of that audit?

A. No. 04:32:28

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(Ryan Deposition Exhibit No. 66 was marked for identification.) 04:32:29

Q. Let me show you what I'm marking as Exhibit 66, sir, and we'll be talking about the first paragraph of the third page that I'll be asking you to read into the record. 04:32:39

THE WITNESS: Could you read back your last question though, please.

MR. MURGATROYD: You can have the court reporter do that. 04:32:41

(Record read.)

BY MR. MURGATROYD:

Q. Well, so it's clear, no active participation in taking care of the patients in your study? 04:33:37

A. I'm sorry. You said was -- was my opinion in that matter because I did not have active participation?

Q. Yes.

A. It was not because of that. I answered no. 02:47:32

Q. Okay. Let's take a look at this document.

A. Yes. That is it.

MS. CONNELLY: Document 66 appears to be a SmithKline Beecham document subject to the 04:34:05

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protective order which the Plaintiff -- which Dr. Ryan has not seen before. 04:34:05

BY MR. MURGATROYD:

Q. Okay. And it is a document entitled "Confidential Final Report Investigator Audit Report", correct? 04:34:18

A. Yes.

Q. Okay. And it has a date, right? "Final Report Date" on the front page?

A. 9-11-98. 04:34:28

Q. So that was after the study was concluded, correct?

A. Yes.

Q. Okay. And if you'll turn to the third page. 04:34:35

A. Uh-huh.

Q. Top paragraph.

A. Yes.

Q. Will you read that into the record, please. 04:34:39

A. "The study was started at the site with only Dr. Ryan as the PI. One year into the study Dr. Birmaher was added as the co-PI."

Q. Not too fast.

A. "This action should have taken place 04:34:44

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sooner, as it appears that Dr. Ryan had no active role in the study. All assessments and study activities were performed by the study coordinators, Dr. Birmaher, and the other MD subinvestigators." 04:34:50

Q. Okay. And is that a true statement? 04:35:05

A. Yes. Essentially true. I did a little bit of covering for Dr. Birmaher, but only on vacations.

Q. Okay. Now, in Table three of your study Mr. Davis asked you about that table, I believe? 04:35:24

A. Yes.

MS. CONNELLY: Two minutes.

BY MR. MURGATROYD:

Q. Table three. Do you see that?

A. Yes. **04:35:41**

Q. And from reading that table, Doctor, can you tell how many adolescents tried to kill themselves on Paxil?

A. No.

Q. Okay. Mr. Davis asked you questions about 04:35:50 different letters that you responded to the editor regarding your article?

A. Yes.

Q. Is it true that Sally Laden, the outside medical writer, helped you with the bulk of the 04:36:14

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responses -- all of those with the exception of the 04:36:14 one you drafted in respect to Dr. Jureidini?

MR. DAVIS: Object to the form.

THE WITNESS: Ms. Laden helped with the first one. I don't remember whether she helped 04:36:28 with the second one.

BY MR. MURGATROYD:

Q. And is she a Doctor?

A. No.

MR. MURGATROYD: Thank you. I have no 04:36:31 further questions.

MR. DAVIS: Can I just have two follow-up questions, ma'am?

MR. MURGATROYD: Nope. A deal's a deal, dude. 04:36:46

MR. DAVIS: Is that all right?

MS. CONNELLY: Well, he did only have three hours and you had --

MR. MURGATROYD: That was the deal. We either go by the deal or not. 04:36:58

MR. DAVIS: Come on.

MR. MURGATROYD: Listen, Todd, I've had you do this to me too many times.

MS. CONNELLY: Listen. My analysis is if one of you two area going to go to a judge and 04:36:58

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ask for more time I'm going I want to put my 04:36:59 client in the best position to oppose such Motion. I told you all from the beginning I don't want to come back.

Now, he's only had three hours. If at 04:37:09 the end of the day what I'm left with if he goes to the judge and says, Judge, I tried to help this along. I only got three hours. Would have had more cushion if we would have started on time. 04:37:16

MR. MURGATROYD: Now, wait a minute. The cushion hurt me not Mr. Davis. It started late. That took away from my time.

MS. CONNELLY: That's true.

MR. MURGATROYD: That did not take away 04:37:28 from Mr. Davis' time.

MS. CONNELLY: You're right.

MR. MURGATROYD: We had and an agreement. We either hold to the -- did he agree to the agreement? 04:37:31

MS. CONNELLY: Yes.

MR. MURGATROYD: Good. Then I insist that we hold to the agreement or I got another 50 questions and I'll take it to another day.

MR. DAVIS: Come on. Come on. 04:37:37

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MS. CONNELLY: You're not going to insist 04:37:37 on anything.

MR. DAVIS: Come on, Skip.

MS. CONNELLY: This attitude of I'm going to do what I want doesn't lie. You don't have 04:37:41 that power. Don't dilute yourself. You don't have the power to --

MR. MURGATROYD: I can subpoena this witness any time I want.

MR. DAVIS: Come on. 04:37:59

MS. CONNELLY: Well, I hope it's an effective subpoena next time. He's doing his civic duty. He's here. He's produced thousand of pages of documents. We could have had the two questions done by now. 04:38:01

MR. MURGATROYD: Are you going to hold to the deal or not? That's all I want to know?

MR. DAVIS: For two questions that will take two minutes?

MR. MURGATROYD: No, because then I'll 04:38:11 have questions after that and then we go on -- and you did it to me in Philadelphia and it pissed me off and I'm not going to allow it again.

MR. DAVIS: Skip -- 04:38:18

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MR. MURGATROYD: You were on. You said an hour and a half. You went on for three hours, Todd. 04:38:20

MR. DAVIS: Skip, you gave --

MR. MURGATROYD: I refuse to be put in that position again, because I agreed to knock out over 30 questions for Mr. Mccafferty because of your representations. 04:38:20

MR. DAVIS: You're absolutely distorting what happened. Okay? 04:38:33

MR. MURGATROYD: You came to that deposition. You said you had a day and then it went into three days. You had three days. I had a few hours. Come on. Be realistic.

Todd, I've -- 04:38:37

MR. DAVIS: You've asked the question that --

MR. MURGATROYD: I'm not going to argue about it. The record will make it very clear that -- 04:38:44

MR. DAVIS: Then you --

MR. MURGATROYD: I move to strike all of your testimony after we stipulated on the record how long you would go.

MR. DAVIS: We didn't stipulate on the 04:38:52

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record. We outlined what was going to happen in order to get the deposition complet4ed. 04:38:52

MR. MURGATROYD: Pam, Doctor, we had an agreement. I insist that it be held by. If Todd wants to come back to ask his two questions you can do that. I will not participate in that. 04:39:05

MS. CONNELLY: We could also, Todd, you could call me and we could talk about doing an affidavit or we could do it here right now in front of everybody. I mean, we don't want to do that. 04:39:16

MR. DAVIS: What are you afraid of? What are you afraid of?

MR. MURGATROYD: Because you'll start asking questions and then I'm going to want to ask questions and then all of a sudden I'm going to be told by Counsel here, I'm sorry, Mr. Murgatroyd. Your time is long up. 04:39:24

MR. DAVIS: If I take five minutes, will you allow Mr. Murgatroyd ten minutes? 04:39:33

MR. MURGATROYD: And then it --

MS. CONNELLY: I'm not going to -- I could let you do five and five. That's it.

MR. MURGATROYD: I don't agree to break 04:39:46

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the agreement. I've listened. I've gauged this deposition on exact time frames. 04:39:46

MR. DAVIS: You did not. You did not.

MR. MURGATROYD: What are you talking about? Have I abided by the time frames that you set forth in your letter? 04:39:50

MR. DAVIS: Come on. We're talking ten minutes.

MS. CONNELLY: I'm thinking.

MR. DAVIS: We're talking ten minutes. 04:40:09

MS. CONNELLY: Let me talk to my client for a second.

VIDEOGRAPHER: We are now going off the record at 4:41 p.m.

(Recess taken) 04:40:18

VIDEOGRAPHER: We're now back on the record. The time is 4:43 p.m. Please proceed.

MS. CONNELLY: The parties had prior to the deposition reached an agreement as to the time that would be allowed for Dr. Ryan's depositions. 04:41:48

The deposition has proceeded substantially in accordance with the agreement; that being said, the defense agreed to a significantly shorter period of time than the 04:42:05

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Plaintiff was allowed. I think the difference was 11 hours versus 3 hours. 04:42:09

In light of that allocation of time I'm going to allow the witness to be questioned by the Defense five minutes and the Plaintiff five minutes. I understand the Plaintiff says he objects to this. If he chooses to waive the opportunity to his five minutes then he chooses to waive that opportunity and the parties to this case can fight it out with the Judge once we have left. So you have five minutes, Mr. Davis and you have five minutes Mr. Murgatroyd. 04:42:18

MR. MURGATROYD: So the record's is absolutely clear I object to this. This is a breach of the agreement. I move to strike any testimony that is taken after this moment, and to agree that any testimony is allowed after this I will go back to the Court and re-open up this deposition for at least one to two more days. 04:42:29

MR. DAVIS: You know, in fairness Skip, you covered an issue with the witness that was not covered during your multiple hours, and to let me leave and not allowing me to ask questions about that when you did not go into 04:42:58

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it -- 04:43:01
MS. CONNELLY: Gentlemen, let's go. Let's go.
MR. MURGATROYD: My objection is on there and we will take it up with our Judge in Orange 04:43:16
County, California.
MS. CONNELLY: The threaten of a punitive two-day additional deposition of the witness is improper. Let's go.
MR. MURGATROYD: That's your opinion. 04:43:24
That's how many more days I think I need with this witness and I have a lot of cases I can do --
MS. CONNELLY: It's funny that you bring that up in anger at the end of this deposition 04:43:26
when you're unhappy about this additional five minutes.
MR. MURGATROYD: Mo. It's because Mr. Davis also went into areas that I did not discuss at all with the doctor so we'll discuss 04:43:37
that with the Judge. That's why we have judges.

EXAMINATION

BY MR. DAVIS:

Q. Dr. Ryan, with respect to the article that 04:43:39

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you coauthored that discussed the results of Study 04:43:41
329, do you believe that article clearly outlined what were the secondary -- excuse me -- do you believe the article that was published on the results of Study 329, which you authored clearly 04:43:59
outlined what was a primary end-point for the study?

A. Yes.

Q. Now, how many places in the article is the primary end-point discussed?

A. At least quite clearly. 04:44:16

Q. When someone reads the article from beginning to end, including the tables, do you believe that article is in any way misleading or confusing to anybody about the primary end-points of Study 329? 04:44:29
MR. MURGATROYD: Objection; asked and answered.
THE WITNESS: It was certainly not our intention to mislead people. I think it is particularly clear, because it is in the 04:44:39
abstract as well as later. So I think that it -- I think that finding those things and -- I think we did a good job about being clear about that.
Q. So if a physician reads that article from 04:44:46

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beginning to end including that data that's in the 04:44:48
table two as well as a description twice of what is a primary end-points, do you believe that article is confusing or misleading or wrong in any way about what are the primary end-points? 04:45:11

A. No, I do not.

MR. MURGATROYD: Objection; leading.
THE WITNESS: No, I do not.
MR. DAVIS: Thank you, Doctor.
MR. MURGATROYD: Sorry you broke your 04:45:20
agreement. We're going off the record. Doctor, I'll probably see you again. Thank you very much.
MS. CONNELLY: No. On the record. Mr. Murgatroyd has waived his opportunity for his 04:45:24
additional five minute rebuttal testimony of Dr. Ryan.
Dr. Ryan, you have the right to review your testimony for any errors, typographical or substantive and send it back or you can waive 04:45:33
your signature.
MR. MURGATROYD: Actually, that's not California law. There's a standard stipulation we use in all these cases.
MS. CONNELLY: We're not stipulating to 04:45:48

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anything that's standard. We are under the 04:45:48
Federal Rules of Civil Procedure and --
MR. DAVIS: He's kind of in a box as I would be in trying to preserve the original. It's a minute stipulation. 04:45:52
MS. CONNELLY: He still gets the opportunity to review his deposition, correct?
MR. DAVIS: Of course.
MR. MURGATROYD: By stipulation. Stipulation between Counsel. Between Party of 04:46:13
Counsel is that under the code in California we're going to relieve the court reporter of her duties, which requires her to maintain the original. So we are relieving her of those
duties. She is going to send me the original. 04:46:26
She will send -- I think it can either go to Todd first or to you first for the Doctor's review and signature. Which would you care?
MS. CONNELLY: Well, me. Todd --
MR. MURGATROYD: Well, Todd's going to end 04:46:41
up with your copy unless you're going to keep a copy. Are you going to order a copy?
MS. CONNELLY: I may to put with this file. Like I said, I was on the tail one this.
So send me Dr. Ryan's transcript and I'll 04:46:48

forward it to him. 04:46:58
MR. MURGATROYD: Right. And it's going to be agreed that within 30 days of him making any changes you're going to notify me?
MS. CONNELLY: Yes. 04:47:03
MR. DAVIS: Okay. You can do that either directly or through Mr. Davis.
MS. CONNELLY: So do I -- normally you send the errata sheet back to the court reporter? 04:47:14
MR. MURGATROYD: No, that goes -- that's why we're doing -- in California we do it a little bit different.
MS. CONNELLY: Okay. If there's any other instructions you can just send me a letter. 04:47:20
MR. MURGATROYD: And also as part of the stipulation is for any reason the original is lost a certified copy can be used at time of trial.
MR. DAVIS: So stipulated. 04:47:24
MS. CONNELLY: So stipulated.
VIDEOGRAPHER: That now concludes this Video Deposition. The time is 4:48 p.m.
(Ending time: 4:28 p.m.)

REPORTER'S CERTIFICATION

I, Michele Kohar, Court Reporter certify; that the foregoing proceedings were taken by me at the time and place therein set forth;at which time the witness was put under oath by me;

That the testimony of the witness, the questions propounded, and all the objections and statements made at the time of the examination were recorded stenographically by me and were thereafter transcribed;

That the foregoing is a true and correct transcript of my shorthand notes so taken.

I further certify that I am not a relative or employee of any of the attorneys of the parties, nor financially interested in the action.

I declare under penalty of perjury under the laws of Pennsylvania that the foregoing is true and accurate.

Dated this 7th day of September, 2006.

M

Y