

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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IN RE: CELEXA AND LEXAPRO) MDL NO. 2067
MARKETING AND SALES PRACTICES) Master Docket No.
LITIGATION) 09-MD-2067-(NMG)
)
PAINTERS AND ALLIED TRADES) Case No. 13-CV-13113
DISTRICT COUNCIL 82 HEALTH) (NMG)
CARE FUND, A THIRD-PARTY)
HEALTHCARE PAYOR FUND, on) Hon. Nathaniel Gorton
behalf of itself and all)
others similarly situated,) Hon. Marianne Bowler
Plaintiffs,)
v.)
)
FOREST PHARMACEUTICALS, INC.,)
and FOREST LABORATORIES, INC.,)
Defendants.)
-----)
IN RE: CELEXA AND LEXAPRO) MDL NO. 2067
MARKETING AND SALES PRACTICES) Master Docket No.
LITIGATION) 09-MD-2067-(NMG)
DELANA S. KIOSSOVSKI and) Hon. Nathaniel Gorton
RENEE RAMIREZ, on behalf of)
themselves and all others) Case No.
similarly situated,) 14-CV-13848 (NMG)
Plaintiffs,)
v.) Hon. Nathaniel Gorton
)
FOREST PHARMACEUTICALS, INC.) Hon. Marianne Bowler
and FOREST LABORATORIES, INC.,)
Defendants.)
-----X

VIDEOTAPED DEPOSITION OF THOMAS LAUGHREN, M.D.

ROCKVILLE, MARYLAND

FRIDAY, JANUARY 27, 2017

9:08 A.M.

1 Deposition of THOMAS LAUGHREN, M.D., held at the:

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HILTON HOTEL

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1750 Rockville Pike

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Rockville, Maryland 20852

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12 Pursuant to notice, before Leslie Anne Todd, Court

13 Reporter and Notary Public in and for the State of

14 Maryland, who officiated in administering the oath to

15 the witness.

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1 A P P E A R A N C E S

2

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1 P R O C E E D I N G S

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3 THE VIDEOGRAPHER: We are now on the
4 record. My name is Larry Newman. I am a
5 videographer for Golkow Technologies. Today's date
6 is Friday, January 27th, 2017. And the time is
7 9:08 a.m. This video deposition is being held in
8 Rockville, Maryland, In re Celexa and Lexapro
9 Marketing and Sales Practices litigation, Master
10 Docket No. 09-MD-2067-NMG. This is in the United
11 States District Court for the District of
12 Massachusetts.

13 Our deponent today is Dr. Thomas
14 Laughren.

15 Counsel will be noted on the stenographic
16 record.

17 And our court reporter today is Leslie
18 Todd, also with Golkow Technologies, and will now
19 swear in the witness.

20 THOMAS LAUGHREN, M.D.

21 having first been duly sworn, was
22 examined and testified as follows:

23 EXAMINATION BY COUNSEL FOR PLAINTIFFS

24 BY MR. WISNER:

1 Q Good afternoon. My name is Brent
2 Wisner --

3 A Good morning.

4 Q -- and I represent the plaintiffs in this
5 class action, multidistrict litigation.

6 Can you please state your name and spell
7 your last for the record.

8 A Thomas Laughren, L-A-U-G-H-R-E-N.

9 Q What is your current address?

10 A 4709 Kemper Street, Rockville, Maryland
11 28053.

12 Q Have you ever been deposed before?

13 A Yes.

14 Q How many times?

15 A Three.

16 Q And what were the circumstances of those
17 depositions?

18 A When I left FDA, I did some -- some legal
19 work on various cases, and so two of those
20 depositions were for -- on Forest cases and one was
21 for another company.

22 Q Are those the only times you've
23 participated in a deposition?

24 A To my knowledge. I mean, you know, I was

1 at the VA many years ago before I started at FDA,
2 and I did testify a couple of times in cases. I
3 don't honestly recall doing a deposition, but I
4 know that -- that I was in court on several cases,
5 so I...

6 Q And for those three depositions that you
7 did just mention, did all of those occur after your
8 time at the FDA?

9 A Yes. Yes.

10 Q Okay. And you mentioned two of them were
11 in cases involving the Defendant Forest
12 Pharmaceuticals?

13 A Yes.

14 Q Was one of those cases -- did both of
15 those cases involve pediatric suicide?

16 A Yes.

17 Q And for the other case, was that in a
18 case involving Zoloft or sertraline?

19 A Yes.

20 Q And that was for Pfizer; is that right?

21 A That's correct.

22 Q Okay. So other than those three
23 depositions, you don't -- you don't know of any other
24 depositions -- depositions that you've participated

1 in after your time at the FDA?

2 A No.

3 Q You understand that you're under oath
4 today, right?

5 A I -- I do.

6 Q What is your understanding of that oath?

7 A My obligation is to -- is to tell the
8 truth.

9 Q All right. You also understand that this
10 video -- this deposition is being videoed.

11 Do you understand that?

12 A I do.

13 Q And do you also understand that portions
14 of this video may be played before a jury should this
15 matter proceed to trial?

16 A I do.

17 Q Okay. Since you've participated in a
18 deposition before, I won't go through all of the
19 ground rules, but there are a few things I want to
20 stress.

21 First, if at any time during this
22 deposition I ask a question you don't understand, and
23 that will happen, please ask me to rephrase. Okay?

24 A (The witness nods.)

1 Q We need a verbal answer. That's
2 another --

3 A Oh, yes. Yes. Yes.

4 Q Okay, great.

5 And if you don't understand my question,
6 I'm going to assume that you're going to ask me to
7 clarify until you do. Is that okay?

8 A Yes.

9 Q Now, with that understanding and
10 agreement, if I do ask you a question and you do
11 answer, I'm going to assume you understood it and are
12 answering my question. Okay?

13 A I understand.

14 Q All right. The other important thing is
15 during the course of this deposition, defense
16 counsel, your attorney, as well as the attorney who
17 are present from the FDA may object.

18 You understand that?

19 A Yes.

20 Q The purpose of those objections are to
21 preserve the record, and conceivably at some point a
22 judge will rule on those objections.

23 You understand that?

24 A I understand.

1 Q However, unless your attorney
2 specifically instructs you not to answer a question,
3 I'm going to expect from you an answer to the
4 question. So I'm going to generally ignore
5 objections and keep looking at you.

6 A I understand.

7 Q I'm not trying to stare you down. I'm
8 just getting into the zone. I don't want to be
9 disturbed by objections, okay?

10 All right. Is there any medical
11 condition or medication which would prevent you from
12 giving your best testimony today?

13 A No.

14 Q Is there anything that would prevent you
15 from being able to provide truthful answers to any of
16 my questions?

17 A No.

18 Q Specifically, do you have any contractual
19 agreements with the defendant that you're aware of
20 that would prevent you from being fully honest in
21 your testimony today?

22 A No.

23 Q Are you currently employed or retained or
24 being compensated by Forest Pharmaceuticals or its

1 current iteration, I think it's Allergan?

2 A I don't -- I'm not -- I've terminated
3 my -- my consulting relationship with Forest, now
4 Allergan.

5 I -- my attorney is being -- is being
6 reimbursed by Forest. So I'm not paying for my own
7 representation here, but I'm not being paid for --
8 for my time here today.

9 Q Sure. And I appreciate that answer, and
10 that clears up a question I was going to ask you
11 later.

12 A But let me also clarify.

13 I -- I do -- I do consult for Allergan on
14 drug development issues. Now, I don't -- it's not a
15 direct relationship with -- with Allergan. I work --
16 part of what I do is I work for Massachusetts General
17 Hospital, they have a clinical trials network, and so
18 I'm actually a salaried employee of that -- of that
19 company. And they -- and they have contracts with
20 various drug companies. And so I consult with
21 Allergan as an employee of Mass General. So I'm
22 not -- it's not a direct relationship with -- with
23 Allergan. I'm paid as a salaried employee for -- for
24 the work that I do. So...

1 Q Okay, great.

2 Do you have any operate -- in operation
3 contracts with Allergan that you're aware of today?

4 A No. I mean, I -- I -- basically, you
5 know, for a couple of years when I left FDA, I did
6 work on these few cases for Forest. In I think
7 August of 2015, I let the attorney representing
8 Forest know, John Asaro (phonetic), that I wouldn't
9 be doing any -- any further work on those, and so
10 that was -- that was basically the end of it.

11 Q Are you doing any sort of expert
12 consulting in a litigation capacity for Forest
13 anymore?

14 A No.

15 Q Okay. Are you doing that in a capacity
16 for other pharmaceutical companies?

17 A No, I -- I've basically -- you know, I
18 did that for a couple of years. I've -- I've moved
19 on. I've let, you know, the two companies that I was
20 actively working with, I let -- Forest and Pfizer, I
21 let them know that I wasn't doing that anymore.

22 Q And why did you stop doing it?

23 A Because my primary interest is -- is in
24 psychiatric drug development. That's -- that's what

1 I prefer doing. I'm busy enough with that, you know,
2 to keep me occupied, and so I -- that's what I prefer
3 to do.

4 Q Was there any falling out with Forest?

5 A No.

6 Q Okay.

7 A No.

8 Q Are you familiar with any of the
9 allegations in this lawsuit?

10 A I -- just very briefly, Mr. Ellison --
11 you know, I met with Mr. Ellison last week for about
12 two hours to talk about, you know, today, and what
13 might come up. And so I'm -- you know, I'm vaguely,
14 vaguely familiar with the case, but not -- honestly,
15 not the -- not the details.

16 Q What is your general understanding of the
17 allegations in this case?

18 A My understanding is -- is that it has to
19 do with, you know, an allegation of false marketing
20 practices.

21 Q And you understand it relates to the
22 antidepressants Celexa and Lexapro?

23 A Correct.

24 Q Celexa, that's the brand name for

1 citalopram, correct?

2 A Correct.

3 Q And Celexa is an SSRI, or selective
4 serotonin reuptake inhibitor, correct?

5 A That's correct.

6 Q And Lexapro, that is the brand name for
7 escitalopram, correct?

8 A Yes.

9 Q And that's also an SSRI?

10 A That's correct.

11 Q All right. So you mentioned a second ago
12 that you met with your attorney for two hours last
13 week. Do you remember -- do you remember what day
14 that was?

15 A I think it was Wednesday, January 18th, I
16 think.

17 Q Okay. And that was a two-hour meeting?

18 A Roughly two hours, yes.

19 Q Okay. Have you had any other meetings,
20 substantive meetings with your counsel in preparation
21 for your testimony today?

22 A No, I -- I had several phone
23 conversations with Mr. Ellison, but, you know, mostly
24 about procedural issues, whether or not the

1 deposition was going forward and so forth.

2 Q Okay. Do you know when generally
3 Mr. Ellison started representing you in this
4 litigation?

5 A It was sometime in the fall, probably
6 October. I signed a retainer agreement. I don't --
7 I don't have the exact date of that.

8 Q That's fine.

9 Now, prior to Mr. Ellison's
10 representation of you, you were represented by a
11 different attorney. Do you recall?

12 A Well, Mike -- Mike Geoke is -- is the
13 person that I called, and I think he may have
14 interacted with you about the -- again, the details
15 of setting up the deposition. So I had one or two
16 conversations with him.

17 Q Okay. Mr. Geoke, was he being -- was his
18 time being compensated for by Forest or --

19 A No, no, he didn't charge anything. It
20 was just very minimal, so he didn't -- no. If there
21 would have been any payment, it would have been from
22 me, but he didn't charge me.

23 Q And then subsequent to Mr. Geoke
24 representing you, Mr. Ellison started representing

1 you; is that right?

2 A That's right.

3 Q And Mr. Ellison is being compensated by
4 Forest for his time; is that right?

5 A That -- that's my understanding, yes.

6 Q Okay. Have you spoken with anybody at
7 Forest about your deposition today?

8 A Not about Forest. I spoke with -- with
9 Kristin, I think just once back in probably
10 September, October, something like that.

11 Q Okay. And during that conversation --
12 was it by phone?

13 A Yes.

14 Q And was Mr. Ellison present?

15 A No, no, no. No, that was just Kristin
16 and myself.

17 Q Okay. What did you guys talk about?

18 A Just about whether or not -- it was
19 procedural. It was about whether or not the
20 deposition was going to go forward. That, you know,
21 Forest was going to try to stop it, so...

22 Q Mm-hmm. Did you talk about any of the
23 substance of this case with Ms. Kiehn?

24 A I -- I don't -- again, that was -- that

1 conversation was probably back in late September. I
2 don't -- I don't recall talking about the case.

3 Q Okay. Did you look at any deposition
4 transcripts of any of the witnesses that have been
5 deposited in this litigation?

6 A No.

7 Q Okay. Did you review any of the
8 deposition transcripts of your prior testimony?

9 A When -- when Mr. Ellison and I met last
10 week, he showed me a deposition transcript from one
11 of my depositions on the Forest case.

12 Q And was that the Brown case?

13 A Yes.

14 Q Okay. And did you review the entire
15 deposition or just a portion of it?

16 A Just a small expert -- excerpt of it.

17 Q Okay. Did you review any other documents
18 during that meeting with Mr. Ellison?

19 A There were several documents. A memo
20 that I had written on the -- on the Celexa
21 supplement. A memo that had been written by the
22 medical reviewer, Dr. Earl Hearst. There were a
23 couple of other documents. I don't offhand recall
24 what they were.

1 Q Do you recall if you looked at a legal
2 filing with him?

3 A A legal filing?

4 Q Yeah, like a motion that had been filed
5 in this case, specifically in regards to your
6 deposition.

7 A I think -- I think I -- again, I -- I
8 believe that's the case, but there were -- there were
9 several documents. I mean, I --

10 Q Sure. And I just -- to the best of your
11 recollection, so if you recall --

12 A I -- I think -- I think there was a legal
13 document that -- that he showed me, yes.

14 Q And did you also review a legal document
15 that was prepared by Forest?

16 A They -- no. I mean, Forest didn't send
17 me any -- any documents to -- to look at.

18 Q Okay.

19 A I -- I got -- I got a subpoena to
20 testify. That -- that's the document that I --

21 Q Okay. So you looked at the subpoena; is
22 that right?

23 A Well, I was -- I was -- it was delivered
24 to me.

1 Q Sure. Sure. Fair enough. And let me
2 ask you a more direct question.

3 Do you recall one way or the other
4 whether or not you reviewed the motion to compel your
5 deposition that was filed by my law firm in this
6 litigation?

7 A I -- I don't believe that I ever saw that
8 document.

9 Q Okay. Thank you.
10 Have you been given any instruction or
11 direction from Forest about what you should or should
12 not testify about today?

13 A No.

14 Q So the testimony you're giving today then
15 is going to be testimony that you yourself believe to
16 be true; is that right?

17 A Whether -- whether -- you know, whether I
18 was working for Forest or working for FDA or working
19 for nobody, my testimony would be the same.

20 Q That's good to hear.

21 (Exhibit No. 1 was marked for
22 identification.)

23 BY MR. WISNER:

24 Q I'm handing you what I've marked as

1 Exhibit 1 to your deposition.

2 Give it one second for the copies to be
3 distributed.

4 This appears to be a copy of your
5 curriculum vitae that you brought with you today; is
6 that right?

7 A That's correct.

8 Q Is this a fair and accurate copy of that
9 CV?

10 A It appears to be, certainly.

11 Q And do you think this fairly captures and
12 reflects your educational work history?

13 A Yeah. No, I updated this this month, so
14 this is -- this is very current.

15 Q So you haven't changed any jobs in the
16 last month that you're aware of?

17 A No.

18 Q Okay.

19 A No.

20 Q All right. Well, let's -- could you
21 briefly explain to the jury your sort of educational
22 background as it pertains to medicine.

23 A I'm a -- a physician. I went to medical
24 school at University of Wisconsin, and then I did a

1 residency in psychiatry, also at the University of
2 Wisconsin.

3 Q Following your residency, what did you do
4 in your career?

5 A My first position was at -- at the VA in
6 Providence, and I was also on the faculty of Brown
7 University. I did that -- I started that position in
8 I think probably late July of 1974. I finished my
9 residency in June of that year. I worked at -- at
10 the VA and at Brown for roughly nine years, and I
11 left there in -- in September of 1983 and went to
12 work at the FDA.

13 Q And during that time that you were
14 working at the VA and with Brown University, were you
15 treating patients?

16 A I was, yes.

17 Q And were you treating patients in your
18 capacity as a psychiatrist?

19 A Yes.

20 Q And during that time, were you treating
21 patients with various pharmaceutical agents?

22 A I was.

23 Q When you left the FDA in 1983, why did
24 you make that decision?

1 A I was very interested in -- in
2 psychopharmacology and in clinical trials. And, you
3 know, FDA was the place where, you know, all of this
4 happens. You know, the FDA works with companies on
5 their development programs, and so I wanted to give
6 that a try.

7 MS. KIEHN: Brent, can I clarify for the
8 record, I think you misspoke. You asked him "When
9 you left the FDA in 1983..."

10 MR. WISNER: I'm sorry.

11 MS. KIEHN: Did you mean to say the VA?

12 BY MR. WISNER:

13 Q Sorry, when you left the VA in 19 --

14 A Oh, that's the way I understood your
15 question. I'm sorry.

16 MS. KIEHN: Just to make sure we're
17 clear.

18 MR. WISNER: We're connected here.

19 Thank you for that correction, Ms. Kiehn.

20 BY MR. WISNER:

21 Q The -- prior to your joining the FDA,
22 were you aware if there were any SSRIs on the market
23 at that time?

24 A There were no SSRIs at the time.

1 Oh, at the time I left the VA?

2 Q Yes.

3 A No, that was -- that was pre-SSRI.

4 Q So the first SSRI that I'm aware of was
5 Prozac; is that right?

6 A That's correct.

7 Q And that was approved after you arrived
8 at the FDA.

9 A That was -- that was late '80s. That was
10 probably '87, something like that.

11 Q Were you at all involved with the
12 approval or review of Prozac?

13 A Very much so, yes.

14 Q Okay. And subsequent to Prozac, there's
15 been a host of other SSRIs that have been approved by
16 the FDA; is that right?

17 A That's correct.

18 Q Some of those include Paxil, Zoloft,
19 Celexa, Lexapro.

20 Are you aware of those?

21 A Luvox.

22 Q Luvox.

23 Would it be fair to say that during your
24 time at the FDA, you were involved in some capacity

1 with the approval or review of all of those SSRIs?

2 A Every one of them, because I was -- about
3 three years after I started at FDA, I became team
4 leader for psychopharmacology in the division of
5 neuropharmacological drug products, and so I was
6 involved with -- with every -- every psychiatric drug
7 development program.

8 Q And that also includes, I assume,
9 antipsychotics as well?

10 A Absolutely.

11 Q Now, the most recent SSRI that I'm
12 familiar with that's been approved is -- you can
13 correct me if I'm wrong, you probably know better
14 than me -- but is it Viibryd?

15 A Vilazodone. It's a --

16 Q Vilazodone.

17 A -- it's not a -- is not an SSRI. It's a
18 much more complicated product. It has other -- it
19 has some -- some serotonin reuptake activities, but
20 it also has some other activities, 5-HT_{1A} and so
21 forth. It's not -- it's not considered an SSRI,
22 although it has -- it has effects on the serotonin
23 transporter which is characteristic of the SSRIs, but
24 it's a more complex drug.

1 Q Okay, great. And you were at the FDA for
2 29 years; is that right?

3 A That's correct.

4 Q Can you brief -- briefly explain to the
5 jury the various posts that you held while you were
6 at the FDA.

7 A So when I started at FDA, I was a -- a
8 clinical reviewer in the division of
9 neuropharmacological drug products, and I was -- you
10 know, my job then was to review IND and NDA
11 applications that came in.

12 As I mentioned, after about three years,
13 I became the team leader for psycho -- psychiatric
14 drugs, psychopharmacology in the division. And then
15 I -- I oversaw the reviews done by -- by primary
16 clinical reviewers. And I did -- I was in that
17 capacity roughly, you know, from probably 1986
18 through 2005, when I became division director. At
19 that point the neuropharm division split into
20 psychiatry and neurology, and -- and so I became then
21 the director of that newly formed division.

22 Q When you were a team leader -- sorry,
23 strike that.

24 When you were a clinical reviewer, were

1 you reviewing -- you said INDs and NDAs, right?

2 A Yes.

3 Q Can you just explain to the jury what IND
4 and NDA are?

5 A Okay. An IND is -- it stands for
6 investigational new drug application. So when a --
7 when a drug company wants to -- it has a product that
8 it's developing for human use and wants to introduce
9 it into humans for the first time, they -- they have
10 to submit what's called an IND application to get,
11 you know, approval from FDA to go ahead and -- and do
12 a human study. So, you know, that -- that's the
13 first interaction with the company.

14 When a company has -- has completed a
15 program and is ready to, you know -- you know, and
16 wants FDA to consider approving its drug, it's a new
17 drug application, an NDA. Excuse me.

18 Q And is it your understanding that the
19 approval of an NDA is required before a drug company
20 is allowed to sell or market the drug in that sense?

21 A Yes.

22 Q Are you also familiar with something
23 called an SNDA?

24 A That's a supplemental NDA. So -- so

1 once -- once a drug is approved for one indication,
2 if a company wants to -- to get it approved for a
3 different indication, it submits what's called a
4 supplemental NDA.

5 Q In your experience at the FDA, do the
6 same rigorous scientific principles apply to an IND,
7 an NDA or an SNDA?

8 A Yes.

9 Q Now, you said in 1986 you became a team
10 leader; is that right?

11 A That's correct.

12 Q And in that capacity you oversaw clinical
13 reviewers; is that right?

14 A That's correct.

15 Q Did you also conduct clinical reviews
16 yourself?

17 A I did some reviews myself as well.

18 Q And when you say you oversaw other
19 clinical reviews, what did that sort of entail?

20 A You know, basic -- basically the primary
21 reviewers that I -- that I oversaw had primary
22 responsibility for -- for doing a review on an
23 application, whether it was an IND or NDA, and I
24 would -- I would basically supervise them in their

1 review of that. So I would -- I would talk to them
2 about the progress of their review, I would look at
3 drafts of their reviews, and then I would sign off
4 on the -- on the ultimate review that they would
5 write.

6 Q And would you frequently prepare a
7 memorandum summarizing the clinical reviews that you
8 had seen on a compound?

9 A Yes. Yes.

10 Q And in preparing those memorandums, did
11 you rely upon the accuracy and validity of the
12 clinicals reviews done by the reviewers at the FDA?

13 A I -- I did, but I also very often looked
14 at -- at primary documents myself.

15 Q And when you say "primary documents," are
16 you talking about documents that were submitted by
17 the drug sponsor --

18 A Yes.

19 Q -- for the application?

20 A Yes. Either, you know, in the case of an
21 NDA, you know, NDA -- primary NDA documents or in the
22 case of a supplement, you know, the application
23 itself.

24 Q Now, the decision to ultimately approve

1 an NDA or an SNDA or even an IND, who within the FDA
2 makes that final decision?

3 A It -- it depends on -- on the particular
4 application. A division director, you know, makes
5 some of those decisions.

6 So, for example, you know, an IND
7 application, ultimately the division director would
8 decide on whether or not that could go forward. A
9 supplemental NDA, also a division director could do.
10 But a new drug, a completely new entity, would
11 ordinarily be signed out by the office director.

12 Q Okay. But supplemental NDAs, that would
13 typically be approved by the division director?

14 A That's correct.

15 Q So starting in 2005, when you became a
16 division director, you started being the sort of
17 final stamp of approval for SNDAs; is that right?

18 A That's -- that's correct.

19 Q Okay. Prior to that, when you were a
20 team leader, did you make recommendations to the
21 division --

22 A Yes.

23 Q -- director about whether or not an
24 application should be approved or not?

1 A Yes.

2 Q Okay. During your time as team leader
3 between 1986 and 2005, who was your division director
4 or directors?

5 A Paul Lieber was -- was the division
6 director for most of that time. He left FDA, I think
7 probably in the -- in the late '90s, maybe '99. I
8 don't exactly recall.

9 At that point Dr. Russell Katz became
10 the -- you know, the division director, and he was --
11 he was the division director until 2005 when that
12 division, the division of neuropharmacological drug
13 products, split into neurology and psychiatry.

14 Q Are you familiar with Dr. Temple?

15 A Well, Dr. -- Dr. Temple was the office
16 director. So -- so it -- it's a little bit
17 complicated, but the structure of FDA -- so you
18 have -- you have offices that are the next management
19 level above divisions.

20 Q Okay.

21 A And each office is responsible for
22 several review divisions. So, for example, ODE 1,
23 Office of Drug Evaluation 1, which -- which
24 Dr. Temple directed for many, many years, you know,

1 had responsibility for, you know, psychiatry,
2 neurology and cardiorenal.

3 So that's the three divisions that fall
4 under that office.

5 Q And from my understanding, there's
6 actually five offices, right, at FDA?

7 A I -- I believe that's right, five
8 offices.

9 Q And then within each office, you have
10 various divisions, right?

11 A That's correct.

12 Q And between 2005 through 2013, when
13 you -- 2000 --

14 A 2012.

15 Q 2012, when you departed the FDA, you were
16 the division director for the -- what's the title of
17 that division?

18 A The division of psychiatry -- psychiatric
19 drug products.

20 Q Okay, great.

21 Okay. I'm now going to ask you a couple
22 of questions generally about your experience at the
23 FDA and general issues related to scientific
24 investigation.

1 In your personal opinion, do you believe
2 that the FDA is solely responsible for ensuring that
3 drugs are safe and effective?

4 A That -- that is one of its -- its primary
5 missions.

6 Q Do you believe that that responsibility
7 is shared with anyone else?

8 A Well, I -- I think -- I think drug
9 companies also have that responsibility.

10 Q Why would you say that?

11 A Because, you know, we're all in this
12 process together. You know, we all have
13 responsibility for -- for doing rigorous scientific
14 work.

15 Q And during your time with the FDA, is it
16 fair to say that you frequently interacted with
17 members or drug sponsors; is that right?

18 A That -- I mean that's the way the process
19 works. So, as you know, FDA doesn't develop drugs,
20 drug companies develop drugs. And FDA has the
21 responsibility to oversee that process to make sure
22 that it's -- it's done correctly and safely.

23 Q I don't mean this in an offensive way,
24 but do you believe that the FDA is infallible?

1 A No.

2 Q So you agree then that the FDA can make a
3 mistake; is that right?

4 A Yes.

5 Q Do you believe that drug manufacturers
6 need to be honest in their dealings with the FDA?

7 A Yes, they do.

8 Q And why do you believe that?

9 A Well, I mean, number one, it's required
10 by -- as I understand the law, it's required by law.
11 They have to -- they have to submit, you know,
12 accurate and complete information on an application
13 that, you know, is part of an NDA or IND. They have
14 to give -- they have to give FDA everything.

15 Q Do you believe that there could be health
16 consequences if they are -- if a drug sponsor is not
17 truthful and honest in their disclosures to the FDA?

18 A Yeah, of course.

19 Q Do you believe it would ever be
20 appropriate for a drug sponsor to mislead the FDA?

21 A No.

22 Q Do you believe it is acceptable in your
23 opinion for a drug manufacturer to mischaracterize
24 data from a clinical trial to make a result appear

1 positive?

2 A Well, it -- that -- that's a somewhat
3 tricky question to answer because what one person
4 character- -- you know, views as mischaracterization,
5 someone else may view as just an alternative
6 interpretation of the data. So I --

7 Q Sure, but in your view, if it is a
8 mischaracterization in your view, do you think that
9 it's appropriate for a drug manufacturer to
10 mischaracterize data to make it look more positive
11 than it is?

12 A Again, you know, a company is entitled to
13 make its best case. And to -- and therefore, to --
14 you, to provide a number of ways of looking at the
15 same dataset. As you know, different people looking
16 at the same dataset may reach different conclusions.
17 Unless -- unless, you know, a company is -- is
18 purposely omitting information, I -- I think -- I
19 think they're given a fair amount of flexibility in
20 how they choose to make their case for their -- for
21 their product.

22 Q And you agree that in making their case,
23 they should always be honest and straightforward
24 about what occurred during a clinical trial?

1 A Absolutely. Absolutely. As I say,
2 they -- you know, they're expected to give FDA
3 every -- everything they have. You know, all the
4 information, all the data that they have.

5 You know, again, the question comes in
6 how you interpret that data. There are -- obviously,
7 different individuals, different people looking at
8 the same dataset may view it differently.

9 Q In your experience at the FDA, would the
10 FDA ever approve a drug to help a drug company's
11 marketing objectives?

12 MS. KIEHN: Objection.

13 THE WITNESS: I'm sorry?

14 BY MR. WISNER:

15 Q I will rephrase that question in a better
16 way.

17 Would the -- while you were at the FDA,
18 did you ever see the FDA try to get a drug approved
19 to help the financial objectives of a drug company?

20 A No. No. FDA was -- was never focused
21 on -- on finances.

22 Q Are you familiar with something called
23 the placebo effect?

24 A Oh, very much so.

1 Q Can you please explain briefly your
2 understanding of the placebo effect.

3 A So the placebo effect is, again, you
4 know, a concept that's -- that's -- that has
5 different meanings depending on who you talk to.

6 So, for example, some people view the
7 placebo effect as the act of taking an inert
8 substance, a placebo. I view the placebo effect much
9 more broadly than that. So, for example, when you --
10 when you enter patients into a clinical trial,
11 typically in psychiatric trials, there is a placebo
12 arm. You know, there is a group of patients that are
13 assigned to an inert substance. However, getting
14 that inert substance is not the only thing that
15 happens to them. They also are engaged in a very
16 interactive process, you know, with -- as part of
17 being in the trial.

18 And so -- and so I and many other people
19 view the placebo effect as that entire experience.
20 So not just the act of taking a placebo but being in
21 a clinical trial as -- as underlying the so-called
22 placebo effect.

23 Q Now, you would agree, though, that the
24 medical benefit that a patient might receive through

1 that interaction with a physician or an investigator
2 in a clinical trial, that's a known effect to
3 potentially improve a person's psychiatric condition,
4 right?

5 MS. KIEHN: Objection.

6 THE WITNESS: Well, it's -- it's an
7 effect that one observes in a -- certainly in a
8 clinical trial. Yeah, I think it's widely recognized
9 that -- that that process of interacting with a --
10 with a healthcare provider is in itself -- does in
11 itself have a -- very often have a therapeutic
12 effect. I think that's understood and recognized.

13 BY MR. WISNER:

14 Q And in a clinical trial, when you have a
15 placebo arm, isn't it true that both the patients
16 that are in the treatment arm as well as the patients
17 in the placebo arm get exposed to that potential
18 therapeutic effect?

19 A Yes.

20 Q So the purpose of the placebo pill is to
21 help, at best, isolate the effect that the drug is
22 having on the patient's improvement, not the other
23 factors such as --

24 A Yeah, yeah.

1 Q -- the therapeutic effect.

2 A Right. Right. Right. Right.

3 MS. KIEHN: Objection.

4 BY MR. WISNER:

5 Q Placebo pills are often referred to by --
6 in layman's terms as a sugar pill; is that right?

7 A Yeah.

8 Q In the context of treating depression
9 specifically, can people who are given placebo pills
10 experience improvement?

11 A Typically in a -- in a depression trial,
12 you see a fairly substantial improvement. Say it's a
13 two-arm trial where, you know, one group is assigned
14 to the active drug, the drug of interest, and the
15 other group is assigned to the placebo, you're right,
16 they all get the same interaction with staff.

17 Typically what you see in a trial, in a
18 depression trial is -- is a, you know, quite a
19 substantial improvement on the depression ratings in
20 both arms. In a successful trial, you see a greater
21 improvement in those who get the active drug compared
22 to those that get the inert substance.

23 But you're right, that both groups
24 improve, you know, quite -- quite a lot in that -- in

1 that trial.

2 Q And isn't it true that it's also possible
3 for a depressed patient who's receiving placebo
4 treatment to experience a remission of their
5 depressive -- depressive symptoms?

6 MS. KIEHN: Objection.

7 THE WITNESS: That certainly -- you can
8 see remissions in -- in both patients who are
9 assigned to active drugs and those assigned a
10 placebo.

11 One further qualification is that one of
12 the problems in treating and doing acute studies of
13 depression is that depression is a disorder that
14 waxes and wanes. And so very often what happens in a
15 clinical trial is that -- is that patients don't
16 agree to be in the trial until they're at the very
17 worst phase of their illness. And so this -- this is
18 one of the explanations for why you often see such
19 improvement in depressed patients, whatever group
20 they're assigned to, is that they're already on the
21 descending part of that curve when they enter the
22 trial, and so -- and so they all tend to move towards
23 improvement. And the question is whether -- whether
24 or not, you know, the -- you know, the active drug

1 contributes in some -- in some way to that
2 improvement.

3 BY MR. WISNER:

4 Q We've discussed clinical trials briefly
5 already, but I want to get very specific. Are you
6 familiar with the phrase "double-blind, randomized,
7 placebo-controlled clinical trial"?

8 A Yes.

9 Q All right. Briefly, can you explain to
10 the jury what a double-blind, randomized,
11 placebo-controlled trial is?

12 A So there are a couple of parts to that.
13 Random -- a randomized clinical trial is a trial in
14 which assignment to treatment is random. So it's --
15 it's -- basically it's the flip of a coin whether you
16 get one or the other.

17 And the randomization part of that is
18 what's absolutely critical to the validity of that
19 trial. So -- so statistical theory depends on
20 randomization. So that's -- that's fundamental. If
21 a trial doesn't have randomization, it's not -- it's
22 not a valid trial.

23 Blinding is -- is something that is an
24 ideal to strive for. It's another way of controlling

1 bias in a trial or trying to control bias. It's --
2 it's harder to achieve often. And the reason for
3 that is that, you know, many drugs have a
4 characteristic side effect profile. And, you know,
5 you do your best to have a double -- and
6 "double-blind" means that both the patient and the
7 investigator are theoretically blinded to -- to what
8 treatment the patient gets.

9 And so, you know -- and this is something
10 that's actually, you know, relatively recent. This
11 came about in the -- in the '50s doing double-blind
12 trials. Randomization has been around for much
13 longer.

14 Now, in some areas, blinding is -- is
15 very difficult to achieve, and -- but even in
16 psychiatric trials where you -- you certainly strive
17 for that, I think it's generally understood that you
18 often don't achieve that a hundred percent because of
19 the -- of the possibility of the side effect profile
20 on blinding either patients or investigators.

21 So it's -- and, you know, it's also
22 generally accepted that some degree of unblinding
23 is -- does not completely invalidate a trial. In
24 fact, there are some trials, even in psychiatry, that

1 are explicitly open label. So, for example, the drug
2 clozapine was approved for the treatment of
3 suicidality and schizophrenia based on an open label
4 study. So it was randomized. So patients were
5 randomized in that trial to either clozapine or
6 olanzapine. It's called the interSePT trial. And it
7 was considered a valid trial, but the investigators
8 and patients knew whether they were getting clozapine
9 or olanzapine. There was no attempt to blind it.

10 Another more recent study, the PRIDE
11 study, a study looking at -- paliperidone is another
12 antipsychotic, Invega. And, you know, this trial
13 compared oral Invega with DEPO. DEPO is -- is an
14 injectable form of Invega that lasts for a much
15 longer period of time. And so they did a trial, and
16 you really can't easily blind a study like that.
17 And, you know, that -- that was open label, and it
18 was considered a valid study and a successful study,
19 and that both the interSePT study and the -- the
20 PRIDE study are, you know, described in the labeling
21 of these products and considered valid studies.

22 So blinding is -- is ideal. It's one way
23 of controlling -- of trying to control bias, but
24 it's -- it's not as fundamental to the validity of a

1 trial as randomization.

2 Q Thank you for that answer, Doctor.

3 A Sorry, it was a little long, but --

4 Q It's okay. Not a problem.

5 I asked you a very open-ended question,
6 so I appreciate you giving me your thoughts on it.

7 Now, I want to dig into a couple of
8 things a little bit more.

9 Have you ever heard of an open-label,
10 placebo-controlled trial?

11 A Well, I mean, again, in -- in psychiatry,
12 it's considered probably more important than in some
13 other areas to try and achieve double-blind. And so
14 ordinarily in psychiatric trials, you try -- you try
15 to achieve that -- that feature, you try and
16 double-blind it. What I'm saying is that you
17 don't -- you don't always succeed. It's understood
18 that -- that these trials are -- you know, are often
19 not -- not fully double-blind.

20 Q No, I understand that. My question was
21 just a simple question.

22 Have you ever heard of an open-label,
23 placebo-controlled trial?

24 A It would be very unusual.

1 Q Because that would mean that either the
2 investigator or the patient know that they're
3 taking a sugar pill, right?

4 A Yeah.

5 MS. KIEHN: Objection.

6 BY MR. WISNER:

7 Q And you wouldn't expect that to be a fair
8 comparison because if a person knows they're taking a
9 placebo, they know they're taking no drug, and so
10 it's hard to know the efficacy --

11 MS. KIEHN: Objection.

12 THE WITNESS: Yeah, but you're
13 assuming -- you're assuming that -- that the effect
14 of the drug cannot -- cannot overcome, you know, that
15 form of bias, and that's -- and that's not
16 necessarily a fair assumption. A very powerful drug,
17 a very powerful treatment can -- you know, can
18 overcome the bias that might come with -- with
19 unblinding.

20 BY MR. WISNER:

21 Q Well, I mean in the context of a
22 placebo-controlled trial, if a patient knows they're
23 taking the placebo, that would have a tendency to
24 suppress the placebo response, right?

1 MS. KIEHN: Objection.

2 THE WITNESS: Well, that would -- that
3 would be a concern.

4 But, again, what I'm saying is that it
5 doesn't necessarily invalidate the study just because
6 you have a placebo arm.

7 Let me give you a ridiculous example. So
8 if -- if you wanted to do a study of the
9 effectiveness of a parachute, I wouldn't volunteer
10 for such a study, but if one did such a study, you --
11 you would have an active arm where people jumping out
12 of a plane had a parachute. You would have another
13 arm where people had a placebo that didn't actually
14 do anything. And I think that would -- you know,
15 that study would probably clearly demonstrate the
16 effectiveness of -- of the parachute, even though it
17 was -- there was a placebo arm and it was, you know,
18 completely unblinded.

19 BY MR. WISNER:

20 Q Sure. But taking that example a little
21 bit further, no rational human being would
22 participate in such a study if it was unblinded,
23 right, because there's a 50 percent chance that
24 you're going to die, right?

1 A Well, you're assuming you know -- you
2 know the answer before the study is done.

3 Q Fair enough.

4 I guess my point, Doctor, is -- we can
5 get into these hypotheticals all day, but I do want
6 to get you out of here at a reasonable hour.

7 In the context of a placebo-controlled
8 trial, blinding helps mitigate any bias that would be
9 injected because either the investigator or the
10 patient knows that they're taking a sugar pill?

11 MS. KIEHN: Objection.

12 THE WITNESS: Blind -- blinding is -- is
13 definitely something that one strives for in a
14 placebo-controlled study.

15 BY MR. WISNER:

16 Q Now, in the context of a depression
17 trial, typically the patient's depression is assessed
18 against a rating scale; is that right?

19 A That's true, yes.

20 Q And there's rating scales that exist for
21 adult depression as well as rating scales that exist
22 for pediatric depression?

23 A That's correct.

24 Q And in the context of -- of assessing a

1 patient's depression, depending on the study's
2 protocol, the physician typically goes through a
3 checklist of questions with the patient or the
4 patient and their parent to make an assessment of how
5 that patient rates on that particular issue; is that
6 right?

7 A Yeah, that --

8 MS. KIEHN: Objection.

9 THE WITNESS: That's correct.

10 BY MR. WISNER:

11 Q There is no sort of objective measurement
12 for testing a person's depression level like blood
13 pressure, right?

14 A That -- that's correct, there isn't
15 any -- any purely objective measure that one can use
16 to assess the severity of depression. It's -- it's
17 based on -- and typically it's measured, as you say,
18 with a standard rating instrument.

19 Q Now, because of the way that depression
20 is assessed in these clinical trials, the
21 investigator's knowledge of whether or not that
22 patient is taking a placebo or taking the drug
23 treatment really has a risk of injecting bias into
24 that assessment, doesn't it?

1 MS. KIEHN: Objection.

2 THE WITNESS: Although there -- there
3 is -- there is potential bias, I will go back to the
4 earlier point that I made, that it doesn't
5 necessarily invalidate the trial if that objective of
6 double-blinding isn't completely achieved. It
7 doesn't -- in my view, it does not invalidate the
8 trial.

9 BY MR. WISNER:

10 Q Sure. My question was not about whether
11 or not that would invalidate the trial. My question
12 was whether or not if the investigator knows that the
13 patient they're assessing is taking the drug or the
14 placebo, there's a real risk of bias being injected
15 by the investigator.

16 MS. KIEHN: Objection.

17 THE WITNESS: There is a concern that
18 that would introduce bias, and that, of course, is
19 what double-blinding strives to overcome.

20 BY MR. WISNER:

21 Q Similarly, if the patient who -- well,
22 let me back up for a second.

23 We know that depression can wax and wane
24 pretty -- pretty -- strike that.

1 In your experience with depressed
2 patients, the person's mood can shift dramatically
3 relatively quickly. Is that fair to say?

4 MS. KIEHN: Objection.

5 THE WITNESS: Well, it -- there certainly
6 can be shifting in the mood from day to day. It
7 would -- you know, it would be very unusual for a
8 patient with significant major depressive disorder
9 to -- to be suddenly better. That -- you know,
10 completely in remission, that would -- that would be
11 unusual. It can -- it can fluctuate from day to day,
12 but large changes are -- are very unusual.

13 BY MR. WISNER:

14 Q Okay. Now, we talked about -- you
15 mentioned earlier that double-blind is the standard
16 that you strive to achieve in depression or
17 psychiatric trials; is that right?

18 A Yes.

19 Q If there is an unblinding that is known
20 about, do you agree that that protocol violation
21 should be disclosed in assessing the results of the
22 study?

23 MS. KIEHN: Objection.

24 THE WITNESS: If -- if there is -- if

1 there is known unblinding, yes, that should be --
2 that should be part of a -- of a study report.

3 BY MR. WISNER:

4 Q And that's something that at the FDA you
5 would have considered in assessing whether or not
6 that study not only was valid but whether or not it
7 was positive, negative or failed, correct?

8 MS. KIEHN: Objection.

9 THE WITNESS: Well, FDA would have
10 considered that information. Again, where I would
11 push back, it wouldn't necessarily invalidate the
12 study.

13 BY MR. WISNER:

14 Q Sure.

15 A Even if -- even if it were documented
16 that there was some degree of unblinding in a trial
17 in my view.

18 Q Sure. And I'm -- validation aside,
19 whether or not the study is positive or negative or
20 how it affects the integrity of the study, that's
21 something the FDA would want to know. That's all I'm
22 saying.

23 MS. KIEHN: Objection.

24 THE WITNESS: FDA would want to know

1 about -- about unblinding.

2 BY MR. WISNER:

3 Q And because the FDA doesn't conduct
4 clinical trials, would it be fair to say that the FDA
5 relies upon the disclosures about unblindings from
6 the drug sponsor?

7 A As -- as in everything else, yes, you're
8 right. We -- the FDA does not conduct the trials,
9 and so it does rely on companies to -- to give them
10 complete reports on what happened during the conduct
11 of the trial.

12 Q And you also rely on the company, for
13 example, to hire honest investigators, right?

14 MS. KIEHN: Objection.

15 THE WITNESS: Yes.

16 BY MR. WISNER:

17 Q I mean the FDA doesn't determine who the
18 investigators for a clinical trial are going to be,
19 right?

20 A That's correct.

21 Q That's determined by the drug company.

22 A Right.

23 Q The FDA doesn't -- strike that.

24 Are you familiar with something called a

1 clinical trial protocol?

2 A Yes.

3 Q What is that?

4 A The protocol is -- is basically the
5 detailed plan for how the study will be conducted.

6 Q And typically -- strike that.

7 During your time at the FDA, did you
8 review clinical trial protocols before clinical
9 trials began?

10 A Yes.

11 Q And for a double-blind, randomized,
12 placebo-controlled trial, have you reviewed protocols
13 such as those while you were at the FDA?

14 A Yes.

15 Q Why are protocols used?

16 A It -- it's not possible to conduct a
17 complex operation like a clinical trial without
18 having a protocol. Plus the analysis that -- that
19 will ensue after -- after you gather data from the
20 trial, you know, the validity of the analysis depends
21 on the trial having been done according to the -- to
22 the protocol.

23 Q For example, for the efficacy results of
24 a clinical trial, the protocol prespecifies what

1 those outcomes should or should not be; is that
2 right?

3 A Well, it --

4 MS. KIEHN: Objection.

5 THE WITNESS: It -- it specifies exactly,
6 you know, what data are going to be in the final
7 analysis dataset that the analysis relies on.

8 BY MR. WISNER:

9 Q The protocol typically specifies the
10 threshold for statistical significance; is that
11 right?

12 A Well, that -- that's -- the threshold for
13 a statistical significance, P-value of 0.05, is -- is
14 basically a -- a standard that was originally set by
15 R. A. Fisher back in the early, you know, nine --
16 1900s, and, you know, the last century completely
17 arbitrary. But -- but it -- it's a standard that
18 most scientific organizations have -- have adopted
19 and relied on.

20 Q You mentioned P-value. You mentioned
21 that a second ago.

22 A Yes.

23 Q Can you explain to the jury your
24 understanding of what a P-value is.

1 A A P-value in a -- in a clinical trial,
2 for example, you have a hypothesis, and what's known
3 as the null hypothesis is a hypothesis that -- that
4 there is no difference between drug and placebo.

5 And the P-value sort of in a common sense
6 way of thinking is the probability of -- assuming
7 that the null hypothesis is true, of getting the
8 finding that you got, and so it's the -- the chance
9 of getting that, if the null hypothesis is true. And
10 so a P-value of 0.05 comes down to the probability of
11 1 in 20 or less of getting that finding essentially
12 by chance.

13 Q Another way of characterizing it is that
14 the P-value or statistical significance helps you
15 determine whether or not the difference observed
16 between two groups was in fact a true difference or a
17 product of just chance?

18 A Yeah. Well, the P -- the P-value is a
19 separate concept than statistical significant --
20 significance.

21 Q Sure.

22 A The significance is an arbitrary
23 threshold set for evaluating the P-value. You can
24 generate a P-value without any regard to

1 significance. You -- you decide whether or not it
2 was significant based on the threshold that you
3 set.

4 Q In a placebo-controlled trial, typically
5 the -- the statistical significance measure is
6 designed to determine whether or not the difference
7 between placebo and the treatment arms were a product
8 of chance or an actual difference.

9 A Yes. Yeah, that's a fair way of
10 characterizing it.

11 MS. KIEHN: Dr. Laughren, can I just ask
12 you to try to wait until he finishes his question
13 before you answer so I can get my objections in.
14 Thank you.

15 THE WITNESS: Okay.

16 BY MR. WISNER:

17 Q Now, you mentioned a P-value of 0.05.

18 Conventionally the P-value -- a study --
19 a finding is considered statistically significant if
20 the P-value is less than 0.05, right?

21 A Less than or equal to 0.05.

22 Q And if it's greater than 0.05, it passes
23 that threshold into not meeting the -- that
24 particular threshold.

1 A It's -- it's a -- it's a rule, but its
2 application -- there's always some judgment involved
3 in deciding, you know, whether or not the data
4 generated for a particular application meets the
5 threshold where a reasonable person could say, Yeah,
6 this is -- this is an effective drug.

7 So, yes, there's this -- this, you know,
8 0.05 threshold, but I'm certainly aware of -- of
9 applications being approved even if it didn't quite
10 meet that threshold, depending on the -- on the
11 aggregated evidence.

12 Q What is a primary endpoint in a clinical
13 trial?

14 A The primary endpoint -- typically in a
15 clinical trial, there's lots of things that you
16 measure. You mentioned the -- you know, the primary
17 rating scale that's used. And so the primary
18 endpoint is -- is based on some metric for the
19 primary assessment.

20 So if -- if it's the -- in the case of
21 depression trial, CDRS, typically the metric is
22 changed from baseline in that rating instrument as
23 the -- the primary endpoint. So you are looking at
24 the difference between drug and placebo and change

1 from baseline on that rating scale. That would be
2 the primary endpoint.

3 There are other endpoints that are --
4 that are measured, and generally P-values are
5 generated for those -- those endpoints as well. But
6 the primary one is the one that counts. The study
7 rises or falls basically on the -- in the outcome of
8 the primary endpoint.

9 Q Now, the primary endpoint as well as the
10 second endpoint or even additional efficacy
11 endpoints, those are typically prespecified in the
12 protocol before the study begins, correct?

13 A That -- that is correct. But let me
14 again further qualify. There's -- there's the
15 concept of a key secondary endpoint, which is an
16 endpoint that's actually included in the hypothesis
17 testing. And then there are exploratory endpoints
18 that are looked at, but they're not considered part
19 of the hypothesis testing, and so they don't carry
20 much weight in terms of a regulatory decision.

21 Q But -- but, regardless, those endpoints
22 are prespecified in the protocol before the clinical
23 trial begins.

24 A In the analysis plan.

1 Q Okay. Are you familiar with something
2 called a protocol violation?

3 A Yes.

4 Q What is a protocol violation?

5 A A protocol violation is -- is when, you
6 know, the -- an investigator, you know, at a site,
7 you know, does not fully adhere to what's specified
8 in the protocol.

9 So, for example, if the protocol
10 specifies that only patients meeting certain --
11 certain entry criteria can be enrolled in that study,
12 if a patient, you know, who doesn't meet those entry
13 criteria -- say -- say you have a threshold on the
14 HAM-D in a -- in a depression trial, and you say
15 patients have to have a HAM-D of 22 or greater to get
16 entered in, if a patient with a HAM-D of 20 got
17 entered, that would be a protocol violation.

18 So there are many, many examples of
19 protocol violations. That's just one example.

20 Q Sure. Does the existence of a protocol
21 violation necessarily invalidate the results of a
22 study?

23 A No.

24 Q Could systemic protocol violations

1 invalidate a study?

2 A If -- if they -- if they were substantial
3 and, as you say, systemic, it could.

4 Q In assessing the efficacy of a compound
5 specifically with regards to depression, would you
6 agree that double-blind, randomized,
7 placebo-controlled trials are the gold standard?

8 MS. KIEHN: Objection.

9 THE WITNESS: Again, getting back to what
10 I said earlier, randomization is -- is fundamental
11 and sacred, and in a trial that does not have
12 randomization it would be invalid. Blinding is
13 something that one strives for. It's understood that
14 you don't always achieve that, and -- and if it's not
15 completely achieved, in my view it would not
16 necessarily invalidate a study.

17 BY MR. WISNER:

18 Q I appreciate your answer. I'm going to
19 ask the question one more time.

20 A Okay.

21 Q In assessing the efficacy of a compound,
22 do you agree that a double-blind, randomized,
23 placebo-controlled trial is the gold standard?

24 MS. KIEHN: Objection.

1 THE WITNESS: I -- I agree that -- that
2 one should strive for double-blinding in a -- in a
3 trial that's done in the psychiatric domain. I agree
4 that that's a -- that's a reasonable goal.

5 BY MR. WISNER:

6 Q Does the FDA make a determination about
7 whether a drug is effective?

8 A Yes, that's ultimately FDA's judgment.

9 Q What sources of information does the FDA
10 rely upon in assessing the efficacy of a new
11 compound? And let's focus specifically on
12 antidepressants.

13 A FDA relies on the results of the clinical
14 trials that are -- that are done in a drug
15 development program.

16 Q Can you explain to the jury what a drug
17 maker must demonstrate regarding efficacy before the
18 FDA will approve it for a treatment of depression?

19 A So the act -- the Food, Drug and Cosmetic
20 Act requires substantial evidence of efficacy from --
21 from adequate and well controlled trials. And so,
22 you know, that is generally interpreted to mean two
23 or more positive studies that have a positive finding
24 on the -- on the primary endpoint.

1 Q Now, are you familiar with the concept of
2 clinical efficacy?

3 A That's a -- a vague term that, you know,
4 doesn't have any -- any clearly defined meaning.
5 It -- it probably means different things to different
6 people.

7 Q Well, you've published on this issue,
8 haven't you, Doctor?

9 A I've published a lot of things. I don't
10 know specifically what you're referring to.

11 Q Okay. Are you aware of any regulation
12 within the FDA that requires that the FDA find that a
13 drug has a clinically meaningful treatment effect?

14 A That's -- that is -- is generally what's
15 inferred from the Act, that -- that the effect that
16 you're observing is meaningful. But it's a -- it's a
17 concept that is not well defined.

18 So, for example, in depression, typically
19 now these days the trials that are the basis for the
20 approval of new antidepressants, the effect size --
21 and there are many ways of measuring effect size, but
22 if you -- you know, one common meaning for effect
23 size is the difference between drug and placebo and
24 change from baseline on a standard measure, like the

1 HAM-D.

2 So these days approvals are based on a
3 difference of two points between drug and placebo.
4 So that's -- that's -- you know, we did an analysis,
5 we went back and looked at all of our data
6 accumulated over roughly 25 years and looked at the
7 change in the effect size for drugs that had -- had
8 been approved, and, you know, it is -- you know, two
9 decades ago it used to be three. Now it's down to
10 about two.

11 So, the question is, and I -- you know,
12 this is something that's been a source of debate for
13 a long time -- whether or not you know that effect
14 size, a two-point difference on average, is a
15 clinically meaningful effect is something that's been
16 hotly debated.

17 I was interviewed by Leslie Stahl one
18 time and had to talk about that as a defendant.

19 Q I recall, on "60 Minutes."

20 A But that -- that's what it is.

21 Q It was actually going to be an exhibit
22 here, but I decided not to go there. So -- fair
23 enough.

24 I guess my question, though, is are you

1 aware at the FDA in deciding whether or not to
2 approve an indication whether or not the FDA is
3 required to make a determination that the difference
4 observed is clinically meaningful?

5 A It -- it is part -- it is part of the
6 judgment. But what I -- what I'm saying is that it's
7 not well defined.

8 Q Sure. Were you by any chance at the PDAC
9 meeting for Zolofit when it was being approved
10 initially for adults?

11 A I -- I would have been. I was at -- at
12 probably 50 or 60 advisory committees. I certainly
13 would have been at that one.

14 Q During that meeting, do you recall -- if
15 you don't, it's fine -- Dr. Lieber discussing the
16 issue of clinical -- clinical effect versus
17 statistical significance? Do you recall that at all?

18 A He -- that was a favorite topic of his,
19 so --

20 Q Yeah.

21 A -- it wouldn't surprise me that he --
22 that he talked about that.

23 Q And you understand that it was his view
24 that the FDA's assessment of a compound for approval

1 was based solely upon statistical significance and
2 that clinical meaning -- whether or not something was
3 clinically meaningful was something for the academics
4 and the doctors to figure out?

5 MS. KIEHN: Objection.

6 THE WITNESS: I don't -- I don't entirely
7 agree with that. I -- I know Paul Lieber very well.

8 BY MR. WISNER:

9 Q Sure.

10 A I've known him for many, many decades,
11 and -- and he was the division director at the time
12 that Zoloft was under consideration, so he would have
13 approved Zoloft. I don't think he would have
14 approved Zoloft if he didn't think that it was a
15 clinically meaningful effect, despite what he might
16 have said at an advisory committee, because Paul --
17 Paul liked to talk a lot.

18 Q Does the FDA in reviewing a compound for
19 approval review internal correspondence from the drug
20 company?

21 A That's typically not part -- I mean, FDA
22 tends to focus more on the data. And so actually
23 often when a clinical reviewer gets an application,
24 they often go right to the data rather than even

1 reading the summary, because they don't want to be
2 influenced by -- by, you know, the company's spin on
3 the data. So they just go right to the datasets and
4 the tables and look at the data.

5 Q Now, during your time at the FDA, do you
6 ever recall looking at a dataset and going, I think
7 this is all made up?

8 MS. KIEHN: Objection.

9 THE WITNESS: I -- I don't recall ever
10 reaching that judgment on a -- based on a dataset.

11 BY MR. WISNER:

12 Q Would it be fair to say that when a drug
13 sponsor submits the data from a clinical trial, you
14 take it at face value as being true and accurate?

15 MS. KIEHN: Objection.

16 THE WITNESS: I -- I wouldn't say that we
17 took it at face value. You know, we -- we
18 certainly -- you know, part -- the process of
19 reviewing a new drug application is very complex. It
20 includes doing -- you know, there's an Office of
21 Scientific Investigations that goes out and actually
22 looks at trial sites to try and -- and get at that
23 very issue, you know, whether -- a question like
24 whether or not the data are real, whether or not

1 there were actually patients.

2 And so they -- you know, they check
3 the -- you know, the clinical record at the site
4 against the case report forms and so forth. So I --
5 FDA doesn't -- doesn't ignore that -- that aspect.
6 That is part of the review process.

7 BY MR. WISNER:

8 Q Does the FDA audit the case report forms
9 typically?

10 A Again, typically, you know, sites chosen
11 randomly are -- are looked at very carefully by -- by
12 FDA inspectors from the Office of Scientific
13 Investigation.

14 Q Sure, but even in that context, the
15 investigator doesn't look at the case report form,
16 pull the patient aside and go, Hey, is this really
17 true? That -- does that ever happen?

18 MS. KIEHN: Objection.

19 THE WITNESS: No, but you do -- you do
20 check -- there's usually a clinical record at the
21 site apart from the case report form. You might
22 check that against the case report form.

23 BY MR. WISNER:

24 Q Now, after that investigation and that

1 sort of regulatory process occurs, when it gets to
2 you for review, at that point do you review all of
3 the case report forms?

4 A Not -- not every case report form, no.

5 Q Typically they're only required to submit
6 the case report form for any serious adverse effects.

7 MS. KIEHN: Objection.

8 THE WITNESS: You know, it -- it varies
9 from application to application. But -- but, yeah,
10 you're not going to get all the case report forms,
11 that -- that's true.

12 BY MR. WISNER:

13 Q Okay. Are you familiar with something
14 called a final study report?

15 A Yes.

16 Q What is that?

17 A It's -- it's the -- you know, the final
18 report on a study that includes a description of, you
19 know, what the study was, you know, who the patients
20 were, what the findings were, what the analysis
21 showed.

22 Q Who prepares the final study report?

23 A The companies prepare the study report.

24 Q And they submit that to the FDA as part

1 of a -- a regulatory process or an application?

2 A As part of an application, yes.

3 Q Okay. Are you familiar with something
4 called pediatric exclusivity?

5 A Yes.

6 Q Can you explain to the jury what that is.

7 A So, for a number of decades there was a
8 concern about the lack of data that -- that
9 clinicians had for drugs in treating pediatric
10 patients, children and adolescents, and so the FDA
11 over the years tried a number of different things to
12 try and get companies to do more studies in pediatric
13 patients.

14 The one that finally worked is this
15 exclusivity. So this is part of the, I think it was,
16 the '97 FDAMA Amendment, amendment of the act that
17 included the exclusivity provision that basically
18 gave companies an additional six months of
19 exclusivity for conducting pediatric studies.

20 And so, for example, in -- in psychiatry,
21 that -- you know, that initiative, that incentive for
22 doing pediatric studies resulted in a -- in a number
23 of studies done on pediatric depression, and that's
24 what this is all about, because this is focused on

1 studies that were done as -- as part of that
2 incentive.

3 Q And when you say the incentive for six
4 additional months of exclusivity, does that mean that
5 the drug sponsor will be allowed to sell the drug
6 exclusively as the brand name manufacturer for an
7 additional six months?

8 A Yes.

9 Q Because after that six months, then
10 generic manufacturers can start making the compound;
11 is that right?

12 A That's correct.

13 Q And typically when generic manufacturers
14 start making the compound, the price and cost of the
15 drug goes down considerably.

16 A That's true.

17 Q And that's in fact the entire purpose for
18 the Wax-Hatchman Amendments, correct?

19 MS. KIEHN: Objection.

20 THE WITNESS: Yes.

21 BY MR. WISNER:

22 Q All right. When a company wants to
23 obtain that six extra months of pediatric
24 exclusivity, do they have to submit and get approval

1 for the pediatric study protocols that they plan to
2 do?

3 A They -- they -- I mean, typically, the
4 way the process works, they submit a PPSR, Proposed
5 Pediatric Study Request. FDA would then issue a
6 written request specifying, you know, what's needed
7 in a pediatric supplement to -- to get that
8 exclusivity. The company would then do that program
9 and submit it, and FDA would determine whether or not
10 they met the terms of the written request.

11 Q And by met -- "met the terms," does that
12 mean -- well, back up.

13 When they're preparing the protocols that
14 they're going to be doing to -- to meet that written
15 request, do they run those protocols by the FDA
16 before they start?

17 A Well, every -- every protocol has to be
18 submitted. Whether it's part of the exclusivity
19 provision or not, every protocol has to -- has to
20 arrive at FDA for review, either prior to or
21 simultaneous with the initiation of that study. FDA
22 has to look at every protocol for every trial.

23 Q Okay. Does FDA approve protocols or do
24 they just review them?

1 A They -- they review them and -- and if
2 they object, then they tell the company. But there
3 isn't -- there -- it's -- the only protocol that
4 actually has to get FDA approval before it's started
5 is the one that initially comes in with the IND.
6 Typically they will have a protocol in an IND, and
7 FDA has 30 days to review that, and -- and at that
8 point FDA will say, yes or no, you can go ahead with
9 your study.

10 After that, after an IND, the company has
11 an IND, at that point they simply have to submit the
12 protocol for an additional study. It has to arrive
13 at FDA before they actually start the study, but they
14 don't require an actual letter from FDA to say, Yeah,
15 you can go ahead.

16 Q Now, for pediatric depression trials
17 specifically related to pediatric exclusivity, did
18 the FDA take a closer look at those versus other
19 protocols or were they treated the same?

20 MS. KIEHN: Objection.

21 THE WITNESS: I would like to say that
22 FDA looks closely at all protocols that come in.

23 BY MR. WISNER:

24 Q Sure. I just mean relative to the

1 others, were they given special attention or were
2 they just sort of part of the regular process?

3 MS. KIEHN: Objection.

4 THE WITNESS: Again, I would -- I would
5 argue that -- that FDA looks closely at every
6 protocol. Every protocol is important.

7 BY MR. WISNER:

8 Q Sure. I'm not suggesting they're not by
9 my question. I apologize if you think I'm inferring
10 as much.

11 However, I'm just asking in the panoply
12 of all the special attention given to all the
13 protocols, do the pediatric ones get extra attention
14 or no?

15 MS. KIEHN: Objection.

16 THE WITNESS: I -- it's -- it's an
17 impossible question to answer. I mean, again, I -- I
18 think, you know, when -- we took protocols very
19 seriously. We looked at all of them carefully as,
20 you know, we took that responsibility seriously.
21 So...

22 BY MR. WISNER:

23 Q Okay. Would it be fair to say then that
24 whether it was a pediatric protocol or an adult

1 protocol, you guys gave the same level of serious
2 attention to them equally?

3 MS. KIEHN: Objection.

4 THE WITNESS: I would say that, yes,
5 we -- we tried to give serious attention to every
6 protocol that came in.

7 MR. WISNER: Okay, great. Let's take a
8 break.

9 THE WITNESS: Okay.

10 THE VIDEOGRAPHER: The time is 10:25 a.m.
11 This is the end of disc No. 1. We will go off the
12 video record.

13 (Recess.)

14 THE VIDEOGRAPHER: This is the beginning
15 of disc No. 2 in the deposition of Dr. Thomas
16 Laughren. The time is 10:42 a.m. We're back on the
17 video record.

18 BY MR. WISNER:

19 Q All right, Dr. Laughren, I'm going to
20 shift gears a bit here. We're going to come back to
21 clinical trials and -- and Celexa and Lexapro
22 specifically in a minute, but I want to ask you a few
23 questions about some other things.

24 Are you familiar with the phrase

1 "off-label promotion"?

2 A Yes.

3 Q What is your understanding of that
4 phrase?

5 A Generally, off-label promotion would be
6 using a drug for which it does not have an approved
7 indication.

8 Q That would be off-label use, right?

9 A Oh, I'm sorry. Off-label promotion.
10 Okay. That -- that would be, you know, a company
11 promoting a drug for uses for which there are not
12 approved indications.

13 Q Is it your understanding that off-label
14 promotion of a drug is illegal?

15 A I'm not an expert on -- on that aspect of
16 regulation, but that's generally my understanding
17 that that's a violation of the law.

18 Q While you were at the FDA, was -- it was
19 not your job to police off-label promotion, was it?

20 A No.

21 (Exhibit No. 2 was marked for
22 identification.)

23 BY MR. WISNER:

24 Q Okay. I'm handing you what has been

1 marked as Exhibit 2 to your deposition.

2 Have you ever seen this document before?

3 A I don't recall seeing it.

4 Q This is a press release from the
5 Department of Justice dated September 15th, 2010.
6 Please turn to the first paragraph.

7 A Okay.

8 Q It reads: "Forest Pharmaceuticals, Inc.,
9 a subsidiary of New York-based Forest Laboratories,
10 Inc., has agreed to plead guilty to charges related
11 to obstruction of justice, the distribution of
12 Levothroid, which at the time was an unapproved new
13 drug, and the illegal promotion of Celexa for use in
14 treating children and adolescents suffering from
15 depression, the Justice Department announced today.

16 "The companies also agreed to settle
17 pending false claims allegations that Forest caused
18 false claims to be submitted to federal healthcare
19 programs for the drugs Levothroid, Celexa and
20 Lexapro. Forest has agreed to pay more than \$313
21 million to resolve criminal and civil liability
22 arising from these matters."

23 Did I generally read that correctly?

24 A Yes.

1 Q Were you aware that in 2010, Forest
2 agreed to plead guilty to off-label promoting Celexa
3 for use in children?

4 A I -- I don't -- I don't specifically
5 recall that. I mean, I -- you know, again, in
6 this -- in the work I did for Forest, this issue, it
7 might have come up in a prior deposition. I just
8 right now off the top of my head, I don't remember
9 specifically focusing on this. I don't --

10 Q Do you recall being aware -- would you
11 have been aware of this while you were at the FDA?

12 MS. KIEHN: Objection.

13 THE WITNESS: Not necessarily, because,
14 again, my group was focused on -- on reviewing
15 applications, INDs and NDAs, not in the -- in the
16 legal aspects of promotion. That was -- that was not
17 our focus in the review division.

18 BY MR. WISNER:

19 Q And on a personal level, did you
20 remember -- recall seeing or hearing about this
21 criminal plea in September of 2010?

22 MS. KIEHN: Objection.

23 THE WITNESS: I -- I don't.

24 BY MR. WISNER:

1 Q Okay. Following your departure from FDA,
2 you were approached by Forest to consult with them in
3 a litigation capacity, correct?

4 MS. KIEHN: Objection.

5 THE WITNESS: That's correct.

6 BY MR. WISNER:

7 Q And that was within about two months
8 after leaving the FDA; is that right?

9 A I left FDA in December of 2012. I think
10 I got called probably sometime in the spring, so
11 probably it would have been more four to five months,
12 something like that.

13 Q And you were approached by Forest to
14 provide testimony specifically related to Celexa and
15 Lexapro, correct?

16 A Well, specifically with regard to -- to
17 Lexapro. The Brown case was -- was about Lexapro, I
18 believe.

19 Q Okay. But in the Brown case you were
20 being offered as not only an expert on Lexapro but
21 also an expert with regards to Celexa.

22 A Yes.

23 Q When you were approached in 2013 to be a
24 consultant for Forest, did they disclose their

1 criminal conduct to you at that time?

2 MS. KIEHN: Objection.

3 THE WITNESS: I -- I -- I don't recall
4 that.

5 BY MR. WISNER:

6 Q Is that something you would have wanted
7 to have known before you agreed to -- to work with a
8 company in any sort of expert capacity?

9 A I -- my consultation was specifically
10 focused on the -- on the Brown case, so I -- you
11 know, and that -- and that would have been my focus.

12 Q Absolutely, Doctor.

13 However, you would have wanted to have
14 known that the company that was hiring you to be an
15 expert for them was an admitted criminal when it came
16 to their promotional practices with regards to Celexa
17 and specifically with children, correct?

18 MS. KIEHN: Objection.

19 THE WITNESS: I -- I don't -- I don't
20 know that -- again, you -- you use the word
21 "criminal." As a -- as a clinician, I don't think
22 it's inappropriate at all for a -- it wouldn't have
23 been inappropriate for a clinician to use Celexa in
24 treating children with depression even though it

1 wasn't specifically labeled for that. Because, you
2 know, I -- if there is ever a reason to believe that
3 these drugs, even though they were initially studied
4 in adults, would work in children, and -- and
5 childhood depression is a very serious problem that
6 needs to be addressed. So, again, I wouldn't have
7 been focused on that aspect of things. That's all I
8 can say.

9 BY MR. WISNER:

10 Q Okay, Doctor, but you understand that
11 Forest didn't plead guilty because doctors used
12 Celexa off label. They pled guilty because they
13 promoted the off-label use of Celexa in children.

14 You understand that?

15 MS. KIEHN: Objection.

16 THE WITNESS: I understand that.

17 BY MR. WISNER:

18 Q And I guess my question is now, at this
19 moment, the fact that a company that was hiring you
20 had pled guilty to committing the crime of off-label
21 promotion with regards to children, is that something
22 that you would have liked to have known?

23 A I don't --

24 MS. KIEHN: Objection.

1 THE WITNESS: -- have an opinion about
2 that. I just don't have an opinion.

3 BY MR. WISNER:

4 Q Okay. I don't mean to sound crass,
5 Doctor, but you don't typically like to work for
6 admitted criminals; is that right?

7 MS. KIEHN: Objection.

8 THE WITNESS: I -- I -- I -- that's --
9 that's not a question that I can -- that I can
10 answer.

11 BY MR. WISNER:

12 Q Okay. All right. You are aware in 2002
13 Forest actually attempted to secure a pediatric
14 indication for Celexa.

15 MS. KIEHN: Objection.

16 THE WITNESS: That's correct.

17 BY MR. WISNER:

18 Q Do you recall whether you were involved
19 in reviewing that application while you were at the
20 FDA?

21 A Yes.

22 Q And what do you recall your involvement
23 being?

24 A Well, I -- I was the team leader for

1 psychiatric drugs, and -- and so, you know, I would
2 have -- would have overseen the review of that
3 supplement. It would have been a supplement that
4 would have been submitted, and I would have reviewed
5 that. I would have overseen the review of that, and
6 I -- and I know that I did write a memo regarding
7 that supplement as well. So...

8 Q And that memo was specifically with
9 regard to whether or not you believed it would be
10 appropriate to approve Celexa for use in children.

11 A That's correct.

12 MS. KIEHN: Objection.

13 (Exhibit No. 3 was marked for
14 identification.)

15 BY MR. WISNER:

16 Q I'm handing you what has been marked as
17 Exhibit 3 to your deposition.

18 This is a memorandum dated
19 September 16th, 2002. Do you recognize this
20 document?

21 A Yes, I do.

22 Q This is in fact the memo you were just
23 mentioning, correct?

24 A This -- that's correct.

1 Q To be clear, this document was authored
2 by you while you were at the FDA?

3 A Yes.

4 Q And was it part of your duties at the FDA
5 to prepare memorandums recommending the approval or
6 non-approval of supplement applications?

7 A Yes.

8 Q And was this memorandum specifically
9 prepared in the regular course of your work at the
10 FDA?

11 A Yes.

12 Q Do you have any independent recollection
13 of your preparation of this memorandum?

14 A No. No. It's a long time ago.

15 Q Okay. The memorandum is addressed to
16 NDA 20-822/S-016. Do you see that?

17 A That's correct.

18 Q Can you explain what that -- that --
19 those numbers mean?

20 A The -- the NDA number is -- is the NDA
21 for Celexa. The supplement is -- is the number. It
22 means that this is supplement 16 to that NDA.

23 Q So it would be fair to interpret this as
24 this was seeking an additional indication to a drug

1 that had already been approved by the FDA.

2 A That's correct.

3 MS. KIEHN: Objection.

4 BY MR. WISNER:

5 Q And the additional indication was whether
6 or not this drug was specifically indicated for use
7 in pediatric populations.

8 A That's correct.

9 Q In that subject line -- I'm sorry, in the
10 "to" line, it also reads: "This overview should be
11 filed with the April 18th, 2002 original submission
12 of this supplement."

13 Do you see that?

14 A Yes.

15 Q Does that indicate to you that Forest
16 submitted this request for a pediatric indication for
17 Celexa on April 18th, 2002?

18 A That's correct.

19 Q And so this memorandum is dated
20 September 16th, 2002. You see that?

21 A That's correct.

22 Q So it would be fair to say between that
23 submission in April of 2002 and the issuing of your
24 memorandum in September of 2002, that was when you

1 oversaw the review of the application.

2 A That's correct.

3 Q Before the FDA approves a drug for use in
4 children, the FDA must be satisfied that the drug
5 maker has demonstrated efficacy and safety; is that
6 right?

7 MS. KIEHN: Objection.

8 THE WITNESS: That's correct.

9 BY MR. WISNER:

10 Q And part of your job at the FDA was to
11 make sure that before a drug was approved, you
12 believed there was sufficient evidence of safety and
13 efficacy. Is that fair?

14 A That's true.

15 Q As part of its request for a pediatric
16 indication, Forest submitted the results of two
17 double-blind, randomized, placebo-controlled clinical
18 trials, right?

19 A That's correct.

20 Q And what were those two studies?

21 A The first study, and I'm reading --
22 looking at my memo here, was Study 18. And the
23 second study was Study 94404.

24 Q Throughout this deposition I'm going to

1 refer to them as Study MD-18 and Study 94404. Is
2 that okay?

3 A That's fine.

4 Q Okay. Now, if you look on the first page
5 of this memorandum, turn to the last paragraph. Do
6 you see that?

7 A Yes.

8 Q It reads --

9 THE VIDEOGRAPHER: It's the (inaudible)
10 part that's not -- good.

11 BY MR. WISNER:

12 Q Okay. It reads: "Since the proposal was
13 to use the currently approved Celexa formulations for
14 this expanded population, there was no need for
15 chemistry or pharmacological -- pharmacology
16 reviews."

17 You see that?

18 A Yes.

19 Q What is a chemistry review?

20 A When a -- when a new drug application
21 comes in and the FDA is seeing it for the first time,
22 part of the review would be looking at the -- at the
23 data on the chemistry, the purity, stability and so
24 forth of the compound.

1 Q And that's -- that would be the chemistry
2 review?

3 A That's correct.

4 Q And the pharmacology review, what is
5 that?

6 A Pharmacology would be the -- the animal
7 pharmacology and the animal toxicology.

8 Q And because this drug had already gone
9 through those reviews with regards to adults, you did
10 not feel it was necessary to do that because of the
11 use in children, right?

12 A That's correct.

13 Q The sentence -- the next sentence reads:
14 "The primary review of the clinical efficacy and
15 safety was done by Earl Hearst, MD, from the clinical
16 group."

17 Do you see that?

18 A Yes.

19 Q Who is Dr. Hearst?

20 A Dr. Hearst is a psychiatrist who at the
21 time was one of the clinical reviewers in my group.

22 Q You were his supervisor, right?

23 A Yes.

24 Q And at some point there was a

1 reorganization within the division, and Dr. Hearst
2 left; is that correct?

3 A At -- at -- at some point he retired.

4 Q Fair enough.

5 My understanding is Dr. Hearst,
6 subsequent to being in this division, began working
7 specifically in neurology. Do you recall that?

8 A That's -- that's not -- not true. I have
9 no recollection -- I mean, he -- he --

10 Q That's fine. If I'm wrong, I'm wrong.

11 A Yeah. No, he's a psychiatrist, so there
12 isn't any way that he would have gone to the
13 neurology division.

14 Q Okay. So --

15 A He retired from the psychiatry division.
16 I remember going to his going-away party.

17 Q Okay. Do you know when that was?

18 A It was probably in maybe 2011. I -- I'm
19 not exactly sure, but it was -- it was sometime
20 before I left.

21 Q And during the time from -- from 2002 to
22 when he left, did he work under you as a clinical
23 reviewer?

24 A Yes. Well, again, I became division

1 director in -- in 2005, and so then I wasn't his
2 direct supervisor anymore, but he still -- he
3 continued in the -- in the division as a reviewer.

4 Q When you said here "the primary review,"
5 what did you mean by that?

6 A So, there are different levels of review.
7 The primary reviewers are the first line reviewers,
8 so they -- they write a review. The next level would
9 be the team leader. The next level beyond that
10 would -- you know, would be the division director.
11 And for a new drug application, the office director
12 would -- would often also write a memo.

13 Q Okay. So here it says: "The primary
14 review was done by Earl Hearst."

15 Does that mean there was only one primary
16 review done?

17 MS. KIEHN: Objection.

18 THE WITNESS: Well, one -- one primary
19 clinical review. There would have been possibly a
20 review done by -- it probably would have been the
21 only review in this case.

22 BY MR. WISNER:

23 Q Sure. But, for example, if there had
24 been a chemistry review, that would have been done by

1 somebody as well?

2 A Yes.

3 Q And as well as a pharmacology review?

4 A Right.

5 Q Okay. And then after Dr. Hearst
6 completed his primary review, then you would go about
7 conducting your review or would they be done
8 simultaneously?

9 A I -- you know, again, it varies. I don't
10 remember what the sequence was here. I might have
11 been working on it in parallel. I might have waited
12 until he was done. I don't recall.

13 Q Okay. What sort of information would a
14 clinical reviewer like Dr. Hearst rely upon to
15 conduct a primary clinical review?

16 A He would have carefully reviewed the
17 supplement, that document that came in in April of
18 2002.

19 Q And that would have included the final
20 study reports and accompanying tables and appendixes,
21 associated --

22 A Correct.

23 Q -- Study MD-18 as well as 94404?

24 A That's correct.

1 Q All right. If you look at the next
2 sentence, it says: "Since there was agreement
3 between the sponsor and FDA that these trials were
4 negative, there was no need for a statistics review
5 of the efficacy data."

6 Do you see that?

7 A Yeah, I -- I see -- I see that now, and
8 that's a -- of course, a misstatement because one of
9 the studies was positive. And I noticed that I -- I
10 state that in the first paragraph here. I state it
11 again on page 3 in my comment on Study MD-18. I say:
12 "I agree with Dr. Hearst that this is a positive
13 study."

14 And I say it several times later in the
15 document. So I don't -- I don't recall why -- why I
16 said that. But the statement -- you know, the -- the
17 conclusion is still the same. Since our requirement
18 for approving a pediatric supplement would have been
19 two studies, two positive studies, and since it
20 didn't meet that threshold -- so since we knew that
21 we weren't going to approve it, we often wouldn't get
22 a full statistical review at that time.

23 Q Would it be fair to say then that when
24 you stated here that the agreement between the

1 sponsor and FDA that these trials were negative
2 was referring to negative in the sense that it
3 wouldn't be sufficient to secure a pediatric
4 indication?

5 A That's -- that's the way I interpret
6 that, yes.

7 Q Now, it says "sponsor" here. I just want
8 to be clear that's referring to Forest, correct?

9 A Correct.

10 Q Okay. It says: "There was no need for a
11 statistics review of the efficacy data."

12 What is a statistics review?

13 A It -- it's an overlapping review that
14 specifically focuses on the -- on the efficacy data.
15 Somewhat redundant with the clinical review.

16 Q And what -- what is the difference, if
17 there is any, between a statistics review and a
18 clinical review?

19 A The -- the statistical review would
20 likely go into more detail on the -- on the analysis
21 plan and whether or not it was followed in -- in
22 conducting the analysis.

23 Q And by analysis plan, you are referring
24 to the prespecified efficacy parameters and the

1 protocol?

2 A And -- and the plan for analyzing the
3 data.

4 Q So that also would apply to adverse
5 events, safety data as well?

6 A Typically a statistics reviewer would not
7 look at -- at adverse events because there's -- there
8 wouldn't have been any hypothesis testing, and their
9 focus is primarily on hypothesis testing.

10 Q Do you have any independent recollection
11 of having any discussions with Forest about there not
12 being a need for a statistics review of the efficacy
13 data?

14 A No. No.

15 Q Okay. Is that a discussion, based on the
16 sentence you read here, that you probably did have at
17 some point?

18 A I -- I doubt that -- I doubt that we
19 actually had a discussion about that. It was -- it
20 would have been just obvious since everyone knew what
21 the standard was that you had to have two studies to
22 get a claim, and they -- they clearly acknowledged
23 that one of their studies was negative. So there
24 wouldn't have been any basis for a claim.

1 Q All right. If you look at page 2, from
2 page 2 to page 4, you did a sort of overview review
3 of Study MD-18 and Study 94404, correct?

4 A Correct.

5 Q All right. Let's first look at page 4.
6 Do you see the last sentence of the second paragraph
7 that reads: "The results on the primary outcome were
8 as follows"? Do you see that?

9 A Yes.

10 Q Now, when you say "primary outcome" here,
11 you're referring to the primary endpoint, correct?

12 A That's correct.

13 Q Okay. And then you see here listed are
14 the efficacy results on the Kiddie-SADS-P total score
15 for Study 94404, open paren, OC, close paren.

16 Do you see that?

17 A Yes.

18 Q Is it your understanding that the
19 Kiddie-SADS-P total score was the primary efficacy
20 endpoint for Study 94404?

21 A Yes.

22 Q And it says -- and the Kiddie-SADS-P,
23 that's referring to a rating scale for pediatric
24 depression?

1 A That's correct.

2 Q And it says OC, that's referring to
3 observed cases, right?

4 A Right.

5 Q Observed cases is different than last
6 observation carried forward?

7 A That's correct.

8 Q Could you briefly explain to the jury
9 your understanding of the difference between
10 "observed cases," OC, and "last observation carried
11 forward," or LOCF?

12 A An LOCF analysis uses data that are
13 carried forward from the time that a patient drops
14 out of a study. So, for example, if it's in -- you
15 know, this was I think a 12-week study. Yes. So if
16 a patient dropped out at eight weeks in a 12-week
17 study, that last score, that last recording on the
18 Kiddie-SADS would have been carried forward as if
19 that patient continued to 12 weeks. Whereas, an
20 observed cases analysis only includes the data on the
21 patients who completed to 12 weeks.

22 Q Do you have an opinion one way or the
23 other whether an OC analysis or an LOCF analysis is
24 better?

1 A General -- generally, you know, at that
2 time we tended to rely more on LOCF analyses than
3 observed cases. They both have their pros and cons.

4 Q I don't want to get into a longwinded
5 answer, and if it takes too long to explain, that's
6 fine, but what are sort of the pros and cons of the
7 two analyses?

8 A Well, the problem with the observed cases
9 is that it's a -- it's a truncated analysis in the
10 sense that you're not using data from patients who
11 didn't complete.

12 The problem with an LOCF analysis is that
13 you're -- you're assuming that the score at eight
14 weeks is -- that if that patient continued, it would
15 have been that same score at 12 weeks, and that's --
16 that's an assumption that's -- you don't have any way
17 of verifying that. So...

18 Q So you agree then that the OC approach as
19 well as the LOCF approach are really two different
20 ways of looking at the same data?

21 A Yes.

22 Q And typically the protocol will specify
23 whether or not the primary endpoint will use an LOCF
24 or an OC analysis, right?

1 A Yes.

2 Q Now, here you depicted the efficacy
3 results for the primary endpoint for Study 94404,
4 right?

5 A That's right.

6 Q And under the heading, it says "P-val
7 versus placebo." Do you see that? In the table on
8 the far right.

9 MS. KIEHN: P-value versus --

10 MR. WISNER: Yeah.

11 MS. KIEHN: -- P-val.

12 MR. WISNER: Yeah, I misspelled it in my
13 outline. Sorry.

14 THE WITNESS: Oh, P-value --

15 BY MR. WISNER:

16 Q It says "P-value versus placebo," do you
17 see that?

18 A P-value, yeah. Yes, yes.

19 Q And that's -- that's the P-value of the
20 difference observed in the treatment group of Celexa
21 and the placebo arm, correct?

22 A That's correct.

23 Q And that's not statistically significant,
24 correct?

1 A That's correct.

2 Q And if you look at the next sentence
3 below that table, it says: "The results were equally
4 negative on secondary outcomes."

5 Do you see that?

6 A That's correct.

7 Q So would it be fair to say then that all
8 the primary endpoints as well as the secondary
9 endpoints, based on what you said here, were
10 negative?

11 A That's my assumption that that's true,
12 yes.

13 Q All right. Then you have a comment, and
14 it reads: "This is a clearly negative study that
15 provides no support for the efficacy of citalopram in
16 pediatric patients with MDD."

17 Do you see that?

18 A That's correct.

19 Q And that was clearly negative because the
20 primary as well as the secondary endpoints were all
21 negative.

22 MS. KIEHN: Objection.

23 THE WITNESS: It would -- you know,
24 primarily that the primary endpoint was -- was

1 negative. It didn't -- it didn't -- again, that's --
2 that's the standard. It has to -- it has to make it
3 on the primary endpoint in order to be a positive
4 study.

5 BY MR. WISNER:

6 Q But you agree that the fact that in
7 addition to the primary endpoint not being
8 statistically significant, the fact that all the
9 secondary endpoints were also --

10 A It supported the conclusion reached from
11 looking at the primary endpoint.

12 MR. ELLISON: Would you let him finish --

13 BY MR. WISNER:

14 Q Yeah, Doctor, I appreciate you know where
15 I'm going with my questions, but you've got to let me
16 finish my question before you answer.

17 A Sorry.

18 Q I do the same thing to people all the
19 time, so I -- I understand the desire to do that.

20 Okay, great. Let's move on to the next
21 exhibit here.

22 (Exhibit No. 4 was marked for
23 identification.)

24 BY MR. WISNER:

1 Q I'm handing you what has been premarked
2 as Exhibit 4 to your deposition.

3 This is a document titled "A Randomized,
4 Double-Blind, Placebo-Controlled Evaluation of the
5 Safety and Efficacy of Citalopram in Children and
6 Adolescents with Depression," dated September 1st,
7 1999.

8 Do you recognize this document?

9 A Not offhand.

10 Q Okay. Would it be fair to say that this
11 appears to be a copy of the study protocol for MD-18?

12 A It -- it does appear to be the protocol.

13 Q You understand that in addition to
14 seeking a pediatric indication for Celexa, Forest
15 also submitted MD-18 and Study 94404 to obtain an
16 extension on exclusivity for six months.

17 A That's correct.

18 Q However, just because the agency denied
19 the pediatric indication for Celexa, the fact that
20 they did the study allowed them to get the
21 exclusivity for an additional six months, correct?

22 A That's correct.

23 Q Because exclusivity was contingent upon
24 conducting the studies, not necessarily getting

1 positive results in them.

2 A That's correct.

3 Q Okay. Turn to the second page on this
4 document. Do you see the section -- it's
5 double-sided so it's the second page.

6 A Okay.

7 Q It's the page numbered 309 on the top
8 right. Do you see that?

9 A I see that.

10 Q Okay. It's a section titled "Final
11 Protocol Authorization Sign-Off Sheet." Do you see
12 that?

13 A Yes.

14 Q Do you know what this section refers to?

15 A It's fairly typical to see this document
16 in a protocol. It -- it's just an acknowledgment
17 that the final protocol was -- was officially
18 approved by various individuals at the company.

19 Q And you understand that these are all
20 individuals at Forest, correct?

21 A Correct.

22 Q The first person is Paul Tiseo. Do you
23 see that?

24 A Yes.

1 Q Do you know who Paul Tiseo is?

2 A No.

3 Q Have you ever met Paul Tiseo?

4 A Not that I recall. I may have. I met
5 thousands of people from companies. I may have met
6 him. I just don't -- don't recall.

7 Q Sure. So you -- so you have no
8 independent recollection of ever speaking or
9 interacting with Dr. Tiseo?

10 A No.

11 Q Okay. Now, it says here that he's a
12 medical monitor. Do you see that?

13 A I see that.

14 Q Do you know what that is?

15 A He's the, you know, the primary person at
16 the company who has responsibility for overseeing the
17 conduct of that -- that study.

18 Q Okay, great.

19 Now, if you go down here, you also see
20 Charles Flicker, Ph.D. Do you see that?

21 A I see that.

22 Q And it says here he's the senior medical
23 director, CNS.

24 A I see that.

1 Q Okay. Do you know Dr. Flicker?

2 A Same answer. Not -- not offhand, no.

3 Q So you don't have any independent
4 recollection of ever meeting Dr. Flicker?

5 A I -- I don't.

6 Q Okay. Do you recall what role, by any
7 chance, he played in this clinical trial?

8 A It -- it looks from his title that he was
9 the, you know, the senior medical director in the CNS
10 group at -- at Forest.

11 Q And then below that, you see Lawrence
12 Olanoff. Do you see that?

13 A I do.

14 Q And he is also a physician as well.

15 A I see that.

16 Q Okay. Do you know Dr. Olanoff?

17 A I have -- I have met Dr. Olanoff.

18 Q In what capacity have you met
19 Dr. Olanoff?

20 A At -- at FDA.

21 Q At FDA. Do you recall when you met him
22 or how many times you met him?

23 A My -- my recollection is that he would
24 show up at -- at meetings we had with -- with Forest.

1 So it would have been in that context that I -- that
2 I met him.

3 Q Okay. Do you recall having any -- any
4 interaction with Dr. Olanoff in your capacity
5 consulting with Forest or Allergan?

6 A I -- I don't recall.

7 Q If Dr. Olanoff had testified to recall
8 having a phone conference that you were on with him
9 in 2013, do you have any reasons to dispute that?

10 MS. KIEHN: Objection.

11 THE WITNESS: No. I mean it's certainly
12 possible. I mean --

13 BY MR. WISNER:

14 Q But you don't recall any conversations?

15 A I can't recall it.

16 Q Do you recall ever having any
17 conversations with Dr. Olanoff about Celexa or
18 Lexapro specifically?

19 A I don't.

20 Q Okay. So I can't -- if I ask you if you
21 remembered what those conversations entailed, you
22 definitely couldn't answer that.

23 A I could not answer that.

24 Q Okay. If you also look over to the

1 right, there's Ivan Gergel. Oh, we're still on the
2 same page.

3 A Yes, I see that.

4 Q Do you know Dr. Gergel -- Dr. Gergel?

5 A Not offhand.

6 Q Okay. So his -- his name doesn't ring
7 any bells?

8 A No.

9 Q Okay. So you have no recollection of
10 ever meeting with Dr. Gergel?

11 A I don't have any recollection. It's
12 possible that I did, but --

13 Q Okay. And then these last two people,
14 Edward Lakatos and Keith Rotenberg, do you know them,
15 by any chance?

16 A Keith Rotenberg, that name sounds
17 familiar, but I -- I can't -- I can't honestly recall
18 him.

19 Q His title is executive director of
20 Regulatory Affairs and Quality Assurance. That
21 suggests that he may have interacted with you in your
22 capacity at the FDA.

23 MS. KIEHN: Objection.

24 THE WITNESS: Very likely did.

1 BY MR. WISNER:

2 Q I want to come back to this document in a
3 second.

4 (Exhibit No. 5 was marked for
5 identification.)

6 BY MR. WISNER:

7 Q I'm handing you what has been premarked
8 as Exhibit 5 to your deposition.

9 This document contains the excerpts of a
10 deposition taken of Charles Flicker on October 26,
11 2007, in the In re Forest Laboratories, Inc.
12 Securities litigation.

13 Have you ever seen this transcript
14 before?

15 A Not that I recall.

16 Q All right. Please turn to page 34. And
17 by page 34, I'm referring to the small page 34
18 written on the top part.

19 A Okay.

20 Q Okay, great. Starting at line 4, it
21 reads:

22 "Q. Did you have a role in
23 creating the protocol for Study 18?

24 "A. Yes, that came under my

1 supervision."

2 Do you see that?

3 A I see that.

4 Q Okay. If you move down the transcript to
5 line 18, it reads:

6 "Q. What was your role in
7 supervising the creation of Study
8 18's protocol?

9 "A. I would have reviewed the
10 draft, revised it and ultimately
11 have given my approval of it."

12 Do you see that?

13 A I see that.

14 Q So based on this testimony, it appears
15 that Dr. Flicker played a supervisory role in
16 overseeing the creation and approval for the protocol
17 of MD-18.

18 MS. KIEHN: Objection.

19 THE WITNESS: Yes.

20 BY MR. WISNER:

21 Q Okay. Turn to page 36 in this
22 deposition. Starting at line 16, it reads:

23 "Q. Do you recall any other
24 individuals at Forest Labs other

1 than Dr. Heydorn who reported
2 directly to you between the years of
3 your beginning in 1996 to 1998 and
4 ending in 2003?

5 "A. Yes. Mary Mackle -- between
6 when, the entire period I was there?

7 "Q. Correct.

8 "A. Mary Mackle, Paul Tiseo, Bill
9 Heydorn, Paul Butkerait" -- spelled
10 B-U-T-K-E-R-A-I-T -- it continues:

11 "Ralph Bobo, Joan Singh, and Anjana
12 Bose."

13 Do you see that?

14 A I do.

15 Q Okay. Based on his testimony, it appears
16 that Dr. Tiseo worked under Dr. Flicker, correct?

17 A That appears that way.

18 Q Okay. Do you -- do you know Bill
19 Heydorn?

20 A That name sounds familiar. I -- if I'm
21 recalling correctly, I believe that he worked at FDA
22 at one point. I -- I think that's true, but --

23 Q Do you recall what he did at FDA?

24 A I -- again, this goes way back, but I --

1 I believe that he was a pharmacologist.

2 Q Do you remember having a favorable view
3 of Dr. Heydorn's work?

4 A I -- number one, if he was a
5 pharmacologist, I wouldn't have supervised his work,
6 so I --

7 Q All right. Do you recognize any of those
8 other names in that list there, Paul, Ralph or Joan
9 or Anjana?

10 A No.

11 Q Okay.

12 (Exhibit No. 6 was marked for
13 identification.)

14 BY MR. WISNER:

15 Q All right. I'm handing you what has been
16 premarked as Exhibit 6 to your deposition.

17 And, Doctor, I will just advise you that
18 I'm going to be reading various portions of testimony
19 to you, primarily for the purposes of laying the
20 foundation for later questions. So if you're
21 wondering why I'm showing you all these deposition
22 transcripts, that's the intent.

23 The document I just handed you contains
24 the excerpts of a deposition taken of Charles Flicker

1 on November 4th, 2016, in the In re Celexa and
2 Lexapro Marketing Sales and Practices litigation.

3 Have you ever seen this transcript
4 before?

5 A Not that I recall.

6 Q Okay. Please turn to page 121. Starting
7 at line 18, it reads:

8 "Q. Do you know who was
9 responsible for the overall conduct
10 of Study MD-18?

11 "MR. ROBERTS: Objection.

12 "THE WITNESS: Well, Paul Tiseo
13 was the lead clinician.

14 BY MR. BAUM:

15 "Q. What was his role with respect
16 to CIT-MD-18 before he left Forest?

17 "A. Well, I now see that he had a
18 primary role in generating the
19 protocol, and about what documents
20 I've seen yesterday, he was
21 obviously involved in the -- in the
22 oversight of the running of the
23 study."

24 Do you see that?

1 A I do.

2 Q So based on Dr. Flicker's testimony here,
3 it appears that Dr. Tiseo was responsible for
4 overseeing the overall conduct of Study MD-18; is
5 that right?

6 MS. KIEHN: Objection.

7 THE WITNESS: It -- it appears from --
8 from this testimony.

9 BY MR. WISNER:

10 Q Okay. Let's turn back to deposition
11 Exhibit 4, which is the protocol. I told you we're
12 going to be going back and forth, so that's why I
13 warned you.

14 Okay, great. Please turn to page 329 on
15 the top right-hand corner.

16 A Okay.

17 Q Do you see the section that reads
18 "Statistical Evaluation"?

19 A I do.

20 Q Under the primary objective, it reads:
21 "The primary objective is to compare the efficacy of
22 citalopram, 20 to 40 milligrams a day, to placebo in
23 children 7 to 11 years and adolescents 12 to 17 years
24 with major depressive disorder. The primary endpoint

1 is changed from baseline in CDRS-R score at week 8."

2 Did I read that correctly?

3 A Yes.

4 Q Is it your understanding that the primary
5 endpoint of the study was the change from baseline in
6 CDRS-R score at week 8?

7 A That appears to be what it is, yes.

8 Q And the change in baseline from the
9 beginning to the end of the study, that was a typical
10 primary efficacy endpoint and clinical trials related
11 to depression?

12 A That's true.

13 Q And the CDRS-R score at that time was
14 considered a reliable scale for assessing pediatric
15 depression.

16 A That's correct.

17 Q As well as for assessing the change or
18 improvement of pediatric depression.

19 A That's true.

20 Q Now, under the secondary objectives, it
21 reads: "To further compare the efficacy of
22 citalopram to placebo in depressed children and
23 adolescent patients, the endpoints for the secondary
24 objectives are the CGI improvement score and change

1 of baseline in CGI severity score, K-SADS-P
2 depression module score, and CGAS score at week 8."

3 Did I read that correctly?

4 THE WITNESS: That's correct.

5 MS. KIEHN: Let me just -- "change from
6 baseline," not "change of baseline."

7 MR. WISNER: I'm sorry. Did I say "in
8 baseline"?

9 MS. KIEHN: You said "of baseline."

10 MR. WISNER: And it's "change in
11 baseline"?

12 MS. KIEHN: "From baseline."

13 MR. WISNER: "From baseline." Thank you.

14 BY MR. WISNER:

15 Q Is it your understanding that the
16 secondary endpoints for MD-18 were the CGI
17 improvement score and change from baseline in CGI
18 severity score, K-SADS-P depression module score, and
19 CGAS score at week 8?

20 A That is what the protocol states.

21 Q Okay, great. Please turn to page 328.

22 Do you see the section titled "Unblinding
23 Procedures"?

24 A I do.

1 Q Okay. In your experience, is it common
2 for a protocol for a double-blind, placebo-controlled
3 trial to contain a section outlining the unblinding
4 procedures for the study?

5 A There would generally be some mention of
6 that in a protocol, yes.

7 Q What does it mean for there to be
8 unblinding?

9 A Well, there has to be the -- the ability
10 to unblind the medication for a patient in a trial
11 who gets into some medical difficulty.

12 Q And unblinding doesn't refer to just
13 those circumstances, though. It refers to any
14 circumstance wherein either the investigator or a
15 patient becomes aware of what arm they're in in their
16 clinical trial; is that fair?

17 MS. KIEHN: Objection.

18 THE WITNESS: Let -- let me read exactly
19 what -- what this --

20 BY MR. WISNER:

21 Q Well, I'm not talking about what that
22 says. I'm talking about generally the phrase
23 "unblinding." So we'll get back to that section in a
24 second, Doctor.

1 MS. KIEHN: If he needs to read that
2 section to answer the question, he should read that
3 section.

4 MR. WISNER: I'm not asking about that
5 section. I'm asking about the word "unblinding."
6 BY MR. WISNER:

7 Q Generally the word "unblinding" means
8 either the investigator or the patient has become
9 aware of whether or not they're taking the drug or
10 the placebo. Is that fair?

11 A That -- that is the meaning of the
12 general term, whatever the cause, you know, whether
13 it's inadvertent unblinding or purposeful unblinding
14 because the patient has -- you know, the treatment
15 assignment has to be identified because they're
16 having a medical emergency.

17 Q In your opinion, if an investigator
18 learns whether a study participant is being treated
19 with a drug or a placebo, does that mean the blinding
20 has been broken with regards to the investigator?

21 A If -- if the investigator learns what the
22 treatment assignment is, yes, then the investigator
23 is unblinded.

24 Q Okay. Now, going back to this section,

1 in the second to last paragraph in this section of
2 the protocol, it reads, in italics: "Any patient for
3 whom the blind has been broken will immediately be
4 discontinued from the study and no further efficacy
5 evaluations will be performed."

6 Do you see that?

7 A I see that.

8 Q According to the sentence, if the blind
9 has been broken for any patient for any reason, they
10 are to be immediately discontinued from the study and
11 no further efficacy evaluation is performed, correct?

12 MS. KIEHN: Objection.

13 THE WITNESS: That's -- that's not what
14 it says. This is specifically referring to
15 unblinding -- purposeful unblinding, you know, by the
16 site for specific reasons.

17 BY MR. WISNER:

18 Q Now, Dr. Laughren --

19 A That -- I mean that is what this says.
20 I'm just -- I'm just giving you my interpretation of
21 what this -- this "Unblinding Procedure" section is
22 referring to. It's -- because it's talking about the
23 tear-off panel.

24 It's talking about, you know: "The

1 tear-off panel identifying the treatment should be
2 opened only in the event that an emergency
3 necessitates identification of the medication."

4 And then it goes on to say: "For that
5 patient for whom there's been a medical emergency,
6 that patient will be discontinued."

7 It doesn't say any unblinding. It
8 doesn't say that.

9 Q Doctor, first, before I ask you this next
10 question, have you been told to say that today?

11 A I have absolutely not been told to say
12 that. I'm just -- I'm just reading and interpreting,
13 as I understand it, what the protocol is. This is
14 referring to purposeful unblinding for a patient who
15 has had a medical emergency.

16 Q Now, Doctor, to be clear, it's your
17 testimony to this jury and under oath that you have
18 not been told to make that interpretation of that
19 sentence today?

20 A I have absolutely not been told to say --
21 to interpret anything. I -- I'm simply reading
22 from -- from this -- from this section in the
23 protocol, and -- and my interpretation of what -- of
24 what it implies to.

1 Q Okay. I understand that. I was just
2 asking if you've been told to say that --

3 A I -- I --

4 Q -- and your testimony is you have not
5 been?

6 A I have not been told to say that.

7 Q Okay. Now, the sentence does read: "Any
8 patient for whom the blind has been broken will be
9 immediately discontinued from the study and no
10 further efficacy evaluations will be performed."

11 Is your understanding that if a patient
12 is unblinded in a different context, not related to
13 this tear-off panel procedure, that they should no
14 longer be included in the efficacy evaluation for
15 that study?

16 A That -- that is not the way I would
17 interpret this, because it -- first of all, it comes
18 under a section which is specifically referring to a
19 particular type of unblinding, and it immediately
20 follows a paragraph talking about opening of the
21 blind for that patient, you know, for a specific
22 reason.

23 Q Now, Doctor, putting aside this section,
24 if a patient is unblinded or an investigator is

1 unblinded for a specific patient, you agree that that
2 patient's efficacy data should no longer be included?

3 A I do not --

4 MS. KIEHN: Objection.

5 THE WITNESS: I absolutely do not agree.

6 BY MR. WISNER:

7 Q Sorry. Let me just finish my question
8 before the objection and the answer. Sorry, Doctor,
9 I don't mean to interrupt you, but I always wait for
10 you to finish. If could give the same courtesy for
11 me.

12 A I'm sorry. I apologize.

13 Q Now, if a patient has been unblinded in a
14 study, do you agree that that patient should be
15 discontinued -- discontinued from any further
16 efficacy evaluations because that data is no longer
17 subject to the double-blind procedure?

18 MS. KIEHN: Objection.

19 THE WITNESS: The only way that -- that a
20 patient or an investigator can be definitively
21 unblinded is if you break the code and -- and know,
22 this gets back to the discussion that we were having
23 earlier about the notion of -- of blinding in -- in
24 clinical trials, and -- and the fact that an

1 investigator or a patient may guess, they -- they may
2 assume that they're on active medication because they
3 experience a particular side effect. They may assume
4 that or the investigator may assume that if the
5 patient complains of that side effect. That doesn't
6 mean that in fact the investigator or the patient is
7 unblinded.

8 BY MR. WISNER:

9 Q Now, Doctor, if a patient was
10 unmistakably unblinded, in that context you would
11 agree they should be discontinued from the study and
12 no further efficacy evaluations performed?

13 MS. KIEHN: Objection.

14 THE WITNESS: The only -- the only way
15 that a patient can be definitively unblinded is if
16 the code was broken.

17 BY MR. WISNER:

18 Q Doctor, that -- that really was not my
19 question. So if you could answer my question, I
20 would appreciate that.

21 A Could you ask the question again?

22 Q Absolutely.

23 If a patient was in fact unmistakably
24 unblinded, you agree in that circumstance they should

1 be discontinued from the study and no further
2 efficacy evaluation should be performed?

3 MS. KIEHN: Objection.

4 THE WITNESS: Can -- can you say what you
5 mean by "unmistakenly"? I -- I don't understand.

6 BY MR. WISNER:

7 Q Well, "unmistakenly" means there is no
8 mistake, right?

9 MS. KIEHN: Objection.

10 THE WITNESS: I will answer no.

11 BY MR. WISNER:

12 Q Okay. What does the word "unmistakenly"
13 mean to you, Doctor?

14 A I don't -- I don't know what the word
15 means.

16 What I'm telling you is that in my -- in
17 my opinion, the only way that a patient can be
18 definitively unblinded or an investigator definitely
19 unblinded is if the code is broken.

20 Q I understand --

21 A Any -- anything else -- anything else is
22 inference. It's speculation.

23 Q And --

24 A Let me finish.

1 Q Sure. I thought you were finished. I'm
2 sorry. Are you done?

3 A I'm done.

4 Q Okay. I appreciate your answer, and I'm
5 going to move to strike it as nonresponsive after the
6 word "I don't know what 'unmistakenly' means," or
7 whatever that answer was.

8 Is it your testimony to this jury that
9 you do not know the definition of the word
10 "unmistakenly"?

11 MS. KIEHN: Objection.

12 THE WITNESS: What I'm telling you --
13 what I'm telling you is that in my opinion, the only
14 way that an investigator or patient can be
15 definitively unblinded is if the code is broken.

16 BY MR. WISNER:

17 Q Okay. We're going to go back to that in
18 a second. But I'm going to again ask my question
19 because I don't think you've actually answered it
20 yet.

21 Is it your testimony to this jury that
22 you do not know the definition of the word
23 "unmistakenly," yes or no?

24 MS. KIEHN: Objection.

1 THE WITNESS: I -- I don't understand
2 what you mean by the word "unmistakenly."

3 BY MR. WISNER:

4 Q Okay. Typically you would agree with me
5 that the word "unmistakenly" means that there can be
6 no question. Is that fair to say?

7 A I would -- I would use the word
8 "definitive."

9 Q Okay. So the word "unmistakenly" means
10 that there was no mistake in coming to whatever the
11 verb that follows that adverb, right?

12 MS. KIEHN: Objection.

13 THE WITNESS: Let -- let me ask for a
14 further definition of "unmistakenly."

15 BY MR. WISNER:

16 Q Sure.

17 A Does it -- does it mean that -- that with
18 absolute certainty it's known that the patient and
19 the investigator know what the treatment assignment
20 was?

21 If that's what it means -- if that's what
22 it means, then -- then I agree.

23 Q Okay.

24 A But that's -- that's different.

1 That's -- that's different.

2 And -- I mean this all comes down to
3 whether or not you can throw patients out of an
4 analysis. And -- and I -- I feel very strongly about
5 taking that action because it compromises the
6 randomization, which -- which, again, in my view is
7 the most sacred and fundamental thing to a randomized
8 controlled study.

9 Q All right, Doctor, I -- I appreciate your
10 answer, I do. But I'm actually asking a very simple
11 question.

12 When I say that this cup is unmistakably
13 white, that means that there is no question that this
14 cup is white, right?

15 A Yes.

16 MS. KIEHN: Objection.

17 BY MR. WISNER:

18 Q Okay. If I tell you that the integrity
19 of the blind was unmistakably violated, that means
20 there is no question that the integrity of the blind
21 was unmistakably violated -- was violated, right?

22 MS. KIEHN: Objection.

23 THE WITNESS: We've gotten so far into
24 this that I -- I've lost -- I've lost the original

1 question. What was the question?

2 BY MR. WISNER:

3 Q Okay. The original question was: If in
4 fact a patient was unmis- -- the patient's blind was
5 unmistakably violated, okay? In that circumstance,
6 you agree when that happens that there shouldn't be
7 any further efficacy evaluations done of that
8 patient, and those additional efficacy evaluations
9 shouldn't be included in the overall analysis.

10 MS. KIEHN: Objection.

11 THE WITNESS: I actually don't -- I
12 actually don't agree with that.

13 BY MR. WISNER:

14 Q Okay. So if a doctor, let's say, an
15 investigator completely violates the protocol, and
16 instead of issuing the patient the prescribed white
17 tablets that they're supposed to issue pursuant to
18 the protocol, they hand them Celexa branded samples
19 and say, Listen, just take these and we'll do your
20 efficacy evaluations with these Celexa branded
21 tablets.

22 In that circumstance you agree that the
23 blind is broken, right?

24 MS. KIEHN: Objection.

1 THE WITNESS: Yes.

2 BY MR. WISNER:

3 Q Okay. In those circumstances you agree
4 that the data from that patient should not be
5 considered with other patients who were actually
6 subject to a proper double-blind procedure, correct?

7 MS. KIEHN: Objection.

8 THE WITNESS: The -- it -- the -- the
9 data -- the data from -- the investigator, first of
10 all, would -- would be basically engaging in conduct
11 that -- that is completely unacceptable and -- and
12 should be prevented from ever doing any -- any
13 further research.

14 BY MR. WISNER:

15 Q Sure.

16 A And -- and one might consider throwing
17 out all the data from that site, if -- if there was
18 intentional misconduct.

19 Q Okay.

20 A There's a -- there's a big difference
21 between that and inadvertent unblinding, which --
22 which, again, may -- may often occur because of side
23 effects of a drug. And that does not necessarily
24 invalidate the data, in my view, and does not mean

1 that the data cannot be used in the analysis.

2 Again, my -- my concern is always, you
3 know, willy-nilly excluding data from an analysis
4 because of the effect that has on the randomization,
5 but...

6 Q Okay. But you agree, though, at least in
7 principle, that if there has in fact been an
8 unblinding and in fact the patient or the physician
9 who is treating the patient knows definitively
10 whether or not they're in the placebo arm or in the
11 treatment arm, that has the potential to cause bias.

12 MS. KIEHN: Objection.

13 THE WITNESS: That has -- although that
14 has the potential to cause bias, it doesn't mean, in
15 my view, that those data can't be used in an
16 analysis.

17 BY MR. WISNER:

18 Q Fair enough. But should they be used?

19 A I -- I -- I think in -- in general,
20 unless there are very, very compelling reasons,
21 including the reasons that are stated in here -- and
22 honestly, I'm not even sure here that I agree that
23 the data that were collected up to the point, if one
24 does decide to -- to basically remove the patient

1 from the study, that the data up to that point could
2 not be used. They -- they probably should be
3 included in the analysis.

4 Q Sure. And so up to the point of the
5 unblinding, they would be discontinued from the study
6 and you would do an LOCF analysis with the -- the
7 last data point, right?

8 MS. KIEHN: Objection.

9 THE WITNESS: That -- that's -- that's
10 correct. But -- but where we're getting into
11 disagreement is, is whether or not a patient who is
12 inadvertently unblinded, that that patient should be
13 either removed from the study or the data from that
14 patient not used, and that's -- and that's where I --
15 I disagree.

16 BY MR. WISNER:

17 Q Fair enough. And that wasn't the
18 question I asked, Doctor.

19 A Okay.

20 Q So I appreciate your testimony to that
21 effect, but that's not what I'm getting at yet.

22 What I'm getting at here is, you agree
23 that once the unblinding occurs for a patient or an
24 investigator, at that point you shouldn't be

1 conducting further efficacy evaluations of that
2 patient, and including it with the rest of the cohort
3 that was actually fully double-blind because that has
4 the chance to corrupt or bias the data.

5 MS. KIEHN: Objection.

6 THE WITNESS: I -- I actually don't agree
7 with that.

8 BY MR. WISNER:

9 Q Okay. So you don't have a problem
10 considering data from unblinded patients in a
11 double-blind, randomized, placebo-controlled trial.

12 MS. KIEHN: Objection.

13 THE WITNESS: Although that's not ideal,
14 and I -- I agree that in general, in psychiatric
15 trials one should strive to have, you know, adequate
16 blinding. I don't believe that it invalidates the
17 study to have some patients who are unblinded. And
18 I -- and I mentioned earlier that there are other
19 psychiatric trials that are explicitly open label and
20 were considered completely valid trials by FDA.

21 BY MR. WISNER:

22 Q But, Doctor, I'm not talking about
23 validity. I'm talking about appropriateness.

24 A Well --

1 Q Do you think it's appropriate to include
2 that data?

3 MS. KIEHN: Objection.

4 THE WITNESS: Well, validity is -- is
5 what counts --

6 BY MR. WISNER:

7 Q I see.

8 A -- in my mind.

9 Q All right, Doctor, let's continue going
10 through this.

11 It's your opinion then before this jury
12 that this section that says "Unblinding Procedures,"
13 which contains the sentence in italics, "Any patient
14 for whom the blind has been broken will immediately
15 be discontinued from the study and no further
16 efficacy evaluations will be performed," refers only
17 to the procedure of the tear-off panel and does not
18 refer to other forms of unblinding in the study; is
19 that right?

20 A That's my understanding of this -- of
21 this section.

22 Q Okay. Notwithstanding that section, you
23 don't think that if a patient becomes unblinded that
24 they should be discontinued from the study or at

1 least -- at the very least, that their data shouldn't
2 be included in the primary efficacy analysis?

3 MS. KIEHN: Objection.

4 THE WITNESS: I -- I don't agree with
5 that.

6 BY MR. WISNER:

7 Q Okay. If you turn to page 331.

8 Do you see the section titled "Sample
9 Size Considerations"?

10 A Yes.

11 Q It reads: "The primary efficacy variable
12 is the change from baseline in CDRS-R score at
13 week 8. Assuming an effect size, treatment group
14 difference relative to pooled standard deviation of
15 0.05, a sample size of 80 patients in each treatment
16 group will provide at least an 85 percent power at an
17 alpha level of 0.05 (two-sided)."

18 Do you see that?

19 A I do.

20 MS. KIEHN: Brent, just to correct your
21 first reference to 0.5, you said 0.05. I just wanted
22 to correct that. It says 0.5.

23 MR. WISNER: Thank you for the
24 correction, Ms. Kiehn.

1 BY MR. WISNER:

2 Q In this paragraph it is specifying that
3 it expects a sample size of 160 patients to
4 sufficiently power the efficacy analysis for the
5 null hypothesis on the primary efficacy endpoint,
6 correct?

7 MS. KIEHN: Objection.

8 THE WITNESS: That's correct.

9 BY MR. WISNER:

10 Q When it refers to effect size of 0.5, is
11 it your understanding that that's referring to a
12 Cohen effect size?

13 A That's my understanding, yes.

14 Q And is it fair to say pursue -- okay.

15 And under FDA standards, a Cohen effect
16 size of greater than or equal to 0.5 is considered a
17 moderate effect, correct?

18 MS. KIEHN: Objection.

19 THE WITNESS: Well, that -- that's not
20 necessarily an FDA standard, but -- but that is
21 the -- the common understanding of a -- of a Cohen
22 effect size of 0.5, that it's -- it's a moderate
23 effect.

24 BY MR. WISNER:

1 Q I'm sorry, Dr. Laughren, haven't you
2 published publicly that the FDA considers anything
3 below a 0.5 effect size to be small?

4 A I -- I may have stated that in a
5 publication, but what I'm saying is that that --
6 that's much more broadly understood than FDA.
7 That's -- that's the -- the usual community
8 understanding of what -- of what those effect size
9 numbers mean, that a -- that an effect size of 0.5 is
10 considered in the moderate range. You know, 0.3
11 would be considered a rather minimal effect size.
12 Anything larger than that, 0.75, 0.81, would be
13 considered a large effect size. That's -- that's --
14 what I'm saying is that that's a community standard.
15 It's not necessarily FDA standards, it's -- it's a
16 community standard.

17 Q Okay. Turn to page 334.

18 You see the section here where it
19 actually lists that the medical monitor will be Paul
20 Tiseo?

21 A I do.

22 Q You also see that it has a clinical trial
23 manager and it lists Joan Barton. Do you see that?

24 A I do.

1 Q Do you know what a clinical trial manager
2 is?

3 A I -- I -- I don't offhand.

4 Q Okay. Do you know Joan Barton?

5 A Not that I recall.

6 Q Okay. All right. Let's turn back to
7 Exhibit 3, which is your memorandum that we were
8 discussing earlier.

9 If you turn to page 3 in your -- in your
10 memorandum. Do you see the table titled "Efficacy
11 Results on CDRS-R total score for Study CIT-MD-18
12 LOCF"?

13 A I do.

14 Q This chart lists the primary endpoint,
15 correct?

16 A That's correct.

17 Q And based on this chart, patients taking
18 Celexa improved on a CDRS -- CDRS-R scale by 21.7
19 points and patients taking placebo improved by 16.5
20 points. Do you see that?

21 A That's correct.

22 Q And you concluded that this primary
23 endpoint was positive because the P-value for the
24 difference between placebo and Celexa is less than

1 0.05, right?

2 MS. KIEHN: Objection.

3 THE WITNESS: That's correct.

4 BY MR. WISNER:

5 Q It is a statistically significant result.

6 A That's correct.

7 Q Okay. Now, further down this page you
8 see the sentence that reads "Note." Do you see that?

9 A Yes.

10 Q It goes: "There was a packaging error
11 resulting in tablets being distinguishable for drug
12 and placebo for nine patients, although still
13 blinded."

14 Do you see that?

15 A I do.

16 Q Before I ask you about that sentence, I
17 would like to show you some of your previous
18 testimony.

19 Do you recall that you have previously
20 been asked about this sentence in a lawsuit involving
21 the attempted suicide of Heather Brown?

22 A I -- I may have been. I don't -- you
23 know, I may well have been.

24 Q Is this actually the testimony you looked

1 at with your attorney in preparing for your testimony
2 today?

3 A Well, we didn't go through the -- you
4 know, the transcript. I believe that Mr. Ellison
5 showed me -- showed me one section. We didn't -- we
6 certainly didn't go through the whole thing.

7 Q Sure. And don't worry, I'm not going to
8 go through the whole thing.

9 (Exhibit No. 7 was marked for
10 identification.)

11 BY MR. WISNER:

12 Q I'm handing you a document that's been
13 labeled Exhibit 7 to your deposition.

14 Do you recognize this document, Doctor?

15 A It -- it looks like a transcript of my --
16 of my testimony from that deposition.

17 Q And this was taken on July 9th, 2013, in
18 the case Brown v. Demuth in the Circuit County of
19 Montgomery, Alabama?

20 A Yes.

21 Q Now, at the time that you participated in
22 this deposition, you were a retained expert on behalf
23 of Forest Pharmaceuticals?

24 A Yes.

1 Q And you were testifying specifically not
2 only about the efficacy but potential side effects
3 associated with Celexa and/or Lexapro?

4 A Yes.

5 Q And you understand that you had
6 previously been instrumental in the review and
7 approval of both Celexa and Lexapro for use in the
8 United States?

9 MS. KIEHN: Objection.

10 THE WITNESS: That's correct.

11 BY MR. WISNER:

12 Q And in fact, you were called upon to
13 provide testimony because of that expertise and
14 experience you had at the FDA.

15 A I believe that's correct.

16 Q In this deposition you were under the
17 same oath that you are now under, correct?

18 A That's correct.

19 Q All right. If you turn to page 300.
20 It's in the small 300, not the -- the big -- big
21 number.

22 A So we're looking at the page numbers
23 that --

24 Q That's right, the small ones.

1 You got it?

2 A Got it.

3 Q All right. Starting on line 13, it
4 reads -- and I'm going to read for a few pages here,
5 so bear with me.

6 But starting on line 300 -- page 300,
7 line 13, it says:

8 "Focusing on Exhibit 6, page 3, about
9 two-thirds of the way down on the page, there is a
10 note from you. Do you see that?"

11 A I do.

12 Q Sorry. I was reading the transcript.
13 So -- it's confusing. I'm actually going to read the
14 whole testimony.

15 A Oh, sorry.

16 Q And then I will pause and ask the
17 question, so you know when I'm actually asking the
18 question.

19 A Okay. Sorry. Sorry.

20 Q All right. So I will just do it again.

21 "So focusing on Exhibit 6, page 3, about
22 two-thirds of the way down the page, there's a note
23 from you. Do you see that?"

24 "A. Yes.

1 "Q. And it says: 'There was a
2 packaging error resulting in tablets
3 being distinguishable for drug and
4 placebo for nine patients, although
5 still blinded.'"

6 I will stop right there. Doctor, that's
7 the same sentence we just looked at in your
8 memorandum --

9 A Correct.

10 Q -- correct?

11 A Correct.

12 Q So it appears that this testimony is
13 referring specifically to that sentence.

14 A Correct.

15 Q All right. Going back to Exhibit 7, it
16 continues:

17 "That is a representation of the
18 reality that there was at the
19 beginning of Study 18 trial a
20 potentially unblinding event.
21 Correct?

22 "A. Potentially, correct.

23 "Q. I mean that's what we're
24 calling it. There was a potentially

1 unblinding event, correct?

2 "A. Yes. With an emphasis on
3 'potential.'

4 "Q. Yes, sir. We don't know one
5 way or the other whether or not" --
6 oh, sorry.

7 "We don't know one way or the other
8 whether it would have unblinded the
9 study."

10 "MR. IPSARO: Objection.

11 Right.

12 BY MR. ANDREWS:

13 "Q. Right?

14 "A. Correct."

15 Do you see that?

16 A I do.

17 Q At this point when you testified, it was
18 your understanding that the -- the dispensing error
19 that occurred with these nine patients was a
20 potential unblinding, correct?

21 MS. KIEHN: Objection.

22 THE WITNESS: Are you asking me a
23 question or are you reading?

24 BY MR. WISNER:

1 Q I'm asking you the question now: That
2 was your understanding, there was a potential
3 unblinding?

4 A Yes.

5 Q And, in fact, you put emphasis on the
6 fact that it was potential, correct?

7 A That --

8 MS. KIEHN: Objection.

9 THE WITNESS: That's correct.

10 BY MR. WISNER:

11 Q All right. Going back to the exhibit, it
12 says:

13 "Q. And then you say a reanalysis
14 without these patients yielded a
15 P-value of 0.52 in favor of
16 citalopram, correct?

17 "A. Correct.

18 "Q. And 0.52 would not -- would be
19 not statistically significant,
20 correct?

21 "A. That's correct.

22 "Q. So in this potentially
23 unblinding event, if these patients
24 were removed, this would no longer

1 be a positive study?

2 "A. That's correct.

3 "Q. So the approval of Lexapro was
4 based on -- for pediatric use was
5 based on an escitalopram positive
6 study and a citalopram positive
7 study, where if you remove nine
8 patients who were potentially
9 unblinded, it was actually negative.

10 "A. If you remove the nine
11 patients. We considered the issue
12 and made a judgment that they should
13 not be removed.

14 "Q. It seems like a lot of hoops
15 to jump through to approve this drug
16 for pediatric use.

17 "A. I didn't consider this a huge
18 hoop. I considered this a nonissue.
19 That there is no reason to believe
20 that. The fact that tablets have a
21 different color, any one patient
22 would only get one color tablet."

23 Do you see that?

24 A I do.

1 Q Based on your previous testimony -- do
2 you believe that the testimony provided in this
3 deposition was true and accurate?

4 A The problem with this testimony is that
5 the lawyer who was doing the deposition was assuming
6 that the P-value for the sensitivity analysis was
7 0.5, when in fact it was 0.05.

8 I have -- there is a typo in my memo, and
9 I know this because this is -- this is the testimony
10 that Mr. Ellison and I, you know, went over when we
11 met last week, and -- and I -- and this came up
12 previously subsequent to this deposition that -- that
13 I realized that -- that that's a typo. That is
14 0.052, which is statistically significant. And so
15 the -- you know, the sensitivity analysis was
16 statistically significant.

17 I mean, and -- and why -- why are you
18 misrepresenting this to me as -- as being the correct
19 P-value? You -- you know that.

20 Q Sorry, Doctor. I just read you the
21 transcript of your testimony, and I asked you if it
22 was true or accurate. I didn't misrepresent anything
23 to you. So I take offense that you think that I did
24 so.

1 My question was to you, is there anything
2 that was truthful or accurate about this, and you
3 specified that there was a typo, 0.52; is that right?

4 A That -- that's correct.

5 Q Okay.

6 A It's -- it's 0.052.

7 Q Now, you also just testified that a
8 P-value of 0.052 is statistically significant; is
9 that right?

10 A It's close enough.

11 Q I'm sorry, that wasn't my question.

12 Does a P-value of 0.052 meet the
13 threshold of statistical significance, yes or no?

14 A Whether -- whether or not a -- a P-value
15 meets that standard is a judgment. It is a judgment.
16 Most people in looking at a P-value of 0.052 would
17 round it to 0.05. And so in my -- in my view, that's
18 close enough.

19 Q I'm sorry, Doctor. My question to you
20 was not whether it's close enough.

21 My question to you and to this jury and
22 under oath, and as someone who worked at the FDA for
23 29 years, a P-value of 0.052, does that meet the
24 definition of "statistically significant" or not?

1 A It's close enough.

2 Q So you think it's close enough. Does it
3 meet the value or not?

4 Doctor, a P-value -- for a P-value to be
5 statistically significant, it has to be at 0.05 or
6 lower, correct?

7 MS. KIEHN: Objection.

8 THE WITNESS: 0.052 in my mind, in my
9 view and my judgment, and actually in the judgment of
10 most people at FDA who evaluate clinical trials, is
11 close enough.

12 BY MR. WISNER:

13 Q All right. I appreciate your answer.
14 I'm going to ask the question again. I understand
15 you want to say it's close enough, and I appreciate
16 that, but that's not my question.

17 My question to you is, a P-value is
18 statistically significant if it is at 0.05 or lower,
19 correct?

20 MS. KIEHN: Objection.

21 THE WITNESS: That's -- that's one
22 definition of statistical --

23 BY MR. WISNER:

24 Q That is the standard definition, Doctor,

1 isn't it?

2 MS. KIEHN: Objection.

3 THE WITNESS: We're not -- we're not
4 going to agree on this. Because making a judgment --
5 again, this gets back to what I was saying earlier --
6 making a judgment about whether or not a package of
7 data is sufficient to justify approving a drug is a
8 judgment. It is based on the accumulated evidence,
9 and -- and what -- what a thoughtful reviewer at FDA
10 will conclude from that data about whether or not
11 that drug is effective.

12 The difference between 0.052 and 0.050 is
13 2/1000ths.

14 BY MR. WISNER:

15 Q Doctor, I appreciate your answer. I move
16 to strike all of it as nonresponsive.

17 Again, my question to you is not about
18 the package. It's not even about Celexa. So if you
19 could actually answer my question, we can get out of
20 here a lot quicker.

21 MS. KIEHN: I think he has answered your
22 question.

23 MR. WISNER: I appreciate your objection.
24 Let me finish my question, and then you can issue

1 your objection, Ms. Kiehn.

2 BY MR. WISNER:

3 Q My question to you, Doctor, is: Isn't it
4 true that the scientific standard for statistical
5 significance is 0.05 or less? Yes or no, Doctor?

6 MS. KIEHN: Objection. Asked and
7 answered.

8 THE WITNESS: I -- I believe I've
9 answered the question to the best of my ability.

10 BY MR. WISNER:

11 Q Okay. I will reask the question, and you
12 can give me the answer that you think answers the
13 question.

14 Dr. Laughren, isn't it true that the
15 scientific standard for statistical significance is a
16 P-value of 0.05 or less?

17 MS. KIEHN: Objection. Asked and
18 answered.

19 THE WITNESS: I -- I believe I've
20 answered the question.

21 BY MR. WISNER:

22 Q What is your answer then?

23 A The answer --

24 MS. KIEHN: Objection.

1 THE WITNESS: The answer is that a
2 P-value of 0.052 is statistically significant in my
3 view.

4 BY MR. WISNER:

5 Q Doctor, that -- that wasn't my question,
6 and -- that answer doesn't answer my question.

7 So my question is not about the P-value
8 of 0.052. My question to you is actually about the
9 scientific standard for statistical significance, and
10 a P-value has to be at 0.05 or less to be, under the
11 standard rubric of scientific investigation, a
12 statistically significant outcome, correct?

13 MS. KIEHN: Objection. Asked and
14 answered.

15 THE WITNESS: The -- the -- although the
16 usual definition of "statistical significance" is the
17 P-value of 0.05 or less, a judgment about whether or
18 not a particular finding is statistically significant
19 is -- is made by -- by individuals evaluating data.
20 There is not any hard and fast rule that -- that a
21 finding has to be 0.050000 or less to be
22 statistically significant. It is a judgment.

23 BY MR. WISNER:

24 Q Now, Doctor, are you aware that Forest

1 has admitted under oath that a P-value of 0.052 is
2 not statistically significant?

3 MS. KIEHN: Objection. That's false.

4 THE WITNESS: I -- I'm not -- I'm not
5 aware of that. And honestly, I don't care what they
6 think about it.

7 BY MR. WISNER:

8 Q Okay. You are aware that Forest has
9 conceded that in fact if these unblinded patients
10 were removed from the study, the study was negative.
11 Are you aware of that?

12 MS. KIEHN: Objection.

13 THE WITNESS: I -- I'm not aware of that,
14 and -- and honestly, I don't -- I don't agree with
15 that.

16 BY MR. WISNER:

17 Q Okay. You previously testified that if
18 these patients were removed from the clinical trial,
19 the study was negative, didn't you?

20 MS. KIEHN: Objection.

21 THE WITNESS: I was -- I was -- I was
22 misled in this case because the P-value listed here
23 is not the correct P-value.

24 BY MR. WISNER:

1 Q I'm sorry you were misled because the man
2 quoted your own sentence, right, Dr. Laughren?

3 MS. KIEHN: Objection.

4 THE WITNESS: You know, I -- I was not --
5 I was not provided with the complete data at -- at
6 the time of this deposition. If I -- if I had had
7 access to Dr. Hearst's review, I would have
8 recognized immediately that -- that I had made a
9 typo, that this -- that this is actually 0.052 and
10 not 0.52.

11 BY MR. WISNER:

12 Q And, actually, at this point in your
13 deposition back in 2013, when you were working for
14 Forest as an expert consultant, you had your own
15 memorandum in front of you, didn't you?

16 MS. KIEHN: Objection.

17 THE WITNESS: I had my memorandum. I did
18 not have -- I -- I don't believe that I had the rest
19 of the documents to basically, you know, verify what
20 the correct P-value was.

21 BY MR. WISNER:

22 Q Okay. And so to verify what the truth
23 is, you would need more than your own words; is that
24 right?

1 MS. KIEHN: Objection.

2 THE WITNESS: I would need, you know, the
3 full documents because I obviously made a -- made a
4 typo.

5 BY MR. WISNER:

6 Q Okay. Now, in that sentence, before
7 that, you said: "There was a packaging error in
8 tablets being distinguishable for drug and placebo
9 for nine patients, although still blinded."

10 It was your understanding that the
11 patients, despite getting a different color tablet,
12 were still blinded, correct?

13 MS. KIEHN: Objection.

14 THE WITNESS: I -- I'm assuming that I
15 made that statement based on something that I had
16 seen in -- in the supplement.

17 BY MR. WISNER:

18 Q Okay. So it was your understanding that
19 the patients, despite receiving different color
20 tablets, were still blinded, correct?

21 MS. KIEHN: Objection.

22 THE WITNESS: Well, that -- that was --
23 that was my assumption, correct.

24 BY MR. WISNER:

1 Q If in fact the patients were unmistakably
2 unblinded, that is not what you understood at the
3 time that you wrote this memorandum, correct?

4 MS. KIEHN: Objection.

5 THE WITNESS: I -- I -- again, this goes
6 back almost 15 years. I'm not sure what my state of
7 mind was at the time that I -- that I wrote this
8 memo. But my belief was based on what I've written
9 here is that the patients were blinded.

10 BY MR. WISNER:

11 Q Okay.

12 (Exhibit No. 8 was marked for
13 identification.)

14 BY MR. WISNER:

15 Q All right. I'm going to hand you what's
16 marked as Exhibit 8 to your deposition.

17 This is a document titled "Study Report
18 for Protocol No. CIT-MD-18." It is dated April 8,
19 2002.

20 Do you recognize this document, Doctor?

21 A Is this the same document that you gave
22 me previously? Oh, study report. Okay. So this --
23 okay.

24 Q Do you recognize this document?

1 A I don't recognize it, but it looks like
2 it's the full study report for Study 18.

3 Q Okay, great. And it's actually -- just
4 so you know, it's portions of the final study report
5 for MD-18. Okay?

6 A It's portions of the supplement?

7 Q Of the final report for MD-18.

8 A Oh, okay. Okay.

9 Q This is a 2,135-page document. I've only
10 given you portions of it --

11 A Oh, okay. Fair -- fair enough.

12 Q -- to spare our scanning costs in this
13 case.

14 This is the document that Forest
15 submitted to the FDA to represent the results and
16 conduct of Study MD-18, correct?

17 A So this -- this would have been part of
18 the -- of the supplement that my memo was based on
19 from the -- the April 18th, 2002 supplement.

20 Q Okay, great. Turn to page 63.

21 The second paragraph on page 63 reads or
22 begins: "Nine patients, patients 105, 113, 114, 505,
23 506, 507, 509, 513, and 514, were mistakenly
24 dispensed one week of medication with potentially

1 unblinding information. Tablets had an incorrect
2 color coding."

3 Do you see that?

4 A I do.

5 Q This is consistent with what you wrote in
6 your memorandum, correct?

7 MS. KIEHN: Objection.

8 THE WITNESS: It -- it appears to be.

9 BY MR. WISNER:

10 Q In fact, it was your testimony that
11 simply because a patient received a different color
12 tablet, there is no reason to understand that the
13 patient or the investigator was unblinded; isn't that
14 right?

15 A That's correct.

16 Q This sentence here that I just read you
17 does not state that the integrity of the blind was
18 unmistakably violated, does it?

19 A No.

20 Q It didn't say that dispensing the
21 incorrectly colored tablets would automatically
22 unblind the study, does it?

23 A Correct.

24 Q Would you read those two sentences, the

1 unmistakenly unblinded and the automatically
2 unblinded convey different occurrence than what's
3 listed here in the final study.

4 MS. KIEHN: Objection.

5 THE WITNESS: Say that -- automatically
6 unblinded.

7 BY MR. WISNER:

8 Q Sure. It does not say that the
9 dispensing of the incorrectly colored tablets
10 automatically unblinded the study. It does not say
11 that, right?

12 A Correct.

13 Q Okay. You would agree that if it had
14 said that the dispensing of these tablets
15 automatically unblinded the study, that would be
16 different than what it says here in the final study
17 report.

18 MS. KIEHN: Objection.

19 THE WITNESS: What it says here is
20 that -- that basically -- as I understand this, the
21 coloring of the -- the coating of the tablets -- I
22 would -- I would like to see the supplement that I
23 reviewed that was the basis for this statement.
24 That's what I would like to see. I don't -- I don't

1 know if this is a document that -- that we reviewed
2 as -- as part of the supplement.

3 BY MR. WISNER:

4 Q I will represent to you this is the final
5 study report that was submitted to FDA as part of its
6 pediatric supplement. So this is a document that you
7 would have reviewed as part of your consideration
8 of -- of the pediatric indication, correct?

9 A Let me look through this. (Perusing
10 document.)

11 It doesn't even have a table of contents.

12 Q I removed the table of contents to make
13 the document more manageable in size. If you look on
14 the bottom right-hand corner of each page, it's dated
15 April 8, 2002.

16 A I see that.

17 Q And the supplement was submitted on
18 April 18th, 2002, correct?

19 A Right.

20 Q So this suggests that this document was
21 part of the package that was sent to you to review
22 the pediatric submission for Celexa, correct?

23 A Correct.

24 Q So it's fair to say then that in your

1 consideration of the pediatric supplement submitted
2 to FDA, this is a document you likely looked at.

3 A Likely.

4 Q Okay.

5 (Exhibit No. 9 was marked for
6 identification.)

7 BY MR. WISNER:

8 Q All right. I'm going to hand you a
9 document that's labeled Exhibit 9 to your deposition.
10 We're going to come back to this several times, so
11 keep it handy.

12 This is a document titled "Review and
13 Evaluation of Clinical Data." Do you recognize this
14 document?

15 A This looks like it's Dr. Hearst's review
16 of -- of Supplement 16.

17 Q All right. And if you look at the last
18 page, there is an electronic stamp that indicates
19 this document was signed by Dr. Hearst electronically
20 on September 12th, 2002. Do you see that?

21 A I -- I do.

22 Q Okay. And the date of your memo is
23 subsequent to the date of this. Isn't that true?

24 A Correct.

1 Q All right. Would it be fair to say that
2 in preparing your memo, you likely relied upon
3 portions or some of Dr. Hearst's analysis in forming
4 your memo?

5 MS. KIEHN: Objection.

6 THE WITNESS: That is probably true, but
7 I -- as I mentioned earlier, I probably also looked
8 at the -- at the actual supplement.

9 BY MR. WISNER:

10 Q Okay, great. Turn to page 8 in
11 Dr. Hearst's review.

12 A Okay.

13 Q See, starting there on page 8 and
14 continuing on for several pages, he conducts his
15 review of the results of MD-18. You see that?

16 A I see that.

17 Q All right. Turn to page 11. Do you see
18 the portion where he specifically is discussing the
19 efficacy results of MD-18?

20 A I do.

21 Q All right. Do you see the paragraph that
22 starts with the word "because"?

23 A I do.

24 Q That sentence reads: "Because of a drug

1 packaging error, the citalopram or placebo tablets
2 initially dispensed to nine patients at three study
3 centers were distinguishable in color, although
4 otherwise blinded."

5 Do you see that?

6 A I do.

7 Q That is a verbatim copy and paste from
8 the final study report, isn't it?

9 MS. KIEHN: Objection.

10 BY MR. WISNER:

11 Q Page 63, if you need to look at it to
12 compare.

13 A Sorry. Where was the --

14 Q The sentence that begins -- the paragraph
15 that begins "because of a drug packaging error," and
16 then on page 63, it is the first sentence of the
17 second paragraph on Exhibit 4 -- 8.

18 A Well, it's not -- you know, the phrase
19 "although otherwise blinded" does -- does not
20 appear -- I don't see that on page 63.

21 MS. KIEHN: Brent, they don't match.

22 THE WITNESS: It -- it's not -- it's not
23 identical language.

24 BY MR. WISNER:

1 Q Oh, I'm sorry, Doctor. Let's go back to
2 Exhibit 8. I'm having you look at the wrong section.
3 I'm trying to skip portions in my outline. I
4 apologize.

5 If you turn to page 44 in the final study
6 report. If you look at the last paragraph there on
7 page 44, do you see that? "No double-blind
8 treatment," you see that?

9 A Right.

10 Q Okay. Now, this is the section titled
11 "Blinding." Do you see that?

12 A I do.

13 Q And, actually, if you look at the second
14 paragraph in that section, it discusses the tear-off
15 procedure -- the tear-off panel procedure.

16 A I see that.

17 Q Okay. And in this section that relates
18 to the tear-off panel procedure, look at the second
19 paragraph in the -- sorry, the second sentence in the
20 last paragraph on page 44.

21 It reads: "Because of a drug packaging
22 error, the citalopram or placebo tablets initially
23 dispensed to nine patients at three centers were
24 distinguishable in color, although otherwise

1 unblinded. See Section 7.0?"

2 Do you see that?

3 A I do see that.

4 Q And that is a verbatim copy and paste
5 which was in Dr. Hearst's medical review, correct?

6 MS. KIEHN: Objection.

7 THE WITNESS: Yes.

8 BY MR. WISNER:

9 Q Okay.

10 A That -- that does look like it's -- it's
11 identical language.

12 Q Now, earlier you testified that the
13 protocol section about unblinding procedures only
14 applied to incidents involving the tear-off panel.
15 You remember that?

16 A Well, in the -- in the protocol it -- it
17 did.

18 Q Okay.

19 A I forget what page that was on. Oh, here
20 it is on page 328.

21 Q Now -- thank you for referencing that.

22 Now, the fact that the blinding issue was
23 discussed in Section 5.34 in the final study report
24 where it discusses whether or not there was any

1 unblinding due to the tear-off panel, that it also
2 discusses potential unblinding related to these nine
3 patients who were subject to the dispensing error,
4 doesn't that suggest that at least Forest understood
5 that that section of the protocol applied to any form
6 of unblinding in the study?

7 MS. KIEHN: Objection.

8 THE WITNESS: I -- I don't -- I don't
9 agree with that.

10 BY MR. WISNER:

11 Q Okay.

12 A I mean, you know, they -- they recognized
13 that there was a potential problem because
14 apparently, you know, the -- the coloring of the
15 placebo and the active products were different and
16 therefore allowed them to be distinguished. But that
17 doesn't mean -- that doesn't mean that -- that
18 patients were unblinded.

19 Q Okay, great.

20 MR. WISNER: Let's change tapes.

21 THE VIDEOGRAPHER: The time is 12:09 p.m.
22 This is the end of disc No. 2. We will go off the
23 video record.

24 (Recess.)

1 THE VIDEOGRAPHER: This is the beginning
2 of disc No. 3 in the deposition of Dr. Thomas
3 Laughren. The time is 12:21 p.m. Back on the video
4 record.

5 BY MR. WISNER:

6 Q Okay. Doctor, previously we were
7 discussing Dr. Hearst's clinical review and how it
8 had a sentence that was copied and pasted in it from
9 the final study report, do you recall?

10 MS. KIEHN: Objection.

11 THE WITNESS: I do.

12 BY MR. WISNER:

13 Q And that sentence that was copied and
14 pasted specifically dealt with the nine patients that
15 were dispensed the -- the incorrectly colored
16 tablets?

17 MS. KIEHN: Objection.

18 THE WITNESS: That's correct.

19 BY MR. WISNER:

20 Q The -- he goes on to say in his report --
21 now we're in Exhibit 9, I will let you turn to that
22 so you're there. Are you in Exhibit 9, Dr. Hearst's
23 report? Yeah, it's right in front of you, right
24 there (indicating).

1 A Okay.

2 Q All right. After that sentence that was
3 copied and pasted, it reads:

4 "A sponsor presents the results from the
5 LOCF analysis for the change from baseline to week 8,
6 excluding data from the nine patients from whom the
7 study blind was potentially compromised."

8 Do you see that?

9 MS. KIEHN: Objection.

10 THE WITNESS: I do.

11 BY MR. WISNER:

12 Q "The results from the week 8 LOCF
13 analysis comparing the mean change from baseline in
14 CDRS-R in the citalopram and placebo groups was
15 affected by the exclusion of those patients. The LSM
16 difference decreased from 4.6 to 4.3, and the P-value
17 increased from 0.033 to 0.052."

18 Do you see that?

19 A I do.

20 Q Now, Dr. Hearst does not state that --
21 that the P-value of 0.052 was statistically
22 significant, does he?

23 A No.

24 Q He actually states that the analysis

1 changed the results, doesn't he?

2 MS. KIEHN: Objection.

3 THE WITNESS: Well, he -- he states
4 that -- yes, he does state that, you know, that
5 excluding those patients led to a decrease in the
6 least squares' mean difference and increased the
7 P-value.

8 BY MR. WISNER:

9 Q And the exclusion of those nine patients,
10 according to him, changed the P-value from being
11 0.038 to 0.052. Do you see that?

12 A I do.

13 Q Now, you agree that 0.038 is -- is
14 statistically significant?

15 A I do.

16 Q That is clearly statistically
17 significant, right?

18 A Yes.

19 Q That is below 0.05, right?

20 A That's correct.

21 Q Now, 0.052, you testified already that
22 that is statistically significant -- I believe you
23 said it was close enough; is that right?

24 A I did.

1 Q Okay. But you agree that 0.052 is more
2 than 0.050, right?

3 MS. KIEHN: Objection. Asked and
4 answered.

5 THE WITNESS: I -- I do.

6 BY MR. WISNER:

7 Q Okay. It appears, based on the fact that
8 Dr. Hearst copied and pasted a portion of the final
9 study report into his own clinical review, that
10 Dr. Hearst relied upon the statements made in the
11 final study report.

12 MS. KIEHN: Objection.

13 THE WITNESS: It certainly appears that
14 he read it.

15 BY MR. WISNER:

16 Q And do you recall whether or not you had
17 any conversations with Dr. Hearst about this
18 unblinding issue?

19 MS. KIEHN: Objection.

20 MS. WEINMAN: Objection.

21 THE WITNESS: I -- I don't recall.

22 BY MR. WISNER:

23 Q Okay. And I don't want to know any of
24 the substance of any of those conversations, but if

1 you did have a conversation like that, would it have
2 been documented anywhere?

3 MS. KIEHN: Objection.

4 THE WITNESS: Unlikely. I -- just to
5 qualify, typically during a review process we would
6 have had multiple discussions. There wouldn't have
7 been any way to document every one of them.

8 BY MR. WISNER:

9 Q And when you say "discussion," you mean
10 like in person, right?

11 A Yes.

12 Q And you would be sitting in each other's
13 office and talking about stuff.

14 A Yes.

15 Q Okay. There was -- was there any sort of
16 formalized way of communicating with one another
17 internally within the FDA?

18 MS. KIEHN: Objection.

19 THE WITNESS: There were multiple ways of
20 communicating. I mean, sometimes we had formal
21 meetings, sometimes we just, you know, exchanged
22 e-mails, sometimes you would stop down to someone's
23 office.

24 BY MR. WISNER:

1 Q That was an inartfully worded question.

2 Is it customary practice -- and I don't
3 know if it is, so I'm not suggesting that it is. I'm
4 just asking?

5 Was there a customary practice within the
6 FDA to make official recordings of meetings or
7 discussions that happened solely internally within
8 the agency?

9 A No.

10 Q Okay. In 2002, were you guys using
11 e-mail?

12 A Yes.

13 (Exhibit No. 10 was marked for
14 identification.)

15 BY MR. WISNER:

16 Q Okay. I'm handing you what has been
17 marked as Exhibit 10 to your deposition.

18 Before we get into that document,
19 actually, Doctor, I just want you to know I'm going
20 to be showing you a bunch of documents that have been
21 produced by Forest in this litigation. I'm not aware
22 if you've seen any of them. I will ask you if you've
23 seen any of them or have knowledge of them based on
24 your interactions with counsel or Forest. I don't

1 want to know any privileged communications that you
2 may have had with your counsel.

3 MR. WISNER: So if I am calling for that,
4 please do object so we can properly instruct the
5 witness.

6 BY MR. WISNER:

7 Q I've handed you a document that's been
8 marked as Exhibit 10 to your deposition. This is a
9 document that has been produced by Forest in this
10 litigation. I will represent to you that this is a
11 draft of a letter that was going to be sent to the
12 FDA specifically relating to the dispensing error
13 that we were just discussing. The typed text portion
14 of the document was prepared by Dr. Paul Tiseo. The
15 medical monitor of Study MD-18 and the handwriting
16 portion of this document was written by Dr. Charles
17 Flicker.

18 All right. The first paragraph of this
19 document states: "The purpose of this letter is to
20 inform the agency that an error was made during the
21 packaging of the clinical supply to the above-noted
22 study."

23 Do you see that?

24 A I do.

1 Q It is your understanding that in fact a
2 packaging error did occur in the study, right?

3 A Yes.

4 Q Okay. The paragraph continues: "The
5 error came to our attention following enrollment of
6 the first few patients into the study. Two of our
7 investigational sites called in to report that some
8 of their patients were receiving white tablets and
9 others were receiving pink tablets. These reports
10 were passed on to Forest clinical packaging, where it
11 was discovered that a number of bottles of," quote,
12 "active," unquote, "medication were mistakenly packed
13 with the pink-colored commercial Celexa tablets
14 instead of the standard white citalopram tablets used
15 for blinded clinical studies."

16 Did I read that correctly?

17 A Yes.

18 MS. KIEHN: I believe so.

19 MR. WISNER: Okay, great.

20 BY MR. WISNER:

21 Q So based on this letter, it appears that
22 the dispensing error was discovered after two
23 clinical investigators called Forest inquiring about
24 why some of their patients were receiving white

1 tablets and some were receiving pink ones.

2 Do you see that?

3 A I do.

4 Q This letter also indicates that the
5 pink-colored pills were actually the commercial
6 branded Celexa tablets.

7 Do you see that?

8 A I do.

9 Q All right. The letter continues to say:
10 "On March 2nd, all sites were notified of this error
11 by telephone and by fax."

12 Do you see that?

13 A I do.

14 Q All right. We're going to take a look at
15 that fax.

16 (Exhibit No. 11 was marked for
17 identification.)

18 BY MR. WISNER:

19 Q I'm going to hand you what has been
20 marked as Exhibit 11 to your deposition.

21 Like Exhibit 10, this is a document that
22 has been produced by Forest in this litigation.

23 Have you seen this document before?

24 A I don't recall seeing it.

1 Q Okay. You don't recall seeing it with
2 your attorney, by any chance, last Wednesday?

3 A I'm quite sure that we didn't see it that
4 night.

5 Q All right. Please turn to the first
6 page. This appears -- the first page appears to be
7 an e-mail from Dr. Tiseo.

8 Do you see that?

9 A By the first page, you mean --

10 Q This page right here on the front
11 (indicating).

12 A This page (indicating)?

13 Q Yes.

14 A This page. Okay.

15 Q This appears to be an e-mail from
16 Dr. Tiseo. Do you see that?

17 A I do.

18 Q It's dated March 2nd, 2000. Do you see
19 that?

20 A I -- I do.

21 Q The subject of the e-mail reads: "CIT-18
22 faxed to investigational sites."

23 You see that?

24 A I do.

1 Q In the e-mail Dr. Tiseo states: "For
2 your information, a copy of the fax that went out to
3 all the CIT-MD-18 pediatric investigational sites
4 this morning is attached. All sites have been
5 contacted by telephone and given verbal instructions
6 on how to proceed with both drug treatment as well as
7 their patients who have been screened and/or
8 randomized. I would also like to thank everyone
9 involved in this process for their input and their
10 assistance in rectifying this situation in such a
11 timely manner."

12 Did I read that mostly correctly?

13 A Yes.

14 Q All right. If you turn to the next page,
15 you see that there is a -- what appears to be a
16 facsimile that's attached.

17 Do you see that?

18 A I do.

19 Q And this facsimile is also dated
20 March 2nd, 2000?

21 A I do.

22 Q And the subject line reads "CID --
23 CIT-MD-18 Citalopram Pediatric Depression Study."
24 Right?

1 A I do -- yes.

2 Q And it states that it was actually sent
3 by Dr. Tiseo?

4 A I see that.

5 Q All right.

6 The first paragraph of the fax states:

7 "It has come to our attention that an error was made
8 during the packaging of the clinical supplies for
9 above-noted study. A number of bottles of," quote,
10 "active," unquote, "medication were mistakenly packed
11 with pink-colored commercial Celexa tablets, instead
12 of the standard white citalopram tablets used for
13 blinded clinical studies?"

14 Do you see that?

15 A I do.

16 Q It would appear then that this -- this
17 facsimile is noted by the investigational sites that
18 the pink pills that they have were actually
19 commercial Celexa, isn't it?

20 MS. KIEHN: Objection.

21 THE WITNESS: It appears to -- to suggest
22 that, yes.

23 BY MR. WISNER:

24 Q And previously when we looked at the

1 study report, it stated that nine patients were
2 dispensed these incorrectly colored tablets, right?

3 MS. KIEHN: Objection.

4 BY MR. WISNER:

5 Q Do you want to take a look at the final
6 study report?

7 It's on page 63 of the final study
8 report, if you're looking for it.

9 MS. KIEHN: It's also on 44.

10 THE WITNESS: I'm confused by -- yeah, I
11 have page 44.

12 BY MR. WISNER:

13 Q Yeah, turn to page 63 of that -- of the
14 final study report. For the record, we're referring
15 to Exhibit 8 here.

16 Do you see the second paragraph, the
17 sentence --

18 A Right.

19 Q -- "nine patients were dispensed"? Do
20 you see that?

21 A Yes.

22 Q Okay. So according to the final study
23 report, these nine patients were actually dispensed
24 at least one week of medication with potentially

1 unblinding information. Do you see that?

2 MS. KIEHN: Objection.

3 THE WITNESS: So, I mean, do we -- do we
4 infer from this that all nine patients got the
5 pink-colored tablets?

6 BY MR. WISNER:

7 Q Well, that's what the final study report
8 says, doesn't it?

9 MS. KIEHN: Objection.

10 THE WITNESS: This -- this is the final
11 study report.

12 BY MR. WISNER:

13 Q Are you on page 63 there?

14 I think you're in the wrong doc- -- oh,
15 there you go. There you go. Page 63.

16 It says: "Nine patients," and it lists
17 the patient numbers, "were mistakenly dispensed one
18 week of medication with potentially unblinding
19 information. The tablets had an incorrect color
20 coding."

21 Do you see that?

22 A Yes.

23 Q Okay. So according to the final study
24 report, these nine patients were dispensed this pink

1 medication. Do you see that?

2 A Okay.

3 MS. KIEHN: Objection.

4 BY MR. WISNER:

5 Q Right, that's what it says?

6 A That's what it says.

7 Q Okay. All right. Now, if you go back to
8 the fax -- and keep the final study report handy if
9 you want to reference it, but go back to the fax that
10 we were looking at.

11 It reads: "As a result, dispensing these
12 tablets would automatically unblind the study."

13 Do you see that?

14 A I -- I do. I do.

15 Q So according to this facsimile,
16 dispensing this pink medication would automatically
17 unblind the study. Isn't that right?

18 A Yeah, that's what it says.

19 Q And he is the medical monitor for MD-18?

20 A Yep.

21 Q Now, we know from the previous exhibit
22 that Forest became aware of -- sorry. We know from
23 the previous exhibit that Forest became aware of the
24 dispensing error because the investigational sites

1 had actually called Forest and said, Hey, some of my
2 patients are getting pink tablets, some of them are
3 getting white. Right?

4 MS. KIEHN: Objection.

5 THE WITNESS: Correct.

6 BY MR. WISNER:

7 Q And this facsimile is telling the
8 investigational site that the pink tablets are
9 actually branded commercial Celexa.

10 Do you see that?

11 A I do.

12 Q Wouldn't that by definition have
13 unblinded the investigator?

14 MS. KIEHN: Objection.

15 THE WITNESS: I -- it -- if -- if the
16 tablet said "Celexa R" on it, yes, it would have
17 unblinded the investigator.

18 BY MR. WISNER:

19 Q And, in fact, the investigator has now
20 potentially received this facsimile saying, Hey,
21 those pink tablets that you have, they're actually
22 commercial Celexa.

23 Isn't that what this fax is saying?

24 A That's what the fax appears to say.

1 Q And it's saying, Listen, if you dispense
2 this medication, you've automatically unblinded the
3 study.

4 Isn't that what it says?

5 MS. KIEHN: Objection.

6 THE WITNESS: Certainly for the
7 investigator.

8 BY MR. WISNER:

9 Q Okay. All right. If you turn to the
10 third page of -- I'm sorry, the last page -- I'm
11 sorry. Turn to the third page of the facsimile.

12 Do you -- do you see the section up there
13 at the top that says "IRB"?

14 A Yes.

15 Q What is an IRB?

16 A Institutional Review Board.

17 Q And what does an IRB do in relation to a
18 clinical trial?

19 A An IRB is -- is a group that -- that
20 looks at the -- at the trial primarily from the --
21 from the standpoint of its -- of the ethics of the
22 trial with regard to the patient --

23 Q Okay.

24 A -- patient safety and -- and ethical

1 aspects of the trial.

2 Q And the IRB, they're -- they're
3 independent, of course, from the FDA, right?

4 A Independent of the FDA and the company.

5 Q Okay. It reads: "Although this is not a
6 patient safety issue, we recommend that you inform
7 your IRB of the mistake in packaging. A brief letter
8 is attached for your use explaining in detail the
9 reason for the medication recall."

10 Do you see that?

11 A I do.

12 Q And if you actually look at the next
13 page, there is -- it looks like to be a form letter
14 that appears to be that attachment for the IRB. Do
15 you see that?

16 A I see that.

17 Q All right. And if you look at the second
18 paragraph in that letter, the second sentence starts
19 with "a number." Do you see that?

20 MS. KIEHN: Say that again.

21 MR. WISNER: So the second --

22 MS. KIEHN: The first paragraph.

23 BY MR. WISNER:

24 Q Sorry, the first substantive paragraph,

1 but -- sure. You see the paragraph that starts off
2 with "we have"?

3 A Yes.

4 Q All right. The second sentence in that
5 paragraph says: "The number of bottles of active
6 medication" --

7 A That's -- that's --

8 Q I guess they both start with "we have."
9 That's confusing. All right.

10 MR. ELLISON: Yeah. ^ Check.

11 BY MR. WISNER:

12 Q All right. So the first --

13 MS. KIEHN: The top paragraph.

14 BY MR. WISNER:

15 Q -- paragraph, it says: "We have been
16 informed" --

17 A Do I have the right document?

18 Q Yeah, you do. The paragraph that begins
19 "we have been informed." Do you see that?

20 A Yes, I do.

21 Q So the second sentence in that paragraph.

22 A I got you. Okay.

23 Q My mistake.

24 It says: "A number of bottles of active

1 medication were mistakenly packaged with the
2 pink-colored commercial Celexa tablets instead of the
3 standard white citalopram tablets used for blinded
4 clinical studies."

5 You see that?

6 A I see that.

7 Q That's consistent with what we read
8 earlier in the facsimile, right?

9 A Yes.

10 Q And the next sentence reads: "As a
11 result, dispensing these tablets would automatically
12 unblind the study."

13 Do you see that?

14 A I do.

15 Q And it reads: "The study will now be
16 replaced with the appropriate white tablets to
17 maintain the study blind."

18 Do you see that?

19 A I do.

20 Q So again --

21 MR. ROBERTS: "This medication will now
22 be replaced."

23 MR. WISNER: What did I say?

24 MR. ROBERTS: You said, "The study will

1 now be replaced."

2 MR. WISNER: Sorry. Let me -- let me
3 read it again so I -- clearly I'm riddled with
4 illiteracy.

5 BY MR. WISNER:

6 Q It says: "This medication will now be
7 replaced with the appropriate white tablets to
8 maintain the study blind."

9 Do you see that?

10 A I do.

11 Q So, again, it looks like not only is
12 Dr. Tiseo saying to the investigators that it would
13 automatically unblind the study, but he is
14 encouraging the investigators to inform the IRB that
15 dispensing the medication would automatically unblind
16 the study.

17 MS. KIEHN: Objection.

18 THE WITNESS: Yes, I see that.

19 BY MR. WISNER:

20 Q Okay. All right. Let's go back to
21 Exhibit 10, which is the -- that single page draft
22 letter that had the handwriting on it.

23 A Yes.

24 Q Okay. I want to look specifically at the

1 handwritten portion of the document, okay?

2 A Sure.

3 Q Now, this is the handwritten comments by
4 Dr. Flicker, okay?

5 He writes: "Reconsider, no letter."

6 I will stop there for a second. Do you
7 think it would have been appropriate for Forest to
8 not have notified the FDA of this dispensing error?

9 MS. KIEHN: Objection.

10 THE WITNESS: No.

11 BY MR. WISNER:

12 Q Okay. You think they should have
13 notified?

14 A Yes.

15 Q Okay. It continues to read: "Otherwise,
16 I recommend much less narrative, more concise: Due
17 to a packaging error, eight randomized patients at
18 three investigational sites had access to potentially
19 unblinding information. The drug has been repackaged
20 and a full complement of 160 additional patients will
21 be enrolled under standard double-blind conditions.
22 For reporting purposes, the primary efficacy analysis
23 will exclude the potentially unblinded patients and a
24 secondary analysis including them will also be

1 conducted. These patients will be included in all
2 safety analyses."

3 Do you see that?

4 A For the primary analysis will exclude the
5 potentially unblinded patients (reading to himself).

6 Q Do you see that?

7 A Okay. I do see that.

8 Q So Dr. Flicker is recommending here that
9 Forest will enroll a full complement of 160 patients
10 under standard double-blind conditions, and then the
11 primary efficacy analysis, they will exclude these
12 patients that were subject to the dispensing error.

13 MS. KIEHN: Objection.

14 THE WITNESS: I mean, that's -- that's
15 actually not what it says. And he's -- he's
16 suggesting that the primary analysis should be the
17 one that excludes the patients.

18 BY MR. WISNER:

19 Q Precisely. And he is saying -- yeah, I
20 think we're on the same page here, Doctor. I'm sorry
21 if I miss -- misworded that in some way.

22 He's suggesting that Forest is going to
23 enroll a full complement of 160 patients under
24 standard double-blind procedures. Do you see that?

1 MS. KIEHN: Objection.

2 THE WITNESS: That that was the
3 original -- I mean, the original plan was to enroll
4 160 patients, correct?

5 BY MR. WISNER:

6 Q Yeah. So it looks like he's saying here
7 that they tell the FDA, Listen, we're going to enroll
8 a full complement of 160 patients under standard
9 double-blind conditions, and for these nine patients
10 that were subject to the dispensing error, we're
11 going to exclude them from the primary efficacy
12 analysis.

13 MS. KIEHN: Objection.

14 BY MR. WISNER:

15 Q That's what he's written here, right?

16 A That's -- that appears to be what it's --
17 what they're saying.

18 Q Okay, great.

19 (Exhibit No. 12 was marked for
20 identification.)

21 BY MR. WISNER:

22 Q I'm handing you what has been marked as
23 Exhibit 12 to your deposition. This is another
24 internal document that has been produced by Forest in

1 this litigation.

2 As you can see on the top there, there is
3 an e-mail from Dr. Tiseo. It's addressed to
4 Dr. Olanoff, Dr. Gergel, Amy Rubin and Anjana Bose
5 as well as Tracey Varner, Julie Kilbane and
6 Dr. Flicker.

7 Do you see that?

8 A I see that.

9 Q And the subject of the e-mail reads
10 "Letter to FDA for CIT-18." Right?

11 A Yes.

12 Q And it's dated March 8th, 2000. Do you
13 see that?

14 A I do.

15 Q So this is six days after the facsimile
16 that was sent to the investigators, which was
17 March 2nd.

18 A Yes.

19 Q In the e-mail Dr. Tiseo states:
20 "Attached find the letter that Charlie and I put
21 together for the purpose of informing the FDA of our
22 packaging mishap in the citalopram pediatric study."

23 Do you see that?

24 A I do.

1 Q And if you see attached to the document
2 is a letter or a document titled "Letter to FDA
3 Draft." Do you see that?

4 A I'm sorry, which page are you on?

5 Q It's on the next page, attached to this
6 document is a document that is titled "Letter to FDA
7 Draft." You see that?

8 A Yes.

9 Q Also dated March 8th, 2000.

10 A I -- I see that.

11 Q Now, as we know from earlier,
12 Dr. Olanoff, Dr. Gergel, and Dr. Flicker were all
13 signatories to the study protocol for MD-18, right?

14 A Yes.

15 Q And we know that Dr. Flicker was the
16 senior medical director at CNS and that Dr. Tiseo was
17 the one overseeing the conduct of the study.

18 MS. KIEHN: Objection.

19 THE WITNESS: I see that, yes.

20 BY MR. WISNER:

21 Q Okay. Now, here is the -- the letter
22 that was actually drafted.

23 It reads: "The purpose of this letter is
24 to inform the agency that due to a clinical supplies

1 packaging error for the above-referenced trial, eight
2 randomized patients at two investigational sites were
3 dispensed medication that could have potentially
4 unblinded the study. The drug for this study has
5 since been repackaged and a full complement of 160
6 patients will be enrolled under standard double-blind
7 conditions."

8 Do you see that?

9 A I do.

10 Q This appears to closely track
11 Dr. Flicker's handwritten comments in the previous
12 document we looked at, right?

13 A Yes.

14 Q The letter, however, no longer discloses
15 how the investigators -- sorry. The letter no longer
16 discloses how Forest learned about the dispensing
17 error, does it?

18 A No.

19 Q It doesn't talk about how investigators
20 had called Forest asking why some of their patients
21 were getting pink pills and some were getting white,
22 right?

23 A Correct.

24 Q All right. It goes on to read, the

1 second paragraph: "For reporting purposes, the
2 primary efficacy analysis will exclude the eight
3 potentially unblinded patients with a secondary
4 analysis including them also to be conducted."

5 Do you see that?

6 A I do.

7 Q So that sentence read with the previous
8 one about enrolling a full complement of 160 patients
9 under standard double-blind conditions indicates that
10 Forest intended to get a full cohort of patients that
11 they would conduct a primary efficacy analysis on,
12 correct?

13 MS. KIEHN: Objection.

14 THE WITNESS: Correct.

15 BY MR. WISNER:

16 Q And they planned to not include these
17 patients who were subject to the dispensing error, at
18 least in the primary efficacy analysis, right?

19 A Yes.

20 Q And that they would submit separately a
21 secondary analysis which included these potentially
22 unblinded patients.

23 Do you see that?

24 A I do.

1 Q Now, a minute ago, you said that the
2 cardinal thing that's important for a clinical trials
3 validity is that the randomization be maintained,
4 right?

5 A Yes.

6 Q Now, if they're planning to enroll a full
7 complement of 160 randomized patients, focusing just
8 on those newly randomized patients wouldn't
9 compromise the validity of the study, would it?

10 MS. KIEHN: Objection.

11 THE WITNESS: Say -- say again.

12 BY MR. WISNER:

13 Q So they plan to randomize 160 new
14 patients into the study under standard double-blind
15 conditions, right?

16 A Yes.

17 Q If they were to focus exclusively on that
18 160 newly randomized cohort, that wouldn't affect
19 the validity of the randomization of the study, would
20 it?

21 MS. KIEHN: Objection.

22 THE WITNESS: Well, they're not -- it
23 looks like for the primary analysis that they're
24 proposing, they would not include the -- and I'm

1 confused about eight versus nine, I thought it was
2 nine patients. I don't know how we get from there to
3 eight. But regardless, he is saying here that
4 they're going to exclude those patients from the
5 primary analysis.

6 BY MR. WISNER:

7 Q Precisely. And so I guess my question
8 is, is if they did in fact do that, if they did
9 enroll a full 160 patient cohort under proper fully
10 standard double-blind randomized conditions, the
11 issue of validity regarding randomization would still
12 be kept intact, wouldn't it?

13 MS. KIEHN: Objection.

14 THE WITNESS: I -- the problem with that
15 is, is that they're excluding eight randomized
16 patients. And so from my standpoint, that should not
17 be the primary analysis. The primary analysis should
18 include all originally randomized patients. And an
19 exploratory, a sensitivity analysis might be done
20 that looks at -- at all randomized patients, less --
21 you know, excluding those who had had this -- this
22 problem.

23 BY MR. WISNER:

24 Q Now, Forest's decision at this time to

1 exclude these patients who were subject to the
2 dispensing error, patients that Dr. Tiseo said were
3 automatically unblinded, that would be consistent
4 with a practice of making sure that the patients'
5 data that was analyzed was based on -- on -- was
6 based on double-blind data, correct?

7 MS. KIEHN: Objection.

8 THE WITNESS: That -- that would -- that
9 appears to be the intent.

10 BY MR. WISNER:

11 Q And in fact, that would be consistent
12 with my reading of the study protocol, which says if
13 there is an unblinding for any reason, the patient
14 should be discontinued and no further efficacy
15 assessments conducted.

16 MS. KIEHN: Objection.

17 THE WITNESS: That -- that -- that
18 appears to be the case.

19 BY MR. WISNER:

20 Q So it appears, at least from what we see
21 here, that Forest actually read the study protocol
22 the way that I was suggesting it should be read,
23 correct?

24 MS. KIEHN: Objection.

1 THE WITNESS: That -- that appears to be
2 the correct -- what I don't know is -- is the
3 analysis that we saw in the study report, if the
4 primary analysis that led to the P-value of 0.038 was
5 this one that excluded the -- the eight unblinded
6 patients.

7 BY MR. WISNER:

8 Q I promise you, Doctor, we will get there.

9 A Okay.

10 Q Okay, great.

11 (Exhibit No. 13 was marked for
12 identification.)

13 BY MR. WISNER:

14 Q I'm handing you a document that has been
15 marked as Exhibit 13 to your deposition.

16 This is another document that has been
17 produced in the course of this litigation by Forest.
18 As you can see, this document contains a series of
19 e-mails.

20 Do you see that?

21 A Yes.

22 Q All right. So the way you read e-mail
23 chains is you've got to start from the back and move
24 forward, okay?

1 So please turn to the last e-mail
2 exchange in the document.

3 A Okay.

4 Q All right. That e-mail is dated March 8,
5 2000 and -- 2000, right?

6 A I -- yes, I see that.

7 Q And that's actually the e-mail we just
8 looked at a second ago. Do you see that?

9 A Yes. Yes.

10 Q Okay. In response to that e-mail, do you
11 see it -- it goes between page 1 through page 3, but
12 there is a response from Amy Rubin dated March 9,
13 2000, at 8:56 a.m., and she writes an e-mail that is
14 in response to Dr. Tiseo's e-mail.

15 Do you see that?

16 A So -- so the -- the e-mail on the first
17 page, the first one is in response to the -- the last
18 one?

19 Q No, no. If you look at -- on page 1 at
20 the very bottom, it says, "Subject" -- you see that?

21 A Yes.

22 Q Okay. That is the e-mail, and it
23 spans -- if you look, it goes on to page 2 --

24 A I see.

1 Q -- and on to page 3.

2 A I see. I see. That's the next one.

3 Q Yeah, that's the one that's in response
4 to Dr. Tiseo's e-mail. Do you see that?

5 A Yes.

6 Q Okay. Now, Dr. Tiseo's e-mail, it says:
7 "Please review and send your comments back to me
8 within the next few days." Do you see that?

9 A Yes.

10 Q Okay. And if you look at the response
11 from Amy Rubin, starting on the top of page 2, it
12 says: "Paul, I have taken the liberty of editing
13 your letter as follows. Please make any other" --

14 A I -- I'm sorry, where?

15 Q I'm sorry. The top of page 2.

16 A Okay.

17 Q Amy Rubin says: "Paul, I have taken the
18 liberty of editing your letter as follows. Please
19 make any other changes you feel are necessary."

20 You see that?

21 A Yes.

22 Q So it appears that she has taken up
23 Dr. Tiseo's request that people review the proposed
24 letter. Do you see that?

1 A Yes.

2 Q And then you see below that there appears
3 to have been copy and pasted revisions or changes to
4 the letter.

5 Do you see that?

6 A Yes.

7 Q And it reads here: "We are taking this
8 opportunity to notify the division of a clinical
9 supply packaging error for Study CIT-MD-18," open
10 paren, "sites," several dashes, close paren.

11 Do you see that?

12 A I'm sorry?

13 Q Okay. So right under the word "Amy,"
14 there appears to have been copied and pasted her
15 version of the letter in response to Dr. Tiseo.

16 A Yes.

17 Q Okay. So I just read you the first
18 sentence.

19 A Okay.

20 Q Do you see that?

21 A Yes.

22 Q Okay. All right. It goes on to read:
23 "Due to this error, medication was dispensed to eight
24 randomized patients in a fashion that had the

1 potential to cause patient bias."

2 You see that?

3 A I do.

4 Q It goes on to read: "At no time was
5 patient safety an issue. Upon notification of this
6 error, Forest immediately requested that all study
7 drug be accounted for and shipped back to Forest
8 facilities. Upon receipt, the drug was correctly
9 packaged and resent to the sites. Additionally, a
10 fax was sent to the sites explaining the error, the
11 corrective measures taken, and suggesting that
12 although it was not a safety issue, that their IRBs
13 be notified."

14 Do you see that?

15 A Yes.

16 Q And that's all consistent so far with the
17 documents that we've reviewed, right?

18 MS. KIEHN: Objection.

19 THE WITNESS: Right.

20 BY MR. WISNER:

21 Q Now, it says here: "Upon -- upon
22 receipt, the drug was correctly packaged and resent
23 to the sites." You see that?

24 Let me just ask you a general question.

1 Based on what Ms. Rubin cites here, Forest had the
2 investigational sites send all the incorrectly
3 colored tablets to them.

4 Do you see that?

5 MS. KIEHN: Objection.

6 THE WITNESS: Right.

7 BY MR. WISNER:

8 Q So the patient was already randomized in
9 the study and they were receiving pink tablets at
10 that point.

11 A Right.

12 Q This suggests that they were now switched
13 to white ones.

14 MS. KIEHN: Objection.

15 THE WITNESS: That's what it appears to
16 suggest. They replaced the kits with ones that had
17 white tablets rather than --

18 BY MR. WISNER:

19 Q If that happened to a patient that had
20 already been randomized in the study, do you think
21 that might have the potential to unblind the patient?

22 MS. KIEHN: Objection.

23 THE WITNESS: Well, it would certainly
24 confuse the patient. Whether -- whether or not --

1 whether or not they were unblinded is another
2 question, but it certainly would be confusing to
3 them.

4 BY MR. WISNER:

5 Q Okay. All right. In response to this
6 e-mail, so on page 1, you see that Dr. Flicker
7 responds to Amy Rubin. You see that?

8 A Yes.

9 Q And this is dated March 14th, 2000. Do
10 you see that?

11 A Right.

12 Q That's about five days after Amy Rubin's
13 proposed edits.

14 A Yes.

15 Q And he writes: "Although," quote,
16 "potential to cause bias," unquote, "is a masterful
17 stroke of euphemism, I would be a little more up
18 front about the fact that the integrity of the blind
19 was unmistakably violated."

20 You see that?

21 A I do.

22 Q It appears that Dr. Flicker has taken
23 issue with Amy Rubin's editing of the letter to state
24 "potential to cause bias," correct?

1 MS. KIEHN: Objection.

2 THE WITNESS: I see that, yes.

3 BY MR. WISNER:

4 Q According to Dr. Flicker, the phrase
5 "potential to cause bias" in a letter to the FDA is
6 "a masterful stroke of euphemism." You see that?

7 MS. KIEHN: Objection.

8 THE WITNESS: I do.

9 BY MR. WISNER:

10 Q According to Dr. Flicker, the phrase
11 "potential to cause bias" is not being up front with
12 the FDA; isn't that right?

13 MS. KIEHN: Objection.

14 THE WITNESS: That's what it says.

15 BY MR. WISNER:

16 Q According to Dr. Flicker, Forest should
17 just be up front about the fact that the integrity of
18 the blind was unmistakably violated, right?

19 MS. KIEHN: Objection.

20 THE WITNESS: That's what it says.

21 BY MR. WISNER:

22 Q Now, we reviewed the final study report
23 for MD-18. Nowhere in that study report that we
24 reviewed, the portions that we looked at, did it

1 state that the integrity of the blind was
2 unmistakably violated, did it?

3 A No.

4 Q In fact, the final study report stated
5 that they were otherwise blinded, didn't it?

6 A It -- it suggests that there was a
7 potential for unblinding, but didn't acknowledge
8 that -- that the investigators at least, if
9 they received -- if they noticed that the tablets had
10 the -- you know, the name "Celexa" on them and were
11 commercial tablets, that the investigators at least
12 would have -- would have been unblinded with regard
13 to those patients.

14 Q Before we get to the next e-mail, does it
15 concern you that the clinical medical director at the
16 time, Dr. Flicker, believes that a letter that is
17 being proposed to the FDA contains "a masterful
18 stroke of euphemism"?

19 MS. KIEHN: Objection.

20 THE WITNESS: Yeah, no, that's -- that's
21 concerning, I would say.

22 BY MR. WISNER:

23 Q Okay. Let's take a look at Mrs. Rubin's
24 response. Do you see the -- the response right above

1 that that's dated March 15, 2000?

2 A I do.

3 Q This is the day after Dr. Flicker's
4 e-mail. Do you see that?

5 A I do.

6 Q She states: "Thanks for the compliment.
7 Part of my job is to create," quote, "masterful,"
8 unquote, "euphemisms to protect medical and
9 marketing."

10 Do you see that?

11 A I do.

12 Q Now, I will represent to you Amy Rubin
13 was in regulatory affairs for Forest.

14 Does it concern you that an employee for
15 Forest whose job it is to interact with the FDA
16 states that it's part of her job to "create masterful
17 euphemisms to protect medical and marketing"?

18 MS. KIEHN: Objection.

19 THE WITNESS: It -- it is objectionable.
20 I mean, my -- my expectation of -- of companies is
21 that they will be, you know, completely transparent
22 with -- with the FDA about what happened in the
23 conduct of a trial.

24 BY MR. WISNER:

1 Q Now, earlier in 2013 you were actually
2 asked to be an expert for Forest, weren't you?

3 A An expert in -- in litigation, yes.

4 Q For the Brown case, correct?

5 A Yes.

6 Q And, actually, one of the --

7 THE VIDEOGRAPHER: Doctor, if you would,
8 I think your phone is in your shirt pocket.

9 (A discussion was held off the record.)

10 THE VIDEOGRAPHER: Excuse me.

11 MR. WISNER: No problem.

12 BY MR. WISNER:

13 Q I'm sorry, Doctor, you were saying you
14 believed that it's important for pharmaceutical
15 companies to be straightforward and honest with the
16 FDA, right?

17 A Yes.

18 Q And does it concern you -- and I'm sorry
19 if I asked this question already, but I got
20 distracted, so I just want to keep the record clear.

21 Does it concern you that Ms. Rubin, whose
22 job it was to interact with the FDA, believes that
23 it's her job to "create masterful euphemisms to
24 protect medical and marketing"?

1 MS. KIEHN: Objection.

2 THE WITNESS: What -- what concerns me

3 is -- is that -- you know, what was represented to

4 FDA was not precisely what happened.

5 BY MR. WISNER:

6 Q Doctor, it kind of looks like Ms. Rubin
7 here is bragging about misleading the FDA, doesn't
8 it?

9 MS. KIEHN: Objection.

10 THE WITNESS: I -- it -- I must say I --
11 I find that kind of language objectionable. But,
12 again, what I mostly object to is, is the fact that
13 Forest apparently knew that -- that it wasn't just a
14 difference in coloring. The tablets that were sent
15 actually had the brand name on them. That appears to
16 be what happened. It would have been more
17 transparent to say that.

18 I'm not sure that it would have made a
19 difference in this case, you know, based on the data
20 that I've seen, but I think it would have been more
21 up front to -- to be, you know, transparent with FDA.

22 BY MR. WISNER:

23 Q Now, I -- this is where I was going
24 earlier and now I remember. In 2013, you were asked

1 to provide expert testimony for Forest in a pediatric
2 suicide case involving Lexapro, correct?

3 A That's correct.

4 Q And one of the things that you were
5 offered as an expert on was whether or not Study
6 MD-18 was in fact positive for efficacy. Isn't that
7 true?

8 A That's correct.

9 Q In preparing you to testify under oath
10 and to put your reputation on the line, did Forest
11 disclose these e-mails to you?

12 MS. KIEHN: Objection. I'm going to
13 instruct the witness not to reveal any communications
14 that you had with Forest counsel. So if you can
15 answer that question independent of any
16 communications you had with counsel, you can go ahead
17 and answer.

18 MR. GRIFFIN: He's a disclosed expert,
19 and you're instructing him not to answer --

20 MS. KIEHN: I am.

21 MR. GRIFFIN: -- about conversations with
22 outside counsel?

23 MS. KIEHN: In this litigation, yes.

24 MR. WISNER: To be clear, Ms. Kiehn, I'm

1 asking about whether or not you showed him -- I'm
2 sorry, I'm referring to counsel showed him a document
3 in his capacity as an expert testimony. Is it your
4 claim that a document relied on by an expert
5 constitutes privileged communication?

6 MS. KIEHN: You didn't ask him about a
7 document.

8 MR. WISNER: Well, okay.

9 MR. GRIFFIN: Read the question back.

10 MR. WISNER: Read the question --

11 MS. KIEHN: Well, you said disclosed
12 these e-mails.

13 MR. WISNER: So can you please read the
14 question back?

15 (Whereupon, the requested record was
16 read.)

17 THE WITNESS: I don't -- I don't recall
18 seeing these e-mails, but, again, that was coming up
19 on almost four years. So -- but I don't recall
20 seeing them.

21 BY MR. WISNER:

22 Q If you had seen the document where
23 Ms. Rubin was talking about using masterful
24 euphemisms to protect medical and marketing, that's

1 something you probably would have remembered?

2 MS. KIEHN: Objection.

3 THE WITNESS: I -- I -- I likely would
4 have, but I honestly don't know whether or not I -- I
5 saw it, but I don't think so.

6 BY MR. WISNER:

7 Q Let me ask you this, Doctor: Whether or
8 not you did see them or not, do you think that before
9 asking you to put your reputation on the line as an
10 expert testifying on behalf of Forest, they should
11 have shown you these e-mails?

12 MS. KIEHN: Objection.

13 THE WITNESS: I -- I would like to have
14 seen everything.

15 (Exhibit No. 14 was marked for
16 identification.)

17 BY MR. WISNER:

18 Q I'm handing you a document that is marked
19 as Exhibit 14 to your deposition.

20 This appears to be a letter dated
21 March 20th, 2000, from Tracey Varner, manager of
22 Forest Regulatory Affairs, addressed to Russell Katz,
23 director of the Division of Neuropharmacological Drug
24 Products in the FDA.

1 Do you see that?

2 A Yes.

3 Q Have you ever seen this letter before?

4 A I -- I don't recall seeing it, but --

5 but, again, if the letter was sent in March of 2000,

6 that's almost 17 years ago. So I -- even if I had

7 seen it, I wouldn't have remembered it.

8 Q Okay. This appears to be the final draft

9 of the letter that was actually sent to the FDA

10 regarding the dispensing error, doesn't it?

11 MS. KIEHN: Objection.

12 THE WITNESS: Yes.

13 BY MR. WISNER:

14 Q And it -- it appears to have been stamped

15 by the FDA received March 21st, 2000. Do you see

16 that?

17 A Yes.

18 Q Do you recall who Dr. Katz is?

19 A Well, Dr. Katz was the division director.

20 Q He was your boss at the time?

21 A Yes.

22 Q Okay. And in fact, when Dr. Katz left or

23 changed divisions, you replaced him, correct?

24 A Well, the division split into two

1 divisions, and so he remained as division director of
2 the neurology division. I became the division
3 director of the newly formed psychiatry division.

4 Q Okay. Now, the document reads: "We are
5 taking this opportunity to notify the division of a
6 clinical supply packaging error for Study CIT-MD-18.
7 Due to this error, medication was dispensed to eight
8 randomized patients in a fashion that had the
9 potential to cause patient bias."

10 Do you see that?

11 A Yes.

12 Q So that language that Dr. Flicker called
13 "a masterful stroke of euphemism," it made it into
14 the letter, didn't it?

15 MS. KIEHN: Objection.

16 THE WITNESS: Well, this version of the
17 letter was the one that was sent to FDA apparently.

18 BY MR. WISNER:

19 Q So -- exactly. So the language that
20 Dr. Flicker said was "a masterful stroke of
21 euphemism" and wasn't being up front with the FDA,
22 that actually made it into the final letter sent to
23 the FDA, didn't it?

24 MS. KIEHN: Objection.

1 THE WITNESS: This version of the letter
2 is -- is the modified version, yes.

3 BY MR. WISNER:

4 Q Okay. Now, the second paragraph, which
5 is just one sentence, it reads: "A full complement
6 of 160 patients will be enrolled under standard
7 double-blind conditions."

8 Do you see that?

9 A I do.

10 Q What is your understanding of the meaning
11 of that sentence?

12 A As I recall, the original plan was to
13 enroll 160 patients. This -- this suggests that --
14 to me, it -- it's a little bit unclear, but it
15 suggests to me that -- that eight additional patients
16 will be enrolled to bring the complement up to 160,
17 you know, excluding those eight patients who had --
18 you know, had been exposed to the knowledge of -- of
19 the actual tablet.

20 Q The next sentence --

21 A But, again, I'm not -- I'm not entirely
22 clear about it. It's a little bit unclear to me
23 exactly who was included in the primary analysis at
24 this point.

1 Q Sure. The next sentence reads: "For
2 reporting purposes, the primary efficacy analysis
3 will exclude the eight potentially unblinded patients
4 with a secondary analysis including them also to be
5 conducted."

6 Do you see that?

7 A I do.

8 Q It appears that Ms. Varner is stating in
9 this letter that Forest plans to exclude the patients
10 from the primary efficacy analysis, doesn't she?

11 MS. KIEHN: Objection.

12 BY MR. WISNER:

13 Q Let me rephrase that.

14 It appears from this letter that
15 Ms. Varner is telling Forest that they plan to
16 exclude those eight potentially unblinded patients
17 from the primary efficacy analysis?

18 A That -- that's what it says.

19 MS. KIEHN: Objection.

20 BY MR. WISNER:

21 Q And it says, instead, that Forest will
22 include those potentially unblinded patients in a
23 secondary analysis. Do you see that?

24 A I do.

1 Q Okay. It appears that Forest did the
2 exact opposite when it finally issued its final study
3 report, didn't it?

4 A Right. Because what -- if I'm looking
5 at -- at my memo and -- and Dr. Hearst's review, our
6 understanding was that the primary analysis included
7 all patients, including, you know, those patients who
8 were exposed to this medication error, and the
9 sensitivity analysis excluded them, rather than the
10 other way around.

11 Q So it just appears that between when
12 Forest sent this letter and when it finally submitted
13 its final study report, it did the exact opposite of
14 what it said it would do in March of 2000.

15 A Well, if -- if -- what we saw in the
16 study report was a primary analysis that included all
17 patients, and then a sensitivity analysis that
18 excluded those patients. In my view, that -- that is
19 the correct thing to do.

20 Q I understand. But it's the exact
21 opposite of what Forest --

22 A I -- I --

23 Q -- said it was going to do.

24 A Yes. Yes. But I -- you know -- and,

1 again, I don't -- I don't recall seeing this letter.
2 I don't know that -- I mean, what happens with these
3 letters is that, you know, they come into the file.
4 It goes initially to -- to the primary reviewer, even
5 if it's addressed to Dr. Katz, but I'm sure Dr. Katz
6 didn't see this. I may have not seen it. Again,
7 it's 17 years ago. I can't possibly know.

8 If I had seen this, I would -- I would
9 likely have objected to this plan, you know, to
10 exclude the eight patients from the primary analysis.
11 But, you know, it looks like they eventually did what
12 we ordinarily would have expected is to include all
13 patients in the primary analysis.

14 Q Now, Doctor, at this point in March of
15 2000, when Forest is saying they're not going to
16 include them in the primary analysis, Forest doesn't
17 know the results of the study, does it?

18 MS. KIEHN: Objection.

19 THE WITNESS: They -- they could not
20 have.

21 BY MR. WISNER:

22 Q Yeah.

23 When they submitted the final study
24 report where they did include the results of the

1 unblinded patients in the primary efficacy analysis,
2 they did know the results, didn't they?

3 MS. KIEHN: Objection.

4 THE WITNESS: That -- that's -- that's
5 true.

6 MR. WISNER: All right. Let's take a
7 break?

8 THE WITNESS: Well, let me -- let me
9 qualify that. Let me qualify that.

10 BY MR. WISNER:

11 Q Sure.

12 A It's quite possible that when they
13 further thought about this and talked about it with
14 their statisticians, they changed their mind before
15 breaking the blind and -- and decided that they
16 should go with the original plan to include
17 everybody.

18 I -- I can't -- I can't possibly know.

19 Q Fair enough. And that's a possibility, I
20 grant you that, Doctor.

21 But I'm just saying what we do know is
22 that in March of 2000, Forest has agreed to exclude
23 those potentially unblinded patients from the primary
24 efficacy analysis, correct?

1 MS. KIEHN: Objection.

2 THE WITNESS: Well, that's what this
3 letter says.

4 BY MR. WISNER:

5 Q Okay.

6 A I would like to see whether or not there
7 was an amendment to the analysis plan reflecting that
8 as well. Because the -- the analysis -- it appears
9 that -- that the original analysis plan was -- was
10 followed.

11 Q Okay. Fair enough, Doctor. I -- we can
12 get into a lot -- that nuance later, we will after
13 the break.

14 I guess my question, though, is as of
15 March 2000, this letter is representing that Forest
16 intends to exclude those potentially unblinded
17 patients from its primary efficacy analysis.

18 A That -- that's what -- that's what this
19 letter says, yes.

20 Q Okay. And we also know that in the final
21 study report, they included those potentially
22 unblinded patients in the primary efficacy analysis.

23 A Which -- which is -- which is what the
24 original analysis plan very likely called for.

1 Q Sure.

2 And we know that in March of 2000 when
3 they sent this letter, Forest didn't know the results
4 of the study because it wasn't completed yet.

5 A They -- they couldn't possibly have known
6 then.

7 Q Okay. And then -- I don't want to go
8 down the rabbit hole. I'm trying to keep it simple,
9 Doctor. And we know that when they submitted the
10 final study report in April of 2002, they did know
11 the results, right?

12 MS. KIEHN: Objection. Asked and
13 answered.

14 THE WITNESS: Well, when they submitted
15 the second report, but we don't know -- what we don't
16 know is when the decision was made to go back to the
17 original analysis plan.

18 BY MR. WISNER:

19 Q Sure.

20 A When they made --

21 Q Yeah, whether or not they made that
22 decision knowing the results or not, we don't know
23 that. Is that what you're saying?

24 A That's what I'm saying.

1 MR. WISNER: Okay, great. Let's take a
2 break.

3 MS. KIEHN: Lunch break?

4 MR. WISNER: Yeah.

5 THE VIDEOGRAPHER: The time is 1:09 p.m.
6 We will go off the video record.

7 (Lunch recess.)

8 THE VIDEOGRAPHER: The time is 2:06 p.m.
9 We're back on the video record.

10 (Exhibit No. 15 was marked for
11 identification.)

12 BY MR. WISNER:

13 Q Hi, Doctor.

14 A Hi.

15 Q I'm handing you a document that has been
16 marked as Exhibit 15 to your deposition. This is an
17 e-mail from Joan Barton to Dr. Tiseo, Dr. Flicker,
18 Joan Howard, Jane Wu and Carlos Cobles dated
19 December 6, 2000.

20 Have you ever seen this document before?

21 A I don't recall seeing it.

22 Q Okay. You recall earlier that we -- we
23 discussed that Ms. Barton was the clinical trial
24 manager. Do you recall?

1 A Yes.

2 Q It reads: "Attached is a table showing
3 which patients were randomized when the problem was
4 discovered that the study drug was unblinded. A
5 total of six adolescents and three children had
6 already been randomized. Please let me know if this
7 will alter the total number of child or adolescent
8 patients to be randomized for this trial."

9 Do you see that?

10 A Yes.

11 Q This is dated in December of 2000. Do
12 you see that?

13 A Yes.

14 Q So this is about seven months, eight
15 months after the dispensing error occurred; is that
16 right?

17 A Yes.

18 Q And you know at this point in the trial
19 they had not unblinded the results yet, right?

20 A Right.

21 Q She states here: "The problem was
22 discovered that the study drug was unblinded."

23 Do you see that?

24 A Yes.

1 Q She doesn't state that it was potentially
2 unblinded, right?

3 A Correct.

4 Q Or that it had the potential to cause
5 patient bias, does she?

6 A No.

7 Q It also says that a total of six
8 adolescents and three children had been randomized.

9 Is it fair to say that based on that
10 statement, it looks like the majority of the
11 dispensing error occurred in patients in the
12 adolescent arm?

13 MS. KIEHN: Objection.

14 THE WITNESS: Well, two to one.

15 BY MR. WISNER:

16 Q Yeah. Six to three, right?

17 A Yeah.

18 Q Okay. All right. If you turn the page,
19 this is the attached table that she referenced in her
20 e-mail.

21 Do you see that?

22 A Yes.

23 Q And it states that this is CIT-MD-18
24 study drug packaging error, site tracking March 1st,

1 2000.

2 Do you see that?

3 A Yes.

4 Q This suggests that Forest became aware of
5 the dispensing error at least as of March 1st, 2000.
6 Do you see that?

7 MS. KIEHN: Objection.

8 THE WITNESS: Yes.

9 BY MR. WISNER:

10 Q And it lists here all the various
11 investigator sites. Do you see that?

12 A Yes.

13 Q And it appears that the dispensing error
14 occurred in patients in the Busner, Harmon and Wagner
15 investigational sites.

16 Do you see that?

17 A Yes.

18 Q Do you know Dr. Busner?

19 A I've heard the name. I don't -- I don't
20 even know if it's a him or a her.

21 Q Okay. Fair enough.

22 Do you know Dr. Harmon?

23 A Again, the name is familiar, but I -- I
24 don't -- I don't.

1 Q Well, you sure know Dr. Wagner, right?

2 MS. KIEHN: Objection.

3 THE WITNESS: Well, I know -- I know the
4 name. I don't -- I don't know her personally. I
5 know -- I mean, she's, you know, well known, but...

6 BY MR. WISNER:

7 Q Sure. And Dr. Wagner is known for her
8 work specifically in pediatric depression, right?

9 A Correct.

10 Q It appears based on this chart that four
11 of the nine patients subject to the dispensing error
12 occurred at her site.

13 Do you see that?

14 A Yes.

15 (Exhibit No. 16 was marked for
16 identification.)

17 BY MR. WISNER:

18 Q I'm handing you a document that's been
19 premarked as Exhibit 16 to your deposition.

20 Let's keep them in order.

21 A Okay.

22 Q I will help you out here.

23 A Okay.

24 Q Let's get them all in order.

1 A Okay.

2 Q Exhibit 14, do you have it right here?

3 A Sorry. Yes.

4 Q That one right there (indicating)?

5 A This is my -- this is my -- oh, this one
6 here.

7 Q Yeah. I'm just going to put them all
8 together so they're all in order.

9 A Okay. All right. This is 7.

10 Q Okay. All right. I think I got them
11 mostly in order.

12 A And here is 7.

13 Q Okay, great.

14 Okay. I just handed -- I'm going to hand
15 you -- I just handed you Exhibit 16. There you go.

16 All right. These are a series of
17 documents, e-mail exchanges that were produced by
18 Forest in this litigation ranging from August 9th,
19 2001, through August 10th, 2001. The first e-mail
20 appears to have been sent by Jane Wu to Dr. Tiseo and
21 Dr. Flicker on August 9th, 2001.

22 Do you see that?

23 A Yes.

24 Q Okay. I will represent to you that

1 Jane Wu was one of the lead statisticians on Study
2 MD-18 within Forest.

3 Her e-mail reads: "Paul, Charlie, we
4 will meet with you to talk about the results of
5 CIT-18 in the R&D conference room at 9:30 to
6 10:30 a.m., August 10th."

7 Do you see that?

8 A I do.

9 Q Now, if you see the next e-mail, she
10 appears to have forwarded that e-mail to James Jin
11 and Qiong Wang.

12 Do you see that?

13 A Yes.

14 Q I think it's Qiong Wang.

15 Okay. I will represent to you also that
16 Mr. Jin and Ms. Wang were both biostatistics- --
17 biostatisticians working at -- at Forest on MD-18.

18 This e-mail from Ms. Wu to Mr. Jin and
19 Ms. Wang appears to have been sent shortly after
20 midnight.

21 Do you see that?

22 A Yes.

23 Q And it reads: "We need to generate
24 Tables 4.1A and 4.1B for ITT population, excluding

1 the nine patients who were unblinded at the beginning
2 of the study. Can you please tell Qiong who they are
3 and try to get the results before 9:30 Friday
4 morning."

5 Do you see that?

6 A I do.

7 Q Ms. Wu has characterized these patients
8 as being unblinded at the beginning of the study.

9 Do you see that?

10 A I do.

11 Q She does not say "potentially unblinded."

12 Do you see that?

13 A Yes.

14 Q And she references Tables 4.1A and 4.1B,
15 right?

16 A Yes.

17 Q And she appears to be trying to obtain
18 Tables 4.1A and 1B without the nine unblend --
19 unblinded patients included; isn't that right?

20 A Correct.

21 Q And she appears to be doing this in
22 anticipation of a meeting, quote, about the results
23 of CIT-18, right?

24 A Correct.

1 Q All right. So please turn to Exhibit 8,
2 which is the final study report. It should be in
3 order now.

4 All right. If you could please turn to
5 page 108.

6 This is a document, it has the title
7 "Table 4.1A." Do you see that?

8 A I do.

9 Q And this is Table 4.1A as it was
10 submitted to the FDA, right?

11 A Okay.

12 Q All right. The title of it is "Change
13 From Baseline By Visit for CDRS-R."

14 Do you see that?

15 A I do.

16 Q And it specifies that this is an LOCF
17 analysis?

18 A Yes.

19 Q And it has the by week results of that
20 primary efficacy point from week 1 to week 8.

21 Do you see that? It goes on to the next
22 page.

23 A Oh, okay.

24 Q Do you see that?

1 A I do.

2 Q Okay. It appears that in the final study
3 report the nine patients that were subject to the
4 dispensing error were actually included in
5 Table 4.1A, doesn't it?

6 MS. KIEHN: Objection.

7 THE WITNESS: Right.

8 BY MR. WISNER:

9 Q And that's different than what Ms. Wu has
10 asked them to do in preparation for a meeting about
11 the study results in August; isn't that right?

12 MS. KIEHN: Objection.

13 THE WITNESS: Well, I mean, she -- she
14 asked for tables. She doesn't say what Table 4.1A is
15 supposed to do here in the e-mail.

16 BY MR. WISNER:

17 Q Well, fair enough.

18 If we look at the final study report,
19 Table 4.1A is the primary efficacy endpoint by week,
20 right?

21 A What I -- what I don't know is what
22 Tables 4.1A and 4.1B, how they -- how they differ.

23 Q Oh, we will get into the difference
24 between 4.1A and 4.1B in one second.

1 A So -- so your understanding of 4.1A from
2 this is that it excludes or does not exclude?

3 Q The final study report it does not
4 exclude. Do you see that? If you look at --

5 MS. KIEHN: I don't think he can tell
6 that by looking at it.

7 BY MR. WISNER:

8 Q Well, if you look at week 8, the
9 P-value --

10 A Well, the P-value is -- is the P-value
11 that was reported in the study report --

12 Q Exactly.

13 A -- for the primary analysis, presumably
14 including all patients, including those nine patients
15 or eight patients, whatever.

16 Q All right. Do you know whether or not
17 those eight patients were included?

18 A I -- I don't -- I don't offhand. I
19 mean --

20 Q Okay. Let me show you something that
21 might help you figure that out.

22 Turn to page -- page 70 in the final
23 study report.

24 A Okay.

1 Q If you look underneath the chart that's
2 graphing the study results --

3 A 85 and 89. N equals 85 and N equals 89,
4 those are the numbers that were included in this
5 analysis set that generated the P-value of 0.038.

6 Q There you go. So the 85 and 89 -- and
7 that's a good way of doing it. And if you look at
8 Table 4.1A, those are the corresponding entries.

9 A Okay. Okay. So -- so it includes
10 those -- those patients.

11 Q Precisely.

12 Okay. So it appears then that Jane Wu is
13 requesting in August in anticipation of a meeting to
14 discuss the efficacy results -- well, let's back up.
15 Okay. Let's back up.

16 On Exhibit 16, you see that this e-mail
17 she sends is at -- on August 10th, 2001.

18 A Yes.

19 Q Okay. In this e-mail --

20 A Well, uh --

21 Q From Jane Wu on the top.

22 A Okay, correct.

23 Q So it's August 10, 2001, and that's the
24 one that's just after midnight.

1 A Right.

2 Q And this is in anticipation of a meeting
3 at 9:30 Friday morning, right?

4 A Right.

5 Q Okay. And in this e-mail she is asking
6 to generate these tables excluding the nine
7 patients --

8 A Right.

9 Q -- that were, quote, unblinded at the
10 beginning of the study, right?

11 A Right. Correct.

12 Q Okay. Now, if you look at the final
13 study report, on page 108 --

14 A Okay.

15 Q -- this is Table 4.1A.
16 Do you see that?

17 A Right.

18 Q And if you look at the top right, there
19 is actually a date, August -- October 30th, 2001,
20 right?

21 A Right.

22 Q So this was generated, it appears, after
23 that meeting on August 10th, right?

24 A Yes.

1 Q Okay. So in the meeting she had asked to
2 generate this table excluding the nine patients, but
3 in this table that's represented to the FDA, those
4 patients are included, aren't they?

5 A Yes.

6 Q Okay. Now, if you turn to the next
7 table, 4.1B, which is on page 110 of the same
8 exhibit.

9 A Okay.

10 Q And this represents the same endpoint,
11 but instead of using the LOCF, it's using observed
12 cases. Do you see that?

13 A Okay. Got you.

14 Q Do you see that, Doctor?

15 A I do. I do.

16 Q Okay. And if you actually look at
17 week 8, the final week in the study, which was the
18 prespecified endpoint, the P-value is 0.167, right?

19 A Correct.

20 Q And you agree with me that a P-value of
21 0.167 is not statistically significant.

22 A Correct.

23 MS. KIEHN: Objection.

24 BY MR. WISNER:

1 Q It's not a -- it's not close enough,
2 right?

3 A It's not close enough.

4 Q Okay. All right.

5 (Exhibit No. 17 was marked for
6 identification.)

7 BY MR. WISNER:

8 Q Okay. I'm handing you a document that's
9 Exhibit 17 to your deposition.

10 This is another document that has been
11 produced by Forest in this litigation containing an
12 e-mail from Joan Howard to a large number of
13 individuals dated September 14th, 2001.

14 Dr. Laughren, if you look at the
15 recipient line in that e-mail -- it's not Joan
16 Barton, it's Joan Howard. It's a different person.
17 If you look at the recipient line, you will see in
18 the recipient line Dr. Flicker, Dr. Tiseo, Jane Wu,
19 James Jin, William Heydorn and Ms. Barton, right?

20 A Yes.

21 Q Okay. At the bottom of the e-mail,
22 Ms. Howard writes: "Attached are minutes from the
23 meeting held August 21st."

24 Do you see that?

1 A Yes.

2 Q Okay, great. And if you turn the page,
3 there's a document attached to this titled "Forest
4 Laboratories, Inc.'s Citalopram Clinical Team
5 Meeting, Minutes of Meeting, August 21, 2001."

6 Do you see that?

7 A Right.

8 Q All right. So this appears to be the
9 minutes of -- of a meeting that happened in August of
10 2000 -- August 21st of 2001, right?

11 A Correct.

12 Q And this also appears to have been after
13 that meeting of August 10th, 2001, correct?

14 A Right.

15 Q Okay. And if you look at the -- the
16 highlight section, there is a section that says
17 "CIT-MD-18." Do you see the -- see that,
18 "CIT-MD-18"?

19 A Correct.

20 Q And it says: "Databases locked and
21 headline results available. Timing of pediatric
22 submission needs to be determined. Final report is
23 contracted out to Pharmanet."

24 Do you see that?

1 A Yes.

2 Q All right. So it appears by at least
3 this point in August of 2001 that the database has
4 been in fact locked and that they had the results of
5 the study.

6 A Correct.

7 Q All right. Are you familiar with a
8 company called Pharmanet?

9 A I -- I've heard the name. It's a -- it's
10 one of many companies that I believe provides
11 services to -- to drug companies. I don't know if
12 they do primarily data analysis or what they do, but
13 I -- I have heard the name. I honestly don't know
14 exactly what they do.

15 Q Okay. It appears here that they've
16 contracted out to Pharmanet to help prepare the final
17 study report; is that right?

18 A Yes.

19 Q Is it -- have you heard of something
20 called a contract research organization?

21 A Yes. Yes.

22 Q Is Pharmanet a contract research
23 organization?

24 A I -- I -- based -- based on what's

1 characterized here, they probably would -- would fall
2 under that general rubric of a contract research
3 organization. Contract research organizations assist
4 companies in various ways, often in the conduct of a
5 trial and other things. So I --

6 Q Is it unusual in your experience for a
7 company like Forest to contract with a CRO to help
8 prepare a final study report?

9 A I just don't know the answer to that.
10 I...

11 Q Okay. Do you have any opinion about
12 whether or not it's appropriate for a drug company to
13 use a contract research organization to prepare a
14 report to be submitted in a regulatory filing?

15 A I don't have an opinion one way or the
16 other.

17 Q Okay. In the submit -- in the submitting
18 of a final study report to the FDA, do you think
19 it's -- the fact that a contract research
20 organization was used to prepare it should have been
21 disclosed?

22 A I -- I -- I don't -- I don't -- you know,
23 I don't have an opinion about that. I -- you know,
24 the assumption is that however -- however the study

1 is conducted, however the data are analyzed, however
2 the study report is put together, that it has -- it
3 has to follow, you know, certain basic standards.
4 And whether that's done within the company or whether
5 it's contracted out, I -- I don't -- I don't know
6 that FDA has a particular concern about that. I...

7 Q At the end of the day, though, the
8 accuracy and content of a final study report, the
9 buck stops with the drug sponsor submitting it,
10 right?

11 A Yeah, no, they --

12 MS. KIEHN: Objection.

13 THE WITNESS: They take -- they have to
14 take responsibility for the final product that
15 they're submitting.

16 BY MR. WISNER:

17 Q Great.

18 (Exhibit No. 18 was marked for
19 identification.)

20 BY MR. WISNER:

21 Q I'm handing you a document, it's
22 Exhibit 18 to your deposition.

23 This document contains excerpts of a
24 deposition taken of William Heydorn on August 29th,

1 2007, in the In re Forest Laboratories, Inc.
2 Securities litigation.

3 By any chance, have you ever seen this
4 deposition before?

5 A No, I don't. I don't -- I don't recall
6 seeing it.

7 Q Okay. If you could turn to page 42 of
8 the deposition. It shouldn't be too many pages in
9 there. It's just the excerpts.

10 Are you there, Doctor?

11 A I am there.

12 Q Okay. Starting on line 16, it reads:

13 "Q. Did you have any role in the
14 creation of the study report for
15 CIT-MD-18?

16 "A. Yes.

17 "Q. And what was your role?

18 "A. I was the primary author on
19 the study report for CIT-MD-18.

20 "Q. When you say 'primary author,'
21 what did that entail?

22 "A. I was the individual
23 responsible for ensuring that the
24 study report was written and

1 completed as accurate and was
2 completed on time and was available
3 when needed for submission to the
4 FDA."

5 Did I read that correctly?

6 A Yes.

7 Q Okay. If you turn to page 47 in that
8 same exhibit, line 4. Are you there?

9 A Yes.

10 Q Okay.

11 "Q. And what did the department
12 work on with regards to submitting
13 information to the FDA?

14 "A. So the department was
15 responsible for writing up the
16 clinical study report, and that was
17 my primary -- I took on that role
18 personally as my primary
19 responsibility. We subcontracted
20 that to a third party to generate
21 the first draft of the study report,
22 and then I worked closely with the
23 third party and with Dr. Flicker to
24 complete the study report, making

1 sure it was accurate and completely
2 summarized the available data for
3 submission to the FDA."

4 Do you see that?

5 A I do.

6 Q All right. So based on the testimony I
7 just read you, it appears that Dr. Heydorn was the
8 primary author of the final study report for MD-18,
9 right?

10 A Correct.

11 MS. KIEHN: Objection.

12 THE WITNESS: Correct.

13 BY MR. WISNER:

14 Q It also appears, and it's consistent with
15 the document we just looked at, that Dr. Heydorn
16 worked with a third party to help generate the first
17 draft of the study report, right?

18 MS. KIEHN: Objection.

19 THE WITNESS: Correct.

20 (Exhibit No. 19 was marked for
21 identification.)

22 BY MR. WISNER:

23 Q I'm handing you what has been marked as
24 Exhibit 19 to your deposition.

1 Again, this is a document that has been
2 produced in the course of this litigation. This
3 appears to be an e-mail sent from Dr. Heydorn to
4 several individuals dated October 4th, 2001.

5 Do you see that?

6 A Yes.

7 Q Okay. Copied on this e-mail are
8 Dr. Flicker, James Jin and Jane Wu, right?

9 A Correct.

10 Q And the subject of the e-mail is, quote:
11 Notes from Conference Call, October 4th. Do you see
12 that?

13 A Yes.

14 Q In the body of the e-mail, it reads:
15 "Attached are my notes from our conference call
16 today."

17 Do you see that?

18 A I do.

19 Q Now, if you turn the page, there's an
20 attachment, and the attachment is titled "Notes from
21 Conference Call with Pharmanet, October 4th, 2001."
22 Do you see that?

23 A I do.

24 Q And it appears that from Forest,

1 Dr. Flicker, Dr. Heydorn, James Jin and Jane Wu were
2 participants for Forest, right?

3 A Yes.

4 Q And it appears to have two participants
5 from Pharmanet.

6 Do you see that?

7 A Yes.

8 Q I don't know how to say their names, but
9 do you -- do you recognize those individuals from
10 Pharmanet?

11 A No.

12 Q Okay. This document appears to contain
13 the notes of a conference call that Forest had with
14 Pharmanet regarding Study MD-18, doesn't it?

15 A Yeah --

16 MS. KIEHN: Objection.

17 THE WITNESS: Yes.

18 BY MR. WISNER:

19 Q All right. Now, if you look down at
20 point 11, it's the second to the bottom.

21 A Yes.

22 Q It states: "Dosing error. Some
23 citalopram tables" -- and I will tell you that
24 Dr. Heydorn has subsequently testified that that

1 should read "tablets," so I'm going to read it that
2 way -- "There was a dosing error. Some citalopram
3 tablets were not blinded. The nine patients who
4 received unblinded medication were included in the
5 main analysis. A secondary post hoc analysis of the
6 ITT subpopulation was done. Refer to these analyses
7 briefly in the methods and results, and reference the
8 reader to the appendix table."

9 Do you see that?

10 A I do.

11 Q That appears to be what they ultimately
12 did in the final study report, correct?

13 MS. KIEHN: Objection.

14 THE WITNESS: Correct. That's what it
15 appears that that's indicating, yes.

16 BY MR. WISNER:

17 Q Okay. Notably, he says that the nine
18 patients who received the unblinded medication were
19 included in the main analysis. It does not state
20 that the patients were potentially unblinded, does
21 it?

22 MS. KIEHN: Objection.

23 THE WITNESS: It -- it says they received
24 unblinded medication.

1 BY MR. WISNER:

2 Q So it appears, at least at this point
3 when they're meeting with Pharmanet in October of
4 2001, Forest had made the decision to renege on its
5 statement to the FDA that it would not include the
6 potentially unblinded patients in the prior efficacy
7 analysis, correct?

8 MS. KIEHN: Objection.

9 THE WITNESS: I don't know that that's
10 correct. I don't know based on what you've given
11 me whether or not there was a change in the analysis
12 plan consistent with what was written in that -- in
13 that e-mail that -- that basically that memo or
14 whatever it was to the FDA, a letter -- I forget
15 whether it was a letter or an e-mail or what it was,
16 it was probably a letter -- in which they said that
17 the primary analysis would -- would not include them.

18 BY MR. WISNER:

19 Q Sure.

20 And I guess my question is, it appears by
21 this point in October of 2001, Forest had made the
22 decision to not do what it said it would do in that
23 letter, correct?

24 MS. KIEHN: Objection.

1 THE WITNESS: That -- that appears to be
2 the case. Yes.

3 (Exhibit No. 20 was marked for
4 identification.)

5 BY MR. WISNER:

6 Q All right. Coming at you fast here,
7 Doctor. I'm handing you what has been marked as
8 Exhibit 20 to your deposition.

9 Thank you.

10 All right. These are the excerpts of a
11 deposition taken of William Heydorn taken on -- the
12 deposition of William Heydorn taken in this
13 litigation, in this case on October 14th, 2016.
14 Okay?

15 A Okay.

16 Q Have you ever seen this deposition
17 transcript before?

18 A I don't -- I don't believe so, no.

19 Q All right. During the course of
20 Dr. Heydorn's deposition we showed him many of the
21 documents that I've shown you today about the
22 unblinding and the e-mail correspondence, and he
23 provided testimony. And considering he was the
24 primary author on the report, I would like to show

1 you what he had to say, okay?

2 MS. KIEHN: Objection. You're
3 testifying.

4 BY MR. WISNER:

5 Q Okay?

6 A Yes.

7 Q I'm just telling you that's what I'm
8 going to do. Just telling you what I'm doing.

9 All right. So let's start off with
10 page 87, and these are just excerpts so they -- they
11 should all be pretty much one after the other.

12 A Okay.

13 Q On page 87, it reads: "So" -- on
14 line 19, it reads:

15 "So with the dispensing error
16 patients excluded from the MD-18
17 primary efficacy outcome measure,
18 Celexa failed to -- failed to
19 significantly outperform placebo in
20 treating pediatric depression.

21 Right?

22 "MR. ABRAHAM: Objection.

23 "THE WITNESS: "That appears to
24 be the case.

1 BY MR. BAUM:

2 "Q. Would it an important
3 substantial diff-" -- sorry.

4 "Q. That would be an important
5 substantial difference, wouldn't it?

6 "MR. ABRAHAM: Objection.

7 "THE WITNESS: Yes."

8 According to Dr. Heydorn, excluding those
9 nine patients rendered the results of the study no
10 longer statistically significant.

11 Do you see that.

12 MS. KIEHN: Objection.

13 THE WITNESS: I -- I see that's what he
14 says, yes.

15 BY MR. WISNER:

16 Q And he also agrees that that shift in
17 statistical significant on the primary endpoint was
18 an important and substantial difference.

19 Do you see that?

20 MS. KIEHN: Objection.

21 THE WITNESS: I -- I see that's what he
22 said, yes.

23 BY MR. WISNER:

24 Q Okay. Turn to page 109. I'm sorry, turn

1 to page 107.

2 A 107. Okay.

3 Q On line 13:

4 "Q. So if these eight patients or
5 nine patients who were unblinded or
6 if the investigators working with
7 them were unblinded, the efficacy
8 scores for those individuals should
9 not have been included in the
10 primary outcome measure, correct?

11 "MR. ABRAHAM: Objection.

12 "THE WITNESS: Yeah. Apparently
13 from the wording in the protocol, if
14 they were indeed unblinded."

15 Do you see that?

16 A I do.

17 Q So according to Dr. Heydorn, who
18 ultimately actually wrote the final study report, if
19 these patients were unblinded, they should have been
20 excluded from the primary efficacy analysis.

21 Do you see that?

22 MS. KIEHN: Objection.

23 THE WITNESS: That -- that -- that's what
24 he says, yes.

1 BY MR. WISNER:

2 Q Okay. Now, if you could turn to
3 page 157. We're going to skip a few pages. We'll
4 come back to them later.

5 Are you on page 157, Doctor?

6 A Yes.

7 Q All right. Starting on the first line,
8 it reads:

9 "Q. Well, if they received the pink
10 tablets and they're being told just
11 now that they were active
12 medication, those patients were
13 given active medication, correct?

14 "MR. ABRAHAM: Objection.

15 "THE WITNESS: Yes, I would
16 assume so, yeah.

17 "MR. BAUM:

18 "Q. And the investigators would
19 know that.

20 "MR. ABRAHAM: Objection.

21 "MR. BAUM:

22 "Q. They would know which patients
23 reached them, right?

24 "MR. ABRAHAM: Objection.

1 "THE WITNESS: I would have no
2 direct knowledge, but I would assume
3 so.

4 "Q. So they were unblinded as
5 well, correct?

6 "MR. ABRAHAM: Objection.

7 "THE WITNESS: With respect to
8 those patients, I would assume so."
9 Do you see that?

10 A I do.

11 Q So it appears that Dr. Heydorn is
12 concurring with what you said earlier that if the
13 investigator knew that the pink pills being
14 distributed to a patient were in fact Celexa, that
15 would unblind the study with regards to that
16 investigator, right?

17 MS. KIEHN: Objection. Misstates prior
18 testimony.

19 THE WITNESS: The -- I mean, the problem
20 is what I -- the problem is that I don't know the
21 actual operational details of -- of what happened. I
22 don't know if -- you know, who provided the kit to
23 the patient. It -- it -- it may have been, you know,
24 a different person certainly than the investigator.

1 I -- I don't -- I mean the problem is
2 we're making a lot of assumptions here about -- I
3 mean, I understand that the tablets were pink and
4 they presumably had the Celexa brand on them, which
5 certainly, you know, would be expected to unblind the
6 patients if -- if they looked at that.

7 Whether or not the investigator --
8 whether or not the person who ultimately did the
9 rating on that patient was unblinded, I don't know
10 that from this.

11 BY MR. WISNER:

12 Q Fair enough.

13 But we do know that Dr. Flicker, who was
14 a director -- medical director at Forest overseeing
15 this trial, stated that the integrity of the blind
16 was unmistakably violated, right?

17 MS. KIEHN: Objection.

18 THE WITNESS: I -- yes.

19 BY MR. WISNER:

20 Q And we do know that Dr. Tiseo, the guy
21 overseeing the conduct of the trial, he said that
22 dispensing these medications would automatically
23 unblind the study, right?

24 MS. KIEHN: Objection.

1 THE WITNESS: Yes.

2 BY MR. WISNER:

3 Q So at least according to Dr. Heydorn,
4 Dr. Tiseo, as well as Dr. Flicker, they at least seem
5 to have read these documents and came to the
6 conclusion that there was an unblinding, right?

7 MS. KIEHN: Objection.

8 THE WITNESS: Well, the -- I agree that's
9 what was said. Again, the problem is they may --
10 they may have meant that it was unblinded with regard
11 to the patients. It doesn't necessarily mean that
12 the patient doing the rating on that patient was
13 unblinded. That's -- that's the distinction I want
14 to make.

15 BY MR. WISNER:

16 Q I understand that, but let's -- let's use
17 a little bit of common sense here, right. The
18 investigators who are doing these analyses raise an
19 issue that some of them -- their patients that
20 they're doing this with are having white -- white
21 pills and some are getting pink, right?

22 MS. KIEHN: Objection.

23 THE WITNESS: I agree.

24 BY MR. WISNER:

1 Q And they bring this attention to Forest,
2 and then Forest sends them a memo explaining the
3 whole situation, right?

4 A I agree.

5 Q And that memo says, Listen, you know,
6 these pink tablets that you're dispensing, they're
7 actually branded Celexa.

8 Do you see that?

9 MS. KIEHN: Objection.

10 THE WITNESS: I see that.

11 BY MR. WISNER:

12 Q Okay. So while I agree there's an
13 assumption being made here, it's a pretty reasonable
14 assumption that in response to that facsimile from
15 Forest, the investigators -- the investigation site
16 said, Hey, guys, those pink pills, by the way, we got
17 the solution, it turns out that's the drug.

18 MS. KIEHN: Objection.

19 THE WITNESS: Those findings certainly
20 raise a concern. I will -- I will agree with you
21 there.

22 BY MR. WISNER:

23 Q Okay. Now, on page 202, it's the next
24 one over, line 13, it reads:

1 "Q. Okay. If an investigator
2 knows which patients are taking
3 branded Celexa and which ones are
4 taking white pills" --

5 A I'm sorry, which --

6 Q Oh, I'm sorry. We're on page 102,
7 line 13.

8 A You mean 202, line 13. Okay.

9 Q Page 202, line 13. I apologize. It
10 reads:

11 "Q. Okay. And if an investigator
12 knows which patients are taking
13 branded Celexa and which ones are
14 taking white pills, doesn't that
15 mean the integrity of the blind was
16 un -- was mistakenly -- unmistakably
17 compromised?

18 "MR. ABRAHAM: Objection.

19 "THE WITNESS: It does raise
20 questions about the integrity of the
21 blind."

22 Do you see that?

23 A Yes.

24 Q And you would agree with that statement,

1 right?

2 A Yes.

3 Q Okay. All right. If you turn to the
4 next page, page 218. All right. Starting on
5 line 6 -- I'm going to read quite a bit here, so
6 forgive me, but I will try to read it all correctly.

7 Starting at line 6, it reads:

8 "Q. Now, having seen this e-mail
9 from Dr. Flicker and the fax from
10 Dr. Tiseo, would you agree that the
11 patients who are subject to the
12 dispensing error were actually
13 unblinded?

14 "MR. ABRAHAM: Objection.

15 "THE WITNESS: I don't know for a
16 fact, but that's the implication
17 from these letters, yes.

18 "MR. BAUM:

19 "Q. Does it concern you that the
20 clinical medical director at the
21 time, Dr. Flicker, believed that the
22 letter being sent to the FDA
23 contains a masterful stroke of
24 euphemism?

1 "MR. ABRAHAM: Objection.

2 "THE WITNESS: I don't know what
3 his frame of mind was when he wrote
4 that.

5 "MR. BAUM:

6 "Q. But they had the obligation to
7 be up front, truthful and honest
8 with the FDA, correct?

9 "MR. ABRAHAM: Objection.

10 "THE WITNESS: Yes.

11 "MR. BAUM:

12 "Q. And this shows that they
13 weren't, correct?

14 "MR. ABRAHAM: Objection.

15 "THE WITNESS: He apparently had
16 some concerns about this, yes.

17 "MR. BAUM:

18 "Q. Well, it was more than just
19 concerns. He said it was
20 unmistakably unblinded, and they
21 said it had the potential for bias.
22 That's a misrepresentation, isn't
23 it?

24 "MR. ABRAHAM: Objection.

1 "THE WITNESS: It's a
2 misrepresentation of what Charlie
3 Flicker thought should be
4 communicated to the FDA.

5 "MR. BAUM:

6 "Q. Did Dr. Flicker ever tell you
7 directly that the integrity of the
8 blind was unmistakably violated
9 because of the dispensing error?

10 "A. No."

11 All right. Now, if you turn to the next
12 page, starting on page 229, line 2:

13 "Q. Now, when you helped draft the
14 MD-18 study report, the MD-18
15 posters and the PowerPoints that
16 were used for CME and the
17 publication in the American Journal
18 of Psychiatry in MD-18, were you
19 aware that Forest personnel like
20 Tiseo and Joan Barton and Charlie
21 Flicker, viewed these patients as
22 unblinded as opposed to potentially
23 unblinded?

24 "MR. ABRAHAM: Objection.

1 "THE WITNESS: No, not to my
2 knowledge -- not to my recollection.

3 "MR. BAUM.

4 "Q. Do you think academics and
5 physicians exposed to the poster CME
6 and the MD-18 journal article ought
7 to have been apprised of the
8 unblinding issue in order to fully
9 weigh the pros and cons of
10 prescribing Celexa or Lexapro to
11 kids?

12 "MR. ABRAHAM: Objection.

13 "THE WITNESS: Probably, yes."

14 Do you see that, Doctor?

15 A I do.

16 Q Now, do you agree with Dr. Heydorn that
17 this issue of the unblinding should have been
18 disclosed by Forest in its publication of the results
19 regarding Study MD-18?

20 MS. KIEHN: Objection.

21 THE WITNESS: I -- I -- I think in -- in
22 full transparency, it should have been more fully
23 disclosed both to FDA in the final study report
24 and -- and it's reasonable, as -- as we did in our

1 reviews, to mention the potential unblinding in our
2 reviews. So I -- I do agree with -- with that
3 statement.

4 MR. WISNER: Thank you.

5 Let's take a break so he can change the
6 tape.

7 THE VIDEOGRAPHER: The time is 2:41 p.m.
8 This is the end of disc No. 3. We'll go off the
9 video record.

10 (Recess.)

11 THE VIDEOGRAPHER: This is the beginning
12 of disc No. 4 in the deposition of Dr. Thomas
13 Laughren. The time is 2:48 p.m. Back on the video
14 record.

15 BY MR. WISNER:

16 Q All right. Now, if you turn to page 307
17 in Exhibit 20, which is the deposition of
18 Dr. Heydorn, do you see the line starting at 21,
19 Doctor?

20 A I do.

21 Q All right. It reads:

22 "Q. Do you have any regrets about
23 your involvement with the CIT-MD-18
24 based on what I've shown you today?

1 "A. I wish we had done things a
2 little differently.

3 "Q. Like what?

4 "A. I wish I had known for certain
5 whether the patients -- those nine
6 patients were unblinded. But
7 obviously I don't. You showed me a
8 lot of documents today suggesting
9 that people knew the patients were
10 unblinded. I don't know for a fact
11 that they knew that. All I know is
12 what they wrote on the paper. I
13 wish I was aware of the
14 correspondence with the FDA.

15 "Q. Do you think based on what
16 I've shown you today that Forest
17 misled anyone about the results of
18 MD-18?

19 "A. It probably should have been
20 more forthcoming."

21 Now, I'm going to skip down to the
22 question starting on line 24:

23 "Q. Would you have changed
24 anything in the final study report?

1 "MR. ABRAHAM: Objection. Calls
2 for speculation.

3 "THE WITNESS: If I were the only
4 one involved in writing it, I
5 probably would have written it
6 somewhat differently."

7 Do you see that?

8 A Yes.

9 Q It appears based on Dr. Heydorn's
10 testimony, he did not believe that the final study
11 report was fully up front or forthcoming with the
12 FDA; isn't that true?

13 MS. KIEHN: Objection.

14 THE WITNESS: That's what he's saying.

15 BY MR. WISNER:

16 Q And he's the man who actually was
17 responsible for the final study report for Study
18 MD-18, right?

19 MS. KIEHN: Objection.

20 THE WITNESS: He appears to have been,
21 yes.

22 BY MR. WISNER:

23 Q Does it concern you that Dr. Heydorn, who
24 was a former FDA employee himself, thinks that Forest

1 was not as forthcoming as it should have been with
2 the FDA about its representation of the results from
3 MD-18?

4 MS. KIEHN: Objection.

5 THE WITNESS: Yes.

6 BY MR. WISNER:

7 Q You would agree, Dr. Laughren, that I've
8 shown you several documents today that suggest that
9 at least people within Forest believed that these
10 nine patients who were subject to the dispensing
11 error were unblinded.

12 MS. KIEHN: Objection.

13 THE WITNESS: It appears that that is the
14 conclusion that -- that some people reached.

15 BY MR. WISNER:

16 Q And you would agree with me that the
17 final study report did not disclose unequivocally
18 that these patients were unblinded, correct?

19 MS. KIEHN: Objection.

20 THE WITNESS: It -- it referred -- it
21 referred to them as potentially unblinded. And --
22 and that is still a possibility, but probably less a
23 probability than if they had just been different
24 colored tablets without the brand name on them.

1 So I -- I think it would have been more
2 transparent to include in the study report that
3 additional information. I'm not sure that it would
4 have made a difference here, but it -- I -- I do
5 object to, you know, a company not being completely
6 transparent with information that they have in
7 reporting on the results of a study.

8 BY MR. WISNER:

9 Q Okay, Doctor, I would like to switch
10 gears a little bit here, get off the unblinding issue
11 for a quick second.

12 You recall that the secondary endpoints
13 for MD-18 were the CGI improvement score and the
14 change from baseline and CGI severity score, K-SADS-P
15 depression module score and CJS -- CGAS score at
16 week 8, correct?

17 A I don't recall that, but I'll take your
18 word for it.

19 Q Okay. Do you recall that we looked at
20 the secondary endpoints earlier in the protocol?

21 A I -- I do. I just don't recall exactly
22 what was stated.

23 Q Okay. Let's turn to Exhibit 8, which is
24 the final study report.

1 All right. If you turn to page 100.

2 Do you see page 100?

3 A Yes, I've got 100.

4 Q All right. This is Table 3.1 and this
5 lists the primary efficacy endpoint, correct?

6 A Yes.

7 Q And this has the P-value of 0.038 at
8 week 8, right?

9 A Right.

10 Q And you agree -- we've all agreed that
11 that is a statistically significant result, right?

12 A Correct.

13 Q All right. If you turn the page to
14 page 101, you have Table 3.2.

15 Do you see that?

16 A Yes.

17 Q And Table 3.2 is the secondary efficacy
18 endpoint of CGI improvement after eight weeks.

19 Do you see that?

20 A Yes.

21 Q And that has a P-value of 0.257, right?

22 A That's correct.

23 Q That's not statistically significant?

24 A No, it's not.

1 Q Definitely not close enough, right?

2 A No.

3 Q Okay. You would agree that that
4 secondary endpoint was negative?

5 A Right, correct.

6 Q Okay. Look at Table 3.3, which is the
7 next one on page 102. This lists the change from
8 baseline in CGI severity after eight weeks.

9 Do you see that?

10 A I -- I do.

11 Q And that's the LOCF analysis as well?

12 A Correct.

13 Q And that has a P-value of 0.226?

14 A Correct.

15 Q Also not statistically significant?

16 A True.

17 Q That's a negative secondary endpoint as
18 well, right?

19 A That's correct.

20 Q All right. Let's turn to the next page
21 to Table 3.4. This lists the secondary efficacy
22 endpoint of change from baseline in CGAS after eight
23 weeks.

24 Do you see that?

1 A I do.

2 Q And again, this has a P-value of 0.309 at
3 week 8.

4 Do you see that?

5 A I do.

6 Q That's not statistically significant?

7 A No.

8 Q That secondary endpoint was also
9 negative?

10 A Correct.

11 Q All right. Next page, page 104. This
12 lists Table 3.5, which is the secondary endpoint of
13 change from baseline in K-SADS-P depression module
14 after eight weeks.

15 Do you see that?

16 A I do.

17 Q Again, this has a P-value of 0.105.

18 Do you see that?

19 A Right.

20 Q That is not statistically significant?

21 A Right.

22 Q That's negative, correct?

23 A Correct.

24 Q Okay. It appears then that all four

1 prespecified secondary endpoints were negative,
2 correct?

3 MR. ROBERTS: Objection.

4 THE WITNESS: Right.

5 BY MR. WISNER:

6 Q Now, that doesn't make the study
7 negative -- back up.

8 MR. WISNER: Did you just object?

9 MR. ROBERTS: I did.

10 MR. WISNER: Who's defending this
11 deposition?

12 MS. KIEHN: It's okay. Go ahead.

13 MR. ROBERTS: She asked me to take over
14 for a little while.

15 MR. WISNER: Oh.

16 MS. KIEHN: It's fine.

17 MR. WISNER: That's fine. Just give me a
18 heads-up. I was suddenly surprised that you
19 were speaking.

20 MR. ROBERTS: Okay. Sorry. She
21 whispered it to me. You guys were going back and
22 forth. I didn't want to --

23 MS. KIEHN: If it's all right -- if it's
24 all right --

1 MR. ROBERTS: Yeah, yeah.

2 MS. KIEHN: -- he will go for a while.

3 MR. WISNER: That's fine.

4 Let's go off the record.

5 THE VIDEOGRAPHER: The time is 2:56 p.m.

6 Go off the video record.

7 (Brief discussion off the record.)

8 THE VIDEOGRAPHER: 2:56, back on the
9 video record.

10 BY MR. WISNER:

11 Q Now, Doctor, notwithstanding the fact
12 that all the secondary endpoints were negative, the
13 study is still considered positive because the only
14 endpoint that really counts is the primary endpoint,
15 correct?

16 MR. ROBERTS: Objection.

17 THE WITNESS: That's true.

18 BY MR. WISNER:

19 Q And so because it reached statistical
20 significance, you concluded the ultimate, the study
21 was positive, right?

22 A Yes.

23 Q Okay. Let's go back to Exhibit 19.

24 I told you earlier we'll do a lot of

1 jumping around here. I apologize.

2 A Okay.

3 Q This is the e-mail that had attached to
4 it the pharmacy -- Pharmanet note conference notes.
5 Do you see that?

6 A Yes.

7 Q Now, if you turn to the actual conference
8 notes, look at the numbered paragraph 9. Okay?

9 A Okay.

10 Q It reads: "For the secondary efficacy
11 measures, no significant difference at week 8 LOCF
12 analysis."

13 Do you see that?

14 A Yes.

15 Q And that's consistent with the tables we
16 just saw, right?

17 MR. ROBERTS: Objection.

18 THE WITNESS: Yes.

19 BY MR. WISNER:

20 Q In those tables, all of the LOCF analysis
21 for the secondary efficacy measures were negative,
22 right?

23 MR. ROBERTS: Objection.

24 THE WITNESS: At week 8, yes.

1 BY MR. WISNER:

2 Q Okay. It then reads: "There were
3 significant findings early on in treatment. Forest
4 looking at individual patient listings to see if
5 there were any clues as to why week 8 findings are
6 not positive. For now emphasize the positive
7 findings at earlier time points for the secondary
8 efficacy variables."

9 Do you see that?

10 A I do.

11 Q Earlier you talked about how the final
12 study report is the drug sponsor's opportunity to
13 spin the data in the most positive light, right?

14 MR. ROBERTS: Objection.

15 THE WITNESS: Well, I -- I think it's
16 fair to say that -- that most companies will put
17 their best foot forward when they're presenting their
18 data. And -- and that's why I say FDA reviewers
19 often go directly to the datasets and don't bother
20 with the company's interpretation of the findings.

21 BY MR. WISNER:

22 Q Now, here they're specifically saying
23 because all of our secondary endpoints that we gave
24 are negative, we should emphasize the positive

1 findings earlier in the study, right?

2 MR. ROBERTS: Objection.

3 THE WITNESS: I -- I see that, yes.

4 BY MR. WISNER:

5 Q All right. Let's look at the final study
6 report. If you could turn to Exhibit 8.

7 A Oh, do I have 8?

8 Q Yeah, you got it there.

9 A Okay.

10 Q Turn to page 72.

11 A Okay.

12 Q Okay, great. Drawing your -- you see the
13 section titled "Efficacy Conclusions"?

14 A I do.

15 Q And this is the section of the report
16 where in a narrative format the sponsor discloses the
17 overall conclusions of efficacy, right?

18 A Correct.

19 Q Now, you look at the second paragraph,
20 the first sentence, it reads: "Significant
21 differences less than 0.05 indicative of greater
22 improvement in citalopram patients than placebo
23 patients were also observed on the CGI-I, CGIS and
24 CGAS."

1 Do you see that?

2 A I do.

3 Q I'm going to stop right there.

4 That does not say that every single
5 secondary endpoint was negative at week 8, right?

6 A Correct.

7 Q And week 8, that's actually the protocol
8 specified endpoint, isn't it?

9 MR. ROBERTS: Objection.

10 THE WITNESS: Yes.

11 BY MR. WISNER:

12 Q Okay. All right. Let's turn to
13 Exhibit 9, which is Dr. Hearst's clinical review.
14 Got it?

15 A I do.

16 Q Okay, great. Turn to page 11.

17 A Okay.

18 Q All right. Do you see the paragraph
19 beginning "significant differences" that's there?

20 A Yes.

21 Q And this actually appears to be where
22 Dr. Hearst is discussing the secondary endpoints,
23 right?

24 A Okay.

1 Q He writes: "Significant differences,
2 less than 0.05 indicative of greater improvement in
3 citalopram patients than placebo patients, were also
4 observed on the CGI-I, CGIS and CGAS."

5 Do you see that?

6 A Yes.

7 Q It looks like he copied and pasted that
8 sentence again from the final study report, didn't
9 he?

10 MR. ROBERTS: Objection.

11 THE WITNESS: However, he goes on to
12 say --

13 BY MR. WISNER:

14 Q Sure, sure, we're going to go back to
15 that in a second.

16 MS. KIEHN: Let him finish his answer.

17 MR. WISNER: That wasn't responsive to my
18 question.

19 MS. KIEHN: I don't care.

20 THE WITNESS: No, you're right, that's
21 what he -- it looks like. I mean, he is basically
22 agreeing with, you know, their conclusion that if --
23 that they're -- you know, if you look at earlier
24 timewise, it doesn't -- it doesn't actually say

1 that.

2 BY MR. WISNER:

3 Q Sure. But, just to be clear, though,
4 that sentence that I just read to you in his report
5 is a verbatim sentence from the "Efficacy
6 Conclusions" in the final study report.

7 A Yes.

8 Q Okay. While you have the study report in
9 front of you, let's read the rest of it.

10 It said: "Statistically significant
11 effects were not found consistently across study time
12 points for the secondary efficacy parameters as the
13 primary efficacy parameter, but numerically greater
14 improvement in the citalopram group was observed on
15 every efficacy parameter on every clinical visit in
16 both the LOCF and OC analysis. Results from the LOCF
17 and OC analysis were similar."

18 Do you see that?

19 A Yes.

20 MR. ROBERTS: Wait. Where do you see
21 "results" from -- which document are you referring to
22 when you say "results"?

23 MR. WISNER: Doc -- Exhibit 8.

24 MR. ROBERTS: Oh, okay.

1 BY MR. WISNER:

2 Q So you see that, Doctor, in the final
3 study?

4 A I -- I do.

5 Q Okay. Now, if you actually look at the
6 Hearst medical review, he quotes verbatim the same
7 thing with the exception of the last part that says
8 "results."

9 Do you see that?

10 A Yes.

11 Q So it appears that Dr. Hearst copied and
12 pasted almost an entire paragraph directly from the
13 final study report into his medical review as it
14 related to the secondary endpoints.

15 MR. ROBERTS: Objection.

16 THE WITNESS: Yes, it's -- it's
17 identical.

18 BY MR. WISNER:

19 Q So a second ago you said typically
20 medical reviewers don't even look at the study
21 report, they go straight to the data. This does not
22 appear to be one of those cases.

23 MR. ROBERTS: Objection.

24 THE WITNESS: Well, I -- I don't know,

1 you know, what -- what he -- what he looked at before
2 he used this language.

3 So, again, I -- you know, we're making a
4 lot of assumptions that he never actually looked at
5 any of these data tables. I don't -- I don't know
6 that.

7 BY MR. WISNER:

8 Q Fair enough.

9 Now, Doctor, in the course of your work
10 at the FDA, do you recall copying and pasting
11 language from a final study report into your medical
12 review?

13 A No, I -- I -- I did not do that.

14 Q Why not?

15 A Because I preferred to reach my own
16 conclusions.

17 Q Now, the way this is written in the final
18 study report and transcribed into Dr. Hearst's
19 review, that does appear to have been trying to
20 emphasize the positive results to earlier time points
21 and avoid discussion of the fact that all the
22 secondary endpoints that we gave were negative,
23 right?

24 MR. ROBERTS: Objection.

1 THE WITNESS: Well, I -- I don't want to
2 assume motive. I -- I don't know what he had in mind
3 when he did this.

4 BY MR. WISNER:

5 Q Fair enough.

6 Putting Dr. Hearst aside, I'm talking
7 about Forest, we saw that they had a conference where
8 they said they were going to emphasize this.

9 A Yes. Yes. No, it's -- it is consistent
10 with -- with that view of focusing on the positive
11 and not giving a complete picture.

12 Q And it appears that that spin that Forest
13 put into the final study report made it into
14 Dr. Hearst's report, correct?

15 MR. ROBERTS: Objection.

16 THE WITNESS: It -- it appears to have,
17 yes.

18 BY MR. WISNER:

19 Q Okay. Let's go back to Exhibit 3, which
20 is your memorandum.

21 All right. If you turn to page 3. Now,
22 on page 3, just above the paragraph that says
23 "comment," there is a sentence that reads: "Results
24 also significantly favored citalopram over placebo on

1 most secondary outcomes."

2 Do you see that?

3 A Yes.

4 Q Now, you didn't state there that all the
5 prespecified secondary endpoints were negative at
6 week 8, right?

7 MR. ROBERTS: Objection.

8 THE WITNESS: Correct.

9 BY MR. WISNER:

10 Q You're referring here, I assume, to the
11 earlier time points when there were statistically
12 significant results in the secondary endpoints,
13 correct?

14 MR. ROBERTS: Objection.

15 THE WITNESS: I -- again, I don't -- this
16 was written a long time ago. I don't recall what
17 would have been in my mind at the time that I wrote
18 this, but it -- you're correct in saying that it
19 doesn't -- it doesn't emphasize the fact that the
20 eight-week results were all negative on the secondary
21 endpoints.

22 BY MR. WISNER:

23 Q Now, I know you don't recall this, but is
24 it possible that when you were drafting this memo,

1 you looked at the final study report, looked at
2 Dr. Hearst, who you relied upon, and thought, Oh,
3 most of the secondary endpoints must have been
4 positive?

5 MR. ROBERTS: Objection.

6 THE WITNESS: I -- I would -- I would
7 have to speculate about what -- what I was looking at
8 at the time when I wrote this, and I -- I -- I prefer
9 not to do that. I just -- I don't know.

10 BY MR. WISNER:

11 Q Okay. Would you agree with me, though,
12 that it would be accurate to say all the protocol
13 specified secondary endpoints for Study MD-18 were
14 negative at week 8?

15 MR. ROBERTS: Objection.

16 THE WITNESS: That is -- that appears to
17 be correct, yes.

18 BY MR. WISNER:

19 Q And would you agree with me that -- that
20 you don't state that in your memo?

21 A I -- I do not state that in my memo.

22 Q And you would agree with me from what
23 we've seen in Dr. Hearst's clinical review, he did
24 not state that either.

1 A He did not appear -- appear to do that
2 either.

3 Q Okay. So on the same page -- you have
4 your memo in front of you, right?

5 A Yes.

6 Q Okay. You have broken down the efficacy
7 results between children and adolescents. Do you see
8 that?

9 A I do.

10 Q Now, you understand that Dr. Hearst
11 didn't present data this way, right?

12 MR. ROBERTS: Objection.

13 THE WITNESS: I would have to look at --

14 BY MR. WISNER:

15 Q Please take a look and tell me if he did.

16 A (Perusing document.)

17 Can you direct me again to where on
18 his --

19 Q Sure.

20 A -- his review the efficacy findings --

21 Q It's just on page 11, that's -- that's
22 about it. That's the only reference to secondary
23 endpoints or even primary endpoints for MD-18 that
24 I've seen.

1 On page 11, do you see any reference to
2 it?

3 A No. No, I don't. So he didn't break it
4 down that way.

5 Q Okay. Do you know why you did?

6 A It's something that I -- that I generally
7 do. I -- you know, I explore a little bit more.
8 So...

9 Q Were you trying to somehow see if there
10 was any indications from the data that might suggest
11 that there are some positive results somewhere in the
12 data?

13 MR. ROBERTS: Objection.

14 THE WITNESS: What -- what I was trying
15 to do, because, again, you're dealing with a -- with
16 a -- in pediatric years, a fairly wide range there of
17 children and adolescents, and it's, in general, of
18 interest to know -- because there have been many
19 other cases where we have found some differences in
20 the effect of a drug in children compared to
21 adolescents. Adolescents tend to look more like
22 adults.

23 So that -- that's -- that's why I broke
24 it down that way.

1 BY MR. WISNER:

2 Q Okay.

3 A I mean if you look at the findings, it's
4 not as if the findings are entirely coming from
5 adolescents, but the effect size is -- is somewhat
6 bigger in the adolescents. So in children, it's
7 about, you know, about four units difference on this
8 measure. In adolescents, it's closer to seven.
9 So...

10 Q Now, in the -- in your memo you said:
11 "The sponsor did not calculate P-values for these
12 groups separately."

13 Do you see that?

14 MR. ROBERTS: Where is that?

15 THE WITNESS: Where do I say that?

16 Oh, right, right, right. Yeah, you
17 ordinarily wouldn't do that in a -- in an
18 exploratory -- it's -- it's an exploratory analysis.
19 You're not testing a hypothesis. Ordinarily you
20 don't generate a P-value unless you're specifically
21 testing a hypothesis.

22 BY MR. WISNER:

23 Q Fair enough.

24 And so just based on what you said here,

1 do you know whether or not the differences observed
2 here were statistically significant or not?

3 A I -- I don't. And again, from my
4 standpoint, it -- it wouldn't be that important.
5 Because a P-value, whether it met that usual
6 threshold of statistical significance would not be
7 particularly relevant for something that wasn't --
8 that wasn't being prespecified and tested.

9 I mean -- and you could do that. You
10 could say if you make it on the overall analysis,
11 then you get to -- you have another 0.05 to look
12 first at -- at adolescents, and if you win there,
13 then you get to look at -- but it wasn't done that
14 way.

15 Q Okay. And that's all I was saying is the
16 reason why there is no P-value is because that wasn't
17 the hypothesis being tested, right?

18 MR. ROBERTS: Objection.

19 THE INTERPRETER: Right.

20 BY MR. WISNER:

21 Q Okay. Now -- all right.

22 Keep this all here, but can you pull out
23 Exhibit 19, which is the e-mail with the pharma --
24 Pharmanet notes attached to it.

1 A Okay.

2 Q You got it?

3 A Yeah.

4 Q And that's Exhibit No. 19.

5 A Okay.

6 Q Now, if you go to the item number 7. Do
7 you see that?

8 A I do.

9 Q It reads: "Note: The study was not
10 powered to look at differences within the two
11 subgroups, children and adolescents. The sample size
12 was calculated based on the anticipated effect size
13 for the primary efficacy variable."

14 Do you see that?

15 A Correct.

16 Q And that's consistent with what you
17 just --

18 A Yes.

19 Q -- testified to, right?

20 A Yes.

21 Q The study wasn't specifically designed to
22 look at adolescents in isolation or -- or even
23 children in isolation.

24 A Correct.

1 Q Okay. All right. You can put that down.
2 Go back to the final study report, which
3 is Exhibit 8, which is right here.

4 All right. If you turn to page 72.

5 A Okay.

6 Q You beat me.

7 MR. ROBERTS: We were there already.

8 BY MR. WISNER:

9 Q All right. You see the section that says
10 "Treatment By Age Group Interaction"?

11 A Yes.

12 Q What is an interaction variable in a
13 statistical analysis?

14 A It -- it's basically an indication that
15 that -- that that variable, in this case age, you
16 know, may -- may have an effect on the outcome.
17 That's all it is. It's just a -- it's a -- it's a
18 metric to measure whether or not there appears to be
19 a -- a difference by age.

20 Q Okay.

21 A By that -- by that strata. You can
22 stratify this, and you can stratify males versus
23 females, by weight, whatever. You do a lot of
24 different exploratory analyses, and they calculated

1 interaction terms by -- by age and --

2 Q Now, it says here in the second sentence
3 in that section: "No significant treatment by age
4 group interaction was found on the CDRS-R, CGI-I,
5 CGI-S, CGAS or K-SADS-P."

6 You see that?

7 A I do.

8 Q So it appears that based on the
9 statistical analysis represented in the final study
10 report, there was no significant effect by the age of
11 the treatment groups; is that right?

12 MR. ROBERTS: Objection.

13 THE WITNESS: Again, you know, these
14 P-values for these interaction terms are -- are not
15 very -- in my mind, not very useful. But...

16 BY MR. WISNER:

17 Q Fair enough.

18 But according to this, it's saying that
19 there is no treatment by age group interaction,
20 right?

21 MR. ROBERTS: Objection.

22 THE WITNESS: That -- that is what it
23 says.

24 BY MR. WISNER:

1 Q And that's for the primary and all the
2 secondary endpoints, right?

3 MR. ROBERTS: Objection.

4 THE WITNESS: Correct.

5 BY MR. WISNER:

6 Q Okay. Now, on that same page, if you
7 look at the paragraph at the bottom, it says: "No
8 treatment by age group interaction was observed,
9 indicating that the magnitude of the treatment
10 effect was similar in the child and adolescent
11 subgroups."

12 Do you see that?

13 A I do.

14 Q Do you have any reason to dispute that
15 conclusion?

16 A Well, "similar" is a -- is a somewhat
17 vague term. I mean, obviously in my memo, I point
18 out the difference in magnitude between the two
19 different age groups.

20 Q Sure.

21 A So it's -- it's a matter of how you -- of
22 how you interpret "similar." I mean, there is an
23 effect in both strata by this crude nonstatistical
24 approach to looking at it, just exploratory looking

1 at the numbers. Yes, if you calculate an interaction
2 term, it's -- it doesn't have a significant P-value,
3 but I just -- I think -- I prefer this way of looking
4 at the data.

5 Q I understand.

6 A But personal preference.

7 Q If you look at page 243 in the final
8 study report.

9 A Okay.

10 Q This is appendix Table 5. Do you see
11 that?

12 A I do.

13 Q And this lists out the treatment by age
14 group interaction terms, doesn't it?

15 A Right.

16 Q And it has the P-values all listed there.
17 Do you see that?

18 A Yes.

19 Q For the primary as well as all the
20 secondary endpoints. Do you see that?

21 A I -- I -- well, if you go on to 244, you
22 mean? No, no.

23 Q CDRS-R, CGI --

24 A Are we looking at the same page?

1 Q Yeah, 243 in the table.

2 A Yeah.

3 Q Efficacy parameter on the left?

4 A Right.

5 Q And it lists all the primary as well as
6 the secondary --

7 A Oh. No, no -- right. You're exactly
8 right.

9 Q Okay, great. And all the P-values there,
10 they're all not statistically significant, right?

11 A Yeah.

12 Q And you would agree with me that -- okay,
13 great.

14 While we're here, just because we're
15 here, if you turn to the next page, which is appendix
16 Table 6.

17 A Okay.

18 Q As you see here, this is the change in
19 baseline in the CDRS after eight weeks. Do you see
20 that?

21 A Yes.

22 Q And this is the subpopulation. Do you
23 see that?

24 If you look at the bottom, there's a

1 note, it says "Patients," and it lists all of them --

2 A Right. Right. Right.

3 Q -- the drug dispensing error excluded.

4 A Right.

5 Q Do you see that?

6 A Yes.

7 Q So this is actually the table that
8 reflects the statistical analysis --

9 A Yes.

10 Q -- of the primary efficacy endpoint
11 excluding --

12 A Excluding those patients.

13 Q That's right.

14 And the P-value there is 0.052, right?

15 A Correct.

16 Q Okay. Earlier we -- we discussed this a
17 little bit. Do you recall that you participated in a
18 symposium in 2013 that was meant to bring various
19 stakeholders from around the country together to
20 discuss the difference between clinical and
21 statistical significance?

22 MR. ROBERTS: Objection.

23 THE WITNESS: I -- I think there was a --
24 a session at ISCTM. Is that the one that you're

1 referring to?

2 BY MR. WISNER:

3 Q I believe so, yes. Do you recall that
4 meeting at all?

5 A I -- I participate in a lot of meetings.
6 I -- you know, I -- I do vaguely recall it.

7 (Exhibit No. 21 was marked for
8 identification.)

9 BY MR. WISNER:

10 Q All right. I'm going to hand you a
11 document that's been marked as Exhibit 21.

12 A Okay.

13 Q This is a document, it's titled "Defining
14 a Clinically Meaningful Effect for the Design
15 Interpretation of Randomized Controlled Trials."

16 Do you see that?

17 A I do.

18 Q And it has a bunch of authors listed, and
19 one of them is yourself, right?

20 A That's correct.

21 Q Would it be fair to say then that you
22 reviewed this document before it was published with
23 your name?

24 A Yes.

1 Q Okay. Now, if you look at the objective,
2 and I think this will help crystallize your
3 participation in it, it says: "This article captures
4 the proceedings of a meeting aimed at defining
5 clinically meaningful effects for use in randomized
6 controlled trials for psychopharmacological agents?"

7 Do you see that?

8 A I do.

9 Q And if you turn the document and turn to
10 page -- well, I guess 10-S at the bottom. It's in
11 the red box on the bottom.

12 A Okay.

13 Q 10-S, do you see it?

14 A Got you.

15 Q Do you see the section that says "The
16 FDA's perspective"?

17 A Right, right, right.

18 Q Do you see that?

19 A I do.

20 Q Would it be fair to say that you probably
21 played a heavy role in drafting this portion?

22 A Right. Yes --

23 MR. ROBERTS: Objection.

24 THE WITNESS: -- that's very likely.

1 BY MR. WISNER:

2 Q Okay, great.

3 You can go back to the beginning. I'm
4 going to go through a couple of sentences and ask you
5 questions about them. We'll get to your -- the FDA
6 section in a second.

7 But if you turn to page 5-S.

8 A Okay.

9 Q In the column to the far left, do you see
10 the paragraph that begins "the effect"?

11 Do you see that?

12 A Yes.

13 Q It reads: "The effect of a treatment
14 reflects the differential response among patience
15 when treatment is given versus when treatment is not
16 given, control over comparison condition, often
17 placebo. Statistically significant effects are not
18 necessarily clinically meaningful effects."

19 I'll stop right there.

20 A Yes.

21 Q Do you agree with that?

22 A In general, yes.

23 Q Okay. It continues: "While there is
24 broad consensus as to how to establish statistical

1 significance, clinical significance remains elusive."

2 See that?

3 A I -- I do.

4 Q And you agree with that, right?

5 A I do agree with that.

6 Q Okay.

7 A But we were talking about that earlier.

8 Q Exactly.

9 It continues: "Many statistical
10 methodologies have been put forth to measure the
11 magnitude of a clinical effect," open paren, "an
12 effect size," close paren. "One of the most
13 frequently used effect size measures is Cohen's d."

14 Do you see that?

15 A I do.

16 Q Are you familiar with the Cohen's d or
17 Cohen effect size?

18 A Yes.

19 Q Okay. Is that something that you would
20 consider in assessing whether or not the results of a
21 clinical trial are clinically meaningful?

22 A I -- I think -- I think it has value. I
23 don't think it's perfect, and -- and FDA
24 statisticians tend not to like it because it's, in

1 part, dependent on sample size. The standard
2 deviation shrinks as you increase the sample size,
3 and, of course, that's a denominator in the
4 calculation for Cohen's c.

5 Q Yeah.

6 A So they -- they tend not -- not to use
7 it, but I -- I do use it myself. I think it's --
8 it's useful, but it isn't perfect.

9 Q All right. It goes on to say: "A
10 randomized controlled trial, RCT, Cohen's d is the
11 difference between the treatment and control means
12 divided by the assumed common standard deviation. It
13 is a clinically interpretable effect size reflecting
14 a degree of overlap between the patient responses in
15 the treatment and control groups when the responses
16 have normal distributions with equal variances."

17 Do you see that?

18 A Yes.

19 Q For the people here who do not have a
20 degree in statistics, does that generally say that
21 the Cohen effect size can be an effective measure for
22 assessing clinical significance?

23 MR. ROBERTS: Objection.

24 THE WITNESS: It -- it's -- it's a useful

1 way of roughly assessing -- putting -- putting a
2 numeric -- putting a metric on effect size by sort of
3 standardizing it with the standard deviation. And so
4 it's a way of making comparisons across different
5 trials, across different diseases, across different,
6 you know, outcome measures. It's -- it's sort of a
7 standard -- and that's why, you know, we say, you
8 know, an effect size of like 0.3, which is typical of
9 what you get in a depression study, is pretty -- is
10 pretty small. In other disorders like ADHD, you get
11 much bigger effect sizes that are based -- based on
12 Cohen's d. So...

13 BY MR. WISNER:

14 Q Sure. Are you familiar with something
15 called the number needed to treat?

16 A Yes.

17 Q And what is that?

18 A So the number needed to treat is -- is a
19 number that you can calculate if you're -- if you're,
20 you know, basically using percentage of responders,
21 proportion of responders as an outcome.

22 And so, say, if you have a trial where,
23 you know, 75 percent of patients in a -- in a trial
24 were assigned a drug have a, quote, response, however

1 you define "response," and 50 percent on placebo have
2 a response. So then the -- you know, the difference
3 between responders in the drug and placebo groups
4 is -- is 25 percent. So the number needed to treat
5 them is just the inverse of that, so it would be 4.
6 Which is -- you know, by psychiatric standards is
7 a -- is a pretty good number needed to treat. In
8 most psychiatric trials it's -- it's more than that.
9 It's more like 7 or 8.

10 So -- but, again, it's a rough measure of
11 the -- of the -- sort of the clinical impact in the
12 population of a particular treatment that has a -- an
13 effect, but the question is how important is the
14 effect in the population.

15 Q Is one way to express the concept of NNT
16 -- you don't agree with me, you can tell me so -- but
17 that if we have -- let's say the NNT number is 5,
18 okay? That the number of patients that need to be
19 treated with the drug such that you would see an
20 outcome different than what you would see if you just
21 gave placebo is 5?

22 MR. ROBERTS: Objection.

23 THE WITNESS: That -- that's correct.

24 That is the -- the common sense interpretation of

1 that -- of that measure.

2 BY MR. WISNER:

3 Q Okay, great.

4 All right. Let's -- let's turn to the
5 next page, page 6-S, under the "Payer's Perspective."
6 Do you see that?

7 A I do.

8 Q All right. If you look down in the last
9 paragraph there midway through the paragraph, you see
10 the sentence that begins "today"? Do you see?

11 A Yes.

12 Q All right. It says: "Today P less than
13 0.05 is generally accepted to be statistically
14 significant. Besides being an arbitrary limit, it
15 does not necessarily align with clinical
16 significance. Clinicians know well that results from
17 an RCT, or randomized controlled trial, can be
18 statistically significant without being clinically
19 significant and vice versa."

20 Do you see that?

21 A I do.

22 Q Do you agree with that?

23 A In general, yes, that statistical
24 significance by itself is -- is not necessarily a

1 good measure of how impactful a treatment will be in
2 the -- in the population.

3 Q Okay, great. Now, if you turn the page
4 to 7-S, the top of the paragraph, it says: "It may
5 be more appropriate to speak of a clinically
6 meaningful effect size, which has been defined as the
7 smallest difference, i.e., effect size, that patients
8 perceive as beneficial and that would mandate, in the
9 absence of troublesome side effects and costs, a
10 change in the patient's management."

11 Do you see that?

12 A I do.

13 Q Have you ever -- have you ever heard of
14 that concept of clinical significance?

15 A Yeah. I mean, I -- again, I was at this
16 meeting, and I -- as you -- I am an author on this
17 paper, so I -- I am familiar with -- with that
18 notion.

19 Q Sure. Do you agree with that notion?

20 A I -- I -- I do agree that, in general, we
21 need to be thinking more about how to develop
22 treatments that have a real impact on patients'
23 lives. And actually, FDA is -- is moving more in
24 that direction too. There's a lot greater interest

1 now at FDA in looking at, for example, what are
2 called PROs, patient reported outcomes, as an
3 alternative to these standard instruments like the
4 HAM-D and the MADRS and so forth that are typically
5 used now in clinical trials.

6 Q And you're familiar that, for example,
7 agencies in the United Kingdom have -- like the NICE
8 organization, they -- they focus heavily on the idea
9 of clinical significance --

10 A Yeah.

11 Q -- right?

12 MR. ROBERTS: Objection.

13 THE WITNESS: Yeah.

14 BY MR. WISNER:

15 Q And you believe that organizations like
16 NICE are reputable organizations?

17 MR. ROBERTS: Objection.

18 THE WITNESS: I have -- I have a good
19 deal of respect for NICE.

20 BY MR. WISNER:

21 Q Okay. All right. Well, let's turn to
22 page 10-S in the section that says "FDA Perspective."
23 Do you see that?

24 A I do.

1 Q And -- and do you think that you probably
2 wrote this section?

3 MR. ROBERTS: Objection.

4 THE WITNESS: I -- I suspect I probably
5 drafted the first version of it, yes.

6 BY MR. WISNER:

7 Q And it's probably fair to say that before
8 you allowed a document to be published with the "FDA
9 Perspective" as a header, you made sure to read
10 through it and make sure it was accurate, right?

11 MR. ROBERTS: Objection.

12 THE WITNESS: Yes.

13 BY MR. WISNER:

14 Q Okay.

15 A As -- as did my boss at the time.

16 Q Well, this -- well, that's a good
17 question, actually. This says that this supplement
18 was published in May/June of 2013.

19 A Oh, I -- yeah, right. This was after I
20 left FDA, so...

21 Q Okay. So that's what I thought. This
22 was after --

23 A No, no, I -- right.

24 Q Okay. That said, I am still sure you

1 wanted to make sure you didn't get in trouble with
2 your boss or bosses at the FDA. All right.

3 A But -- knowing -- knowing Bob Temple, I
4 would think that -- that he probably would agree with
5 a lot of this.

6 Q Okay.

7 A But I -- I can't speak for Bob Temple.

8 Q Sure. Sure.

9 All right. Well, it says here under the
10 "FDA Perspective," the first paragraph starts off:
11 "The FDA looks for," quote, "substantial evidence,"
12 unquote, "that a drug will do what it's labeled to
13 do, although it does not define 'substantial
14 evidence.' There are no specific regulations
15 defining minimum effect size or how to determine a
16 clinical meaningful effect."

17 Do you see that?

18 A I do.

19 Q Is that your understanding?

20 A It -- it's true. I mean, you know, if
21 you look at the law, it says to support efficacy, you
22 have to have substantial evidence of effectiveness
23 from adequate and well controlled trials. It doesn't
24 say what -- you know, what "substantial" is. Either

1 in terms of the number of trials, although it does
2 say trials, but in terms of the effect size in those
3 trials, it doesn't -- doesn't really get into that.
4 And the regulations don't really get into that much
5 either.

6 Q Now, from my understanding of the law,
7 and you can tell me your understanding insofar as you
8 work with the FDA, but --

9 MR. ROBERTS: With the caveat that he is
10 not a lawyer.

11 MR. WISNER: I'm sorry. I'm asking a
12 question. Please don't interrupt me with testimony.

13 MR. ROBERTS: Okay.

14 BY MR. WISNER:

15 Q So let me ask my question again.

16 Now, Doctor, my understanding of the law
17 is that unless the FDA makes a finding that there is
18 a lack of substantial evidence, an NDA, at least with
19 regards to efficacy, has to approve it.

20 MR. ROBERTS: Objection.

21 THE WITNESS: I think -- I think FDA
22 is -- is obligated to, you know, approve an
23 application unless it can find compelling reasons not
24 to, if it has -- meets that minimum definition of

1 "substantial evidence."

2 BY MR. WISNER:

3 Q And my understanding generally, and this
4 is obviously a generalization, but to meet the burden
5 of substantial evidence of efficacy, a sponsor has to
6 provide two positive clinical trials, right?

7 MR. ROBERTS: Objection.

8 THE WITNESS: That's general -- that's
9 generally the way it's interpreted, yes.

10 BY MR. WISNER:

11 Q And that means, for example, you could
12 have many more negative clinical trials, but so long
13 as you have those two positive ones, you've met that
14 minimum burden of substantial evidence, right?

15 MR. ROBERTS: Objection.

16 THE WITNESS: That -- that -- I mean,
17 in -- in general, that is true. However, I can tell
18 you that FDA does consider the total database of
19 trials. In fact, you can -- you can do -- I don't
20 want to take up too much time with this -- but you
21 can use the binomial formula for calculating the
22 probability of getting out of a set of, say, four
23 trials -- I happen to know this probability by heart
24 because it's such a common thing -- but if you have

1 four trials considered independent, so you can use
2 the binomial formula, you get two that are
3 significant of P less than 0.05 or less, and two that
4 don't make it, the probability of getting that by
5 chance is about four in a thousand.

6 So, it's still -- even if you have some
7 negative trials, that's the point I'm making, it's
8 so -- it's still quite a rare finding by chance to
9 get those two positive. And that's why I think, you
10 know, the drafters of the law, you know, were
11 thinking in terms of replication, that you would like
12 to have replication.

13 BY MR. WISNER:

14 Q Okay. We'll come back to that topic in
15 just a few seconds actually, so I -- I appreciate you
16 bringing that up.

17 A All right.

18 Q All right. Let's turn the page and look
19 at page 11-S. Okay?

20 A Okay.

21 Q And then in the middle of the section
22 there's a paragraph that says "Effect size." Do you
23 see that?

24 A Yes.

1 Q All right. It says: "Effect size is
2 usually measured by regulators as the difference
3 between the drug and placebo mean change from
4 baseline using a standard measure. Cohen's d would
5 be the mean test group minus the mean control over
6 standard deviation. While Cohen defined large,
7 medium and small effects as d, 0.8, 0.5, and 0.2,
8 respectively, an FDA rule of thumb is that an effect
9 size is deemed large if it is greater than 0.8, small
10 if it is less than 0.5, and moderate if it falls
11 between those values."

12 Do you see that?

13 A I -- I do.

14 Q And is that your understanding of
15 generally how the FDA views or labels the Cohen
16 effect size?

17 A Yeah, I think --

18 MR. ROBERTS: Objection.

19 THE WITNESS: I think that's articulated
20 somewhere in some FDA document, but I can't off the
21 top of my head point to it. As I was saying, FDA
22 statisticians tend not to think too highly of Cohen's
23 as a measure of effect size, but clinicians at FDA
24 view it somewhat differently. So...

1 BY MR. WISNER:

2 Q Okay. And just is it a rule of thumb,
3 I'm just saying that it's greater than --

4 A And --

5 Q Sorry.

6 A I'm sorry.

7 Q If it's greater than 0.08, it's
8 considered large, and if it's smaller than 0.5, it's
9 considered small?

10 MR. ROBERTS: Objection.

11 THE WITNESS: I -- I think that's --
12 that's generally accepted.

13 BY MR. WISNER:

14 Q And this is, of course, based -- based on
15 your experience working on psychiatric medications,
16 right?

17 MR. ROBERTS: Objection.

18 THE WITNESS: And that's -- that is
19 consistent with the way these numbers are used in
20 the -- in the academic clinical community.

21 BY MR. WISNER:

22 Q Okay, great.

23 And then the next sentence reads: "On
24 the NNT scale then, large would be smaller than 2,

1 small would be greater than 4, and moderate if it
2 falls between those two values."

3 Do you see that?

4 A Yeah, I'm not sure in retrospect exactly
5 where this comes from.

6 Q Well, do you agree with that?

7 A I -- I think it's -- it's a little -- a
8 little bit severe in terms of a requirement for --
9 and I know that I'm an author on this paper. I'm not
10 sure exactly where that came from, because it
11 isn't -- it isn't consistent with the NNTs that you
12 often see for psychiatric drugs.

13 Q But you would agree with me that the
14 effect sizes in the NNTs that you commonly see in
15 psychiatric drugs are generally pretty small, right?

16 MR. ROBERTS: Objection.

17 THE WITNESS: They're -- generally they
18 are more above this.

19 BY MR. WISNER:

20 Q Okay.

21 A They're more like -- more like 6, 7, 8,
22 even 10. So...

23 Q All right. The next paragraph -- sorry,
24 the paragraph right from the bottom that starts "As

1 briefly." Do you see that?

2 A I do.

3 Q "As briefly described in the introduction
4 above, the NNT value, how many people need to be
5 treated with the new drug rather than placebo for one
6 additional patient to benefit, can also be helpful to
7 regulators."

8 Do you see that?

9 A Yes.

10 Q And you agree that the NNT number is
11 something that's helpful to regulators?

12 A It's -- it's -- it's commonly used, and,
13 you know, FDA is -- is now working on the concept of
14 clinical meaningfulness in trying to come up with
15 some -- some metrics to incorporate into the review
16 process to -- to do something more specific on
17 that -- on that issue.

18 Q Okay. Now, if you go through to the next
19 paragraph -- well, the next -- the end of that
20 paragraph in the next column.

21 Do you see that?

22 A Yes.

23 Q The sentence that begins "overall"?

24 A Right.

1 Q It reads: "Overall, the NNT is a
2 meaningful, well respect -- well accepted, common
3 sense measure, but its value depends on how
4 'response' is defined."

5 Do you see that?

6 A I'm sorry, where exactly are you?

7 Q Sure. Right there in that last
8 paragraph, the sentence that leads "overall."

9 A Okay. Right, right, right.

10 Q All right. So it reads: "Overall, the
11 NNT is a" --

12 A Yes.

13 Q -- "meaningful, well accepted, common
14 sense measure, but its value depends on how
15 'response' is defined," right?

16 A Right.

17 Q And what you mean by "its value depends
18 on how 'response' is defined," that means how the
19 response rate is defined in the protocol for that
20 clinical trial, right?

21 MR. ROBERTS: Objection.

22 THE WITNESS: Yes. For -- for example,
23 typically a response is -- is -- it's a change of
24 50 percent reduction on, say, the HAMD or the CDRS-R

1 is considered a responder, but clearly it depends on
2 how you define that.

3 BY MR. WISNER:

4 Q Yeah. But you don't define the response
5 measure after the study is completed, right?

6 MR. ROBERTS: Objection.

7 THE WITNESS: Ordinarily, no. You would
8 do it before.

9 BY MR. WISNER:

10 Q Okay. All right.

11 All right. Let's turn to page 13-S.

12 A Okay.

13 Q All right. This is a section that says:
14 "Determining how effective a treatment will be for an
15 individual patient" -- do you see that?

16 A I do.

17 Q All right. I'm going to skip the first
18 paragraph and start with the second one that starts
19 with "Paul." Do you see that?

20 A Mm-hmm.

21 Q All right. It reads: "Paul Meehl" -- am
22 I saying that right?

23 A Yes.

24 Q Okay.

1 -- "held that all null hypothesis of
2 randomness are false in that with a large enough
3 sample size and sufficient number of RCTs, there will
4 eventually result one or two or more values of
5 P-value less than 0.05."

6 MR. ROBERTS: "One or two more values."

7 BY MR. WISNER.

8 Q "... result one or two more values of
9 P-value less than 0.05." Do you see that, Doctor?

10 A I do.

11 Q Okay. It continues: "A P-value less
12 than the conventional 0.05 means that the sample size
13 was large enough to detect some deviation from the
14 null hypothesis, not that the deviation was
15 clinically significant or important. A
16 nonstatistically significant result means that the
17 sample size was not large enough and often reflects
18 the adequacy of the study design in terms of sample
19 size and units measured."

20 Do you see that?

21 A I do.

22 Q Do you agree with that?

23 A There's no question that, you know, that
24 P-value is dependent on sample size. You can drive

1 the variance down as you increase the sample size to
2 get a statistically significant finding that
3 potentially may not be clinically meaningful. That
4 is true.

5 Q And so in the context of a depression
6 trial, if the difference between the placebo and the
7 drug treatment -- let's say it was five points on the
8 HAMD scale, okay?

9 A Yeah.

10 Q It's possible that if you had a sample
11 size of 100 patients, you would not have a
12 statistically significant result, but if you had a
13 sample size of 500 patients, the same difference
14 would be statistically significant; is that right?

15 A That's true.

16 MR. ROBERTS: Objection.

17 BY MR. WISNER:

18 Q And so in that --

19 MR. ROBERTS: Do you mind just waiting a
20 second after he finishes the question so I have a
21 chance to object.

22 THE WITNESS: Sorry. Sorry.

23 MR. WISNER: You don't have to object to
24 everything, you know.

1 MR. ROBERTS: I don't object to
2 everything --

3 MR. WISNER: Well, it's true --

4 MR. ROBERTS: -- but your questions are
5 objectionable sometimes.

6 BY MR. WISNER:

7 Q All right, Doctor. So -- so you would
8 agree then that, as a general matter, one of the ways
9 to help ensure that any differences between the
10 placebo group and the treatment group is actually
11 statistically significant is just really increase the
12 sample size, right?

13 MR. ROBERTS: Objection.

14 THE WITNESS: As -- as I said before, you
15 can by driving up a sample size achieve statistical
16 significance that -- that potentially, you know, may
17 not be clinically meaningful.

18 BY MR. WISNER:

19 Q All right. Now, going back to this
20 paragraph, I'm going to skip the next sentence and
21 starts with the sentence that says "if two." Do you
22 see that?

23 A Which column are you in?

24 Q We're in the same area, it's the same

1 paragraph, but it starts with the sentence "if two
2 separate RCTs" -- do you see that?

3 MR. ROBERTS: Doctor, it's still the
4 first column --

5 MR. WISNER: Yeah, still the first --

6 MR. ROBERTS: -- towards the bottom.

7 THE WITNESS: Okay. "If two separate,"
8 yeah.

9 BY MR. WISNER:

10 Q Yeah. Okay.

11 So it reads: "If two separate RCTs with
12 P less than 0.05 were to mean approval of a drug, it
13 would take only 40 RCTs to approve a drug absolutely
14 equivalent to placebo. And if each trial were run at
15 the 80 percent power level, whatever the true effect
16 size, it would only -- it would take only about
17 three. This means that those with deep enough
18 pockets can eventually get their desired results.
19 Essentially anything can be approved with the right
20 number of studies of large enough size."

21 Do you see that?

22 A I do see that.

23 Q So this person's discussing a concern
24 that by just random probability, you will eventually

1 get a sufficient number of studies that have a
2 P-value of less than 0.05.

3 MR. ROBERTS: Objection.

4 THE WITNESS: And -- and as I was saying
5 before, we have done calculations to try and get an
6 idea of where you would cross that threshold of --
7 you know, of getting two trials at 0.05 based on
8 chance, which is what this is saying, and -- and the
9 number is well above 12 trials, it's probably closer
10 to 20.

11 So, I don't -- I don't agree that you
12 can -- you can achieve that by doing -- and I told
13 you that the probability, if you do four trials of
14 getting -- of getting two that are significant and
15 two that are not, is only four in a thousand. So
16 it's -- it's a very low chance probability.

17 Now, you know -- and even as you get up
18 to like ten, it's still -- it's still well below
19 0.05. So it isn't -- it isn't that easy, and it's
20 going to be a rare company that has deep enough
21 pockets to do, you know, 15 trials to get -- they
22 would run out of money long before that given how
23 much clinical trials cost these days.

24 BY MR. WISNER:

1 Q Fair enough.

2 Do you have any idea how much money
3 companies like Allergan have, Doctor?

4 MR. ROBERTS: Objection.

5 BY MR. WISNER:

6 Q All right.

7 A Well, I mean -- I know -- I know you say
8 that, but the truth is that companies are -- these
9 days are backing out of psychiatric drug research and
10 moving into other areas because it is so difficult.
11 So I -- I think --

12 BY MR. WISNER:

13 Q Could it also be, Doctor, that the market
14 is fluttered -- flooded with generic versions of
15 psychiatric medicines and there's no more money to be
16 made?

17 MR. ROBERTS: Objection.

18 THE WITNESS: I mean, I don't -- we don't
19 want to take up all this time debating it.

20 BY MR. WISNER:

21 Q Okay.

22 A But I can -- I can push back against
23 that.

24 Q Okay. That's fine.

1 (Exhibit No. 22 was marked for
2 identification.)

3 BY MR. WISNER:

4 Q I'm handing you what has been marked as
5 Exhibit 22 to your deposition.

6 This is a document titled "A Randomized
7 Placebo-Controlled Trial of Citalopram for the
8 Treatment of Major Depression in Children and
9 Adolescents."

10 Do you see that, Doctor?

11 A I do.

12 Q And this appears to have been published
13 -- at least the lead author is Dr. Wagner. Do you
14 see that?

15 A I do.

16 Q Do you also see that William Heydorn is
17 on this?

18 A Yes.

19 Q Okay. And this was published in the
20 American Journal of Psychiatry in 2004. Do you see
21 that?

22 A I do see that.

23 Q You understand that this is the published
24 version of the results of Study MD-18?

1 A Yeah, I've seen this paper.

2 Q Okay. During your time in your capacity
3 at the FDA and even afterwards, have you had any
4 conversations with anybody about this publication?

5 A No.

6 Q Okay. Have you spoken to Dr. Wagner
7 about this publication?

8 A I -- I've never spoken to Dr. Wagner.

9 Q So fair enough, you don't recall ever
10 speaking to anybody about this publication?

11 A I -- I think in my earlier work with
12 Forest, I -- I believe that this publication was
13 discussed, but I don't specifically recall the
14 conversations.

15 Q Would you have reviewed something like
16 this, by any chance, while you were at the FDA?

17 A A publication?

18 Q Mm-hmm.

19 A We ordinarily would not review published
20 papers because we -- we have the data.

21 Q You have the final study report.

22 A Right.

23 Q And the final study report generally
24 contains a heck of a lot more information than the

1 published paper, right?

2 MR. ROBERTS: Objection.

3 THE WITNESS: Yes.

4 BY MR. WISNER:

5 Q All right. Now, if you turn to page --
6 in the journal, it's 1081.

7 A Okay.

8 Q And in the right-hand column, do you see
9 the paragraph that starts "Citalopram treatment"?

10 A Yes.

11 MR. ROBERTS: They both do. There's two
12 that start "Citalopram" --

13 BY MR. WISNER:

14 Q Fair enough. The one in the middle.

15 A Ah. Okay, got you.

16 Q Thanks.

17 It reads: "Citalotram treat- --
18 citalopram treatment shows statistically significant
19 improvement compared with placebo on the children's
20 depression rating scale revised as early as week 1,
21 which persisted through the study, Figure 1. At
22 week 8, the effect size on the primary outcome
23 measure, Children's Depression Rating Scale R --
24 scale revised, last observation carried forward was

1 2.9."

2 Do you see that?

3 A Yes.

4 Q Now, there's no mention there from what I
5 can tell of -- that results are being based on data
6 from patients that were potentially unblinded,
7 right?

8 MR. ROBERTS: Objection.

9 THE WITNESS: Again, I'd -- I would have
10 to read the whole paper, but I take your word that
11 it's not -- that it's not mentioned.

12 BY MR. WISNER:

13 Q Okay. It says an effect size of 2.9. If
14 that's a Cohen effect size, that is exceptionally
15 high, isn't it?

16 A I --

17 MR. ROBERTS: Objection.

18 THE WITNESS: I'm sorry. I don't mean to
19 interrupt you.

20 BY MR. WISNER:

21 Q Sure.

22 A I'm quite sure that's not the Cohen
23 effect size. It -- it's more likely the difference
24 between drug and placebo and change from baseline

1 as -- as a measure of effect size.

2 Q Okay.

3 (Exhibit No. 23 was marked for
4 identification.)

5 BY MR. WISNER:

6 Q All right. I want to hand you what has
7 been marked as Exhibit 23 to this deposition.

8 This is a copy of the letters to the
9 editor that were submitted --

10 MR. ROBERTS: Wait, just give me one
11 second just to get it, if you don't mind.

12 BY MR. WISNER:

13 Q -- letters to the editor --

14 MR. ROBERTS: Thank you.

15 BY MR. WISNER:

16 Q -- that were published following the
17 publication of the study.

18 A Okay.

19 MR. WISNER: Are you okay?

20 MR. ROBERTS: Yeah. I just wanted to
21 have the exhibit in front of me.

22 MR. WISNER: Sure. Just trying to keep
23 it going.

24 BY MR. WISNER:

1 Q All right. Have you ever looked at these
2 before, by any chance?

3 A I don't recall looking at these.

4 Q Okay. All right. If you look here, if
5 you look on page 817, which is the first page, there
6 is -- it says: "Child psychopharmacology, effect
7 sizes, and the big bang."

8 Do you see that?

9 A Yes.

10 Q And if you look to the right, it says the
11 authors are Andres Martin, Walter Gilliam, Jeffrey
12 Bostic and Joseph Rey. You see that?

13 A I do.

14 Q Do you know Dr. Bostic?

15 A The -- the name is familiar, but I -- I
16 don't -- I don't think I have met him. I --

17 Q I know you're doing work at Massachusetts
18 General; is that right, nowadays?

19 A I -- I am, but I'm not up there very
20 often. I do most of it from home. So...

21 Q Okay. Fair enough.

22 All right. So I want to go through some
23 of this -- and if you actually turn the page, on the
24 bottom right-hand corner, it says: "Dr. Wagner and

1 colleague's reply."

2 Do you see that?

3 A I do.

4 Q So it appears that there were a few
5 letters to the editors published, and then obviously
6 Dr. Wagner and the colleagues responded to those
7 letters.

8 Do you see that?

9 A I do.

10 Q Okay. All right. Let's look to the
11 first one, "The Child Psychopharmacology, Effect
12 Sizes, and the Big Bang."

13 It reads: "We read with interest the
14 article by Karen D. Wagner, M.D., Ph.D., et al., in
15 the June issue in their study comparing citalopram to
16 placebo. We were surprised to find" --

17 A I'm sorry.

18 Q Oh.

19 A Can you tell me again exactly --

20 Q Well, the first page.

21 A Oh, okay.

22 Q The bottom left column.

23 A Oh, okay.

24 Q All right. It continues: "We were

1 surprised to find the authors reporting an overall
2 effect size of 2.9. The commonly cited criteria set
3 forth by Cohen effect sizes can be considered
4 trivial, less than 0.2; small, 0.2 to 0.5; moderate,
5 0.5 to 0.8; or large, greater than 0.8."

6 Do you see that?

7 A I do.

8 Q That's sort of consistent with what we
9 just discussed a few minutes ago, right?

10 A Yes.

11 Q All right. It continues: "By these
12 metrics, the reported effect size can be
13 characterized as gargantuan, big bang-worthy. The
14 value does not appear to be a benign typographical
15 error for the 0.29 given that 2.9 appears twice."

16 Would you agree generally that a Cohen
17 effect size of 2.9 would be -- would be gargantuan?

18 MR. ROBERTS: Objection.

19 THE WITNESS: Yes.

20 BY MR. WISNER:

21 Q Okay. If you turn to the next paragraph,
22 the sentence begins: "A Trickster Decimal," question
23 mark. Do you see that?

24 MR. ROBERTS: Where are you?

1 THE WITNESS: So you're into the
2 second --

3 BY MR. WISNER:

4 Q Yeah, sorry. See the next paragraph?

5 A Yes.

6 Q It says "A trickster" --

7 A The third sentence.

8 Q Yeah, you see that?

9 A Yes.

10 Q Okay, great.

11 So it reads: "A trickster decimal point
12 may be to blame, and a demoted effect size of 0.29
13 may gain in honesty what it loses in sex appeal of an
14 inflated 2.9 status. A smaller effect size seems
15 more plausible and not only because a meta-analysis
16 of 33 trials of selective serotonin reuptake
17 inhibitors, SSRIs, for the treatment of adult
18 depression arrived at a pooled effect size of 0.4,
19 but because the current study, although statistically
20 significant, was not that clinically impressive.
21 Only a 36 percent of patients treated with
22 citalopram responded compared to 24 percent of
23 those with placebo for a lukewarm number needed to
24 treat of 8."

1 Do you see that?

2 A Yes.

3 Q I'm going to first ask you, you would
4 agree that a response rate of 36 percent is pretty
5 small.

6 MR. ROBERTS: Objection.

7 THE WITNESS: I -- I -- again, the
8 problem is that the effect size, as we discussed -- I
9 mean that the -- a response rate depends on how you
10 define "response."

11 BY MR. WISNER:

12 Q Sure.

13 A So you can float it all over the place
14 depending on how you define it.

15 Q Well, at least based on how this study
16 was defined --

17 A Yes.

18 Q -- a priori, it had a 36 response rate,
19 right?

20 A Yeah.

21 Q And you would agree that's pretty small?

22 MR. ROBERTS: Objection.

23 THE WITNESS: It's -- it's -- it's pretty
24 modest, I agree with that.

1 BY MR. WISNER:

2 Q And I mean, to put it in layman's terms,
3 that means about two-thirds of all the children put
4 on citalopram didn't have a response as defined by
5 the study.

6 MR. ROBERTS: Objection.

7 THE WITNESS: That -- that's correct.

8 But, again, it doesn't -- it doesn't mean that the
9 improvement that they had was -- was not meaningful
10 in some way. I'm just cautioning that response rate
11 depends on how you define a response.

12 BY MR. WISNER:

13 Q I hear you, and I'm just saying that
14 based upon how the response rate was defined in MD-18
15 before the study was conducted, it ultimately
16 resulted in about two-thirds of children not
17 responding to the medication.

18 MR. ROBERTS: Objection. Is that a
19 question?

20 THE WITNESS: Based on this definition of
21 "response," that's absolutely correct.

22 BY MR. WISNER:

23 Q Okay. And it says here that the number
24 needed to treat was 8. You see that?

1 A Yes.

2 Q That's a pretty high NNT, right?

3 MR. ROBERTS: Objection.

4 THE WITNESS: It -- it's -- it's fairly
5 high. It's not too far out of line for what we're
6 seeing these days in psychiatric trials,
7 unfortunately.

8 BY MR. WISNER:

9 Q And you say "unfortunately" because you
10 would agree with me that a number needed to treat
11 represents a pretty small effect, doesn't it?

12 MR. ROBERTS: Objection.

13 THE WITNESS: It's -- it's not as big as
14 we would like them to be for sure.

15 BY MR. WISNER:

16 Q I mean it means in layman's terms that
17 for us to see one additional patient to get a benefit
18 from citalopram over taking a placebo, we would need
19 to treat eight different children, right?

20 MR. ROBERTS: Objection.

21 THE WITNESS: That -- that is what it
22 means in common sense terms. Again, we could -- we
23 could have a very extended discussion of this, and I
24 don't want to take up the time here to do that. But

1 it is -- there is no question, these effects are
2 modest.

3 BY MR. WISNER:

4 Q And you also would agree, Doctor, at
5 least from what you can tell, that this response rate
6 as well as the NNT number discussed here, that
7 actually included the data that had the potentially
8 unblinded patients in it, didn't it?

9 MR. ROBERTS: Objection.

10 THE WITNESS: That -- that's true.

11 BY MR. WISNER:

12 Q All right. Now, if you look at the last
13 paragraph in that letter, it reads: "Alternatively,
14 the authors may have used a different definition or
15 formula to calculate the effect size. This would be
16 unfortunate because the basic job description of an
17 effect size is to facilitate communication among
18 investigators and across measures."

19 Do you see that?

20 A I do.

21 Q And that's what you said a minute ago,
22 that one of the reasons we use a Cohen effect size is
23 because it helps standardize comparisons of different
24 outcomes in different studies.

1 MR. ROBERTS: Objection.

2 THE WITNESS: Yes, but, again, in
3 fairness, different groups, you know, are accustomed
4 to using different measures of effect size. At FDA,
5 the Cohen's measure metric is not used that often.
6 They're more -- more likely to use what these authors
7 used.

8 So I think it's a little bit unfair to
9 attack them, you know, for making the assumption that
10 what they're presenting is the Cohen effect size when
11 they were using a more commonly used measure of
12 effect size, say, within FDA or perhaps within some
13 other communities.

14 BY MR. WISNER:

15 Q Okay. And I'm sorry, I don't mean to be
16 attacking Dr. Wagner here and her colleagues. I was
17 just reading what it said here.

18 I just want to know, do you agree that
19 the Cohen effect size is typically used so you can
20 compare the results from different studies across?

21 MR. ROBERTS: Objection.

22 THE WITNESS: I think it would have been
23 better for the authors to -- to present several
24 different measures of effect size, rather than just

1 relying on -- on the -- you know, the one that FDA
2 tends to rely on.

3 BY MR. WISNER:

4 Q Okay. Now, if you turn to page -- where
5 am I -- 818. Do you see that?

6 A I do.

7 Q All right. Sorry, 819. The last
8 paragraph in the left column. Do you see that?

9 It starts with "Dr. Martin and
10 colleagues."

11 A Yes.

12 Q Okay. It reads: "Dr. Martin and
13 colleagues inquire about the value of 2.9, which was
14 calculated as the quotient of the least square mean
15 divided by the common standard -- standard error of
16 the mean for each treatment group."

17 Do you see that?

18 A Yes.

19 Q That's not the -- that's not a Cohen
20 effect size, right? 2.9?

21 A I'm not sure what they mean by "the
22 quotient of the least square mean." It's the
23 difference between the mean change from baseline of
24 drug and placebo divided by the common standard

1 deviation.

2 MR. ROBERTS: And just to clarify for the
3 record, this is the Dr. Wagner and colleagues' reply
4 section.

5 MR. WISNER: Yeah.

6 MR. ROBERTS: Okay.

7 MR. WISNER: I don't think there is any
8 confusion about that, Counsel.

9 MR. ROBERTS: Well, now there's not.

10 MR. WISNER: Okay. Again, if you could
11 limit your commentary objections, I would appreciate
12 that.

13 MR. ROBERTS: Okay.

14 MR. WISNER: Thanks.

15 MR. ROBERTS: And I will clarify for the
16 record every once in a while.

17 MR. WISNER: Okay, great.

18 BY MR. WISNER:

19 Q The next sentence reads: "With Cohen's
20 method, the effect size was 0.32."

21 Do you see that?

22 A I do.

23 Q Okay. So it looks like they ultimately
24 did a -- calculated the Cohen effect size and it was

1 determined to be 0.32, right?

2 A Right.

3 Q And under the standard of the FDA and
4 just generally amongst academics, that's a -- that's
5 a small effect size, right?

6 MR. ROBERTS: Objection.

7 THE WITNESS: It -- it's typical of what
8 you see for antidepressants. But it is modest.
9 It's -- it's small.

10 BY MR. WISNER:

11 Q Okay. And, again, that -- it appears
12 that that effect size was in fact calculated again
13 with including data from those potentially unblinded
14 patients, right?

15 MR. ROBERTS: Objection.

16 THE WITNESS: Most likely.

17 BY MR. WISNER:

18 Q All right. Now, if you could turn back
19 to the page before, on page 818.

20 A Okay.

21 Q You see there's another letter to the
22 editor, it starts at the bottom of the left column.
23 Do you see that to the editor, at the very bottom?

24 A The one right under "Dr. Wagner and

1 colleagues' reply" or --

2 Q No, no, to the left of that.

3 A Yes.

4 Q Just "To the editor, we read with
5 interest."

6 A Okay. Okay.

7 Q So I'm going to go through this letter to
8 the editor and ask you some questions about it. And
9 you can see that it was sent by Maju Mather --
10 Mathews. Do you see that?

11 A I do.

12 Q It has a bunch of different physicians
13 listed there. Do you see that?

14 A I do.

15 Q Just quickly reading through that, do you
16 recognize any of those individuals?

17 A Maju Mathews used to work for me when I
18 was at FDA.

19 Q Oh, really. Well, what did Maju --
20 Dr. Mathews do for you?

21 A He was a clinical reviewer. He's a
22 psychiatrist.

23 Q Do you know what years he worked with
24 you?

1 A I -- I don't -- you know, it's -- I
2 would -- I would have to guess. It was sometime
3 maybe, I'm guessing here, but probably 2007, 2008
4 through maybe 2010, something like that.

5 Q Okay. Anyone else here that you
6 recognize?

7 A Oh. No. No. No. No.

8 Q Okay. All right. Now, in the right
9 column, do you see the sentence -- the paragraph that
10 begins "Our great -- greatest concern"?

11 A Yes.

12 Q Okay. So it reads: "Our greatest
13 concerns -- concern is with the results and
14 conclusions drawn. There is no table showing the
15 results in detail. The authors have only stated that
16 36 percent of citalopram-treated patients met the
17 criteria for response compared to 24 percent of
18 patients receiving placebo. This response rate,
19 while itself marginal compared to other studies of
20 antidepressants, does not in itself show that
21 citalopram is better than placebo."

22 Do you see that, Doctor?

23 A Yes.

24 Q You would agree with me that the response

1 rate seen in depression trials is usually higher than
2 36 percent, right?

3 MR. ROBERTS: Objection.

4 THE WITNESS: It is usually higher, but,
5 again, it -- it depends on how "response" is defined.
6 BY MR. WISNER:

7 Q You are aware that Prozac received a
8 pediatric indication for treatment of depression?

9 A Yes.

10 Q Do you -- do you recall, by any chance,
11 what the fluoxetine response rate was?

12 A I don't.

13 Q Okay. It continues: "We calculated the
14 absolute benefit increase of using citalopram as
15 0.12. 95 percent confidence interval equals 0.015
16 to 0.255."

17 MR. ROBERTS: That's negative 0.015.

18 MR. WISNER: Sorry. Thank you.

19 "Negative 0.015 to 0.255."

20 BY MR. WISNER:

21 Q What is absolute benefit increase?

22 A I -- I don't know offhand.

23 Q Okay. It continues: "The relative
24 benefit increase that could be attributed to

1 citalopram was 50 percent, 95 percent confidence
2 interval, a negative 135 percent to 6 percent."

3 Do you see that?

4 A I do.

5 Q Do you know what relative benefit
6 increase is?

7 A I'm not familiar with these metrics that
8 they're talking about.

9 Q Okay. It continues: "The odds ratio,
10 i.e., the odds of improving while taking citalopram
11 compared to placebo, was 1.75, a confidence -- 95
12 percent CI, 0.92 to 3.43."

13 Do you see that?

14 A Mm-hmm. Yes.

15 Q Do you know what an odds ratio of
16 improvement is?

17 A No, I'd have -- I would have to think
18 about this. I'm not -- these are -- these are not
19 commonly used metrics.

20 Q Okay.

21 A In my view, but...

22 Q All right. Well, then the next sentence
23 reads: "The number needed to treat, i.e., the number
24 of children who need to be treated with citalopram,

1 for one additional positive outcome was 8. 95
2 percent confidential interval equals 4 to infinity.
3 None of these shows that citalopram is any better
4 than placebo."

5 Do you see that?

6 A I see that.

7 Q Do you understand why the authors are
8 concerned that the observed difference between
9 citalopram and placebo was not clinically
10 meaningful?

11 MR. ROBERTS: Objection.

12 THE WITNESS: I -- I understand the
13 concern that the effect size is -- is relatively
14 small. It is in general for antidepressants. I
15 mean, the results in adult depression trials for
16 antidepressants is not so different. It's very
17 challenging to do acute studies in depression.

18 If you -- if you look at, and we did a --
19 sort of an aggregate analysis of maintenance trials
20 in depression that shows a much bigger effect size.
21 So, in other words, for patients who have responded
22 to an antidepressant, the -- you know, there is a
23 much bigger effect size. Basically, the risk of
24 relapse is reduced by about 50 percent, which is

1 quite impressive compared to these kinds of results.

2 But there's no question, it -- it's a
3 real challenge to do studies in acute depression
4 whether you're talking about adults or children.

5 BY MR. WISNER:

6 Q And you would agree based upon the
7 relatively small effect size observed here in this
8 study that this study by itself doesn't provide
9 conclusive evidence that Celexa is in fact effective
10 in treating pediatric patients?

11 MR. ROBERTS: Objection.

12 THE WITNESS: I agree with that, and of
13 course, we didn't approve that supplement.

14 BY MR. WISNER:

15 Q Now, Doctor, we know that all the
16 protocol specified secondary endpoints for
17 Study MD-18 were negative, right?

18 MR. ROBERTS: Objection.

19 THE WITNESS: At the week 8 endpoint,
20 yes.

21 BY MR. WISNER:

22 Q We know that the observed cases endpoint
23 on the primary efficacy variable was negative at
24 week 8, right?

1 MR. ROBERTS: Objection.

2 THE WITNESS: That's correct, although
3 that wasn't the -- that wasn't the protocol specified
4 primary analysis.

5 BY MR. WISNER:

6 Q Sure. But we know that the OC results
7 for the people who actually completed the clinical
8 trial, that actually was negative for efficacy,
9 right?

10 A That's true.

11 Q We know that with Study MD-18 that there
12 were nine patients that Dr. Flicker characterized as
13 being unmistakably unblinded, right?

14 MR. ROBERTS: Objection.

15 Mischaracterizes the evidence.

16 THE WITNESS: That's correct.

17 BY MR. WISNER:

18 Q And we know that when those nine patients
19 are excluded from the primary efficacy analysis
20 pursuant to the LOCF analysis, that the P-value goes
21 higher than 0.050, right?

22 MR. ROBERTS: Objection.

23 THE WITNESS: That's -- that's true.

24 However, I would push back a little bit on that to

1 make the point that that analysis was a sensitivity
2 analysis to get -- to gauge -- you know, to get some
3 sense of sort of the impact of -- of the patients who
4 were -- who were potentially unblinded, or I guess in
5 this case, may be more than potentially unblinded.
6 And you expect when you do a sensitivity analysis and
7 you throw patients away that the power of that study
8 is going to diminish.

9 And so a P-value of 0.052 is not bad for
10 a sensitivity analysis that you know going in is
11 losing power. And that -- that's the purpose frankly
12 of it. It's -- I would argue that it's still not the
13 correct P-value if you're characterizing, you know,
14 that study. It's just -- it's something to do to try
15 and get a sense of -- of the impact of those -- of
16 those patients on the -- on the trial.

17 And to me, it suggests that the impact
18 was not great. In other words, yes, there was
19 potential unblinding or perhaps they were unblinded,
20 I don't know the answer to that, but it didn't have a
21 huge impact on the -- on the significance.

22 Yes, it was 0.052, and I know you want to
23 argue that that's not statistically significant, and,
24 of course, by usual standards, it doesn't meet that

1 threshold, it misses by 2/1000ths. But to me, it
2 argues that those patients were not inordinately
3 impactful on the -- on the outcome of that study.

4 BY MR. WISNER:

5 Q Well, you do know that the inclusion of
6 those unblinded patients in the study results
7 changed the numerical difference between placebo and
8 citalopram at week 8, right?

9 MR. ROBERTS: Objection.

10 THE WITNESS: In terms of the P-value?

11 BY MR. WISNER:

12 Q No, in terms of the actual different --
13 differential between placebo and citalopram.

14 MR. ROBERTS: Objection.

15 THE WITNESS: The effect size is measured
16 by difference between drug and placebo and change
17 from baseline.

18 BY MR. WISNER:

19 Q That's right. You understand the
20 difference at week 8 with the patients included was
21 4.6 points on the CDRS-R score, and that when they're
22 removed, it drops to 4.3.

23 Did you know that?

24 MR. ROBERTS: Objection.

1 THE WITNESS: I -- I think I remember
2 reading it someplace. But, again, I'm not sure how
3 to -- how to evaluate the importance of that.

4 BY MR. WISNER:

5 Q Well, let's -- let's just talk numbers
6 for a second. I mean, you remove nine patients' data
7 from the analysis out of a cohort of over 170, and
8 just the removal of those nine patients creates a
9 numerical point difference of 0.3 in the difference
10 between placebo and citalopram, right?

11 MR. ROBERTS: Objection.

12 THE WITNESS: But the -- the 0.3 is a
13 relatively small number, and I don't -- again, you
14 know, we're getting back to this issue of -- of how
15 do you measure clinical significance. I don't know
16 what the clinical significance of a four-point
17 difference is. I have no idea what the clinical
18 significance of a -- a difference of 0.3 is.

19 BY MR. WISNER:

20 Q I get you there, Doctor.

21 And I guess what I'm trying to say is it
22 wasn't just a powering issue. It actually changed
23 the values of the difference between placebo and the
24 drug group, correct?

1 MR. ROBERTS: Objection.

2 THE WITNESS: I -- I -- I don't really
3 agree with you on that point.

4 BY MR. WISNER:

5 Q Okay. Well, it was a significant
6 enough -- of enough difference to at least have
7 changed the P-value to a number that was above 0.05,
8 correct?

9 MR. ROBERTS: Objection.

10 THE WITNESS: It -- it did do that.

11 BY MR. WISNER:

12 Q Okay. So then, you know, in light of
13 the -- the effect size of Study MD-18, the fact that
14 all the secondary endpoints were negative at week 8,
15 that the OC results on the primary endpoint were
16 negative at week 8, and that Study 94404 was negative
17 on both the primary and secondary endpoints, that
18 data combined together wasn't sufficient in your
19 opinion while you were at the FDA to determine that
20 Celexa was effective for pediatric patients.

21 MR. ROBERTS: Objection.

22 THE WITNESS: That's correct. We didn't
23 approve the supplement.

24 BY MR. WISNER:

1 Q Based on this data, can you definitively
2 say to a degree of scientific certainty that Celexa
3 is superior to placebo in treating pediatric
4 patients?

5 A Well, our -- our ultimate decision on
6 approving Lexapro depended on that positive Celexa
7 study. And so, you know, as you I'm sure know, there
8 were two studies done with Lexapro. The active
9 component of Celexa, of racemic citalopram, is
10 escitalopram. The R-citalopram has no effect on the
11 serotonin transporter, so it's entirely driven by the
12 escitalopram. And that -- that's why we made the
13 judgment that we could -- we could combine the data
14 from those two programs in making a judgment about
15 Lexapro.

16 Q Doctor, we're going to get to Lexapro in
17 a second. I might have said that in my question and
18 that was an error. We will get -- we will get into
19 all this shortly. I don't -- I don't want to get too
20 off -- off track because I really want to get through
21 this --

22 A Okay.

23 Q -- and get you home.

24 But I guess my question is, is based on

1 all the data we know about Celexa specifically, can
2 you as a scientific definitively state that Celexa
3 is superior to placebo in treating pediatric
4 depression?

5 MR. ROBERTS: Objection.

6 THE WITNESS: So, this -- and this is --
7 because the company, of course, never came back with
8 a supplement for Celexa. There was no reason to do
9 that. But the same logic -- and that's why I brought
10 in the Lexapro.

11 BY MR. WISNER:

12 Q Oh, I see.

13 A The same logic applies in the reverse.

14 If you believe that the active ingredient
15 is the escitalopram in terms of an effect on the
16 serotonin transporter, then the Lexapro study can
17 contribute to making a judgment that Celexa is a --
18 because in terms of the active ingredient, they're
19 the same drug. And of course, it's not approved for
20 pediatric depression. Only Lexapro is.

21 But I -- I think one could easily
22 extrapolate back, and as a clinician, say, make that
23 judgment. I personally as a clinician would not use
24 Celexa because it has some other problems that

1 Lexapro doesn't have. But I -- I have -- if I
2 believe that Lexapro works as an antidepressant, I
3 have every reason to believe that Celexa does.

4 Q Okay. Maybe it was an inartfully worded
5 question. I guess I meant based on the data that
6 existed as of 2002, there was no way to definitively
7 determine that Celexa was effective in treating
8 children; is that right?

9 MR. ROBERTS: Objection.

10 THE WITNESS: I -- I agree, and I think
11 that's reflected in our decision not to approve the
12 supplement.

13 BY MR. WISNER:

14 Q And you would agree then that it wasn't
15 until Forest was able to obtain a positive result in
16 adolescents for Lexapro in 2008, prior to that there
17 was not sufficient evidence that either Celexa or
18 Lexapro were effective in pediatric patients.

19 MR. ROBERTS: Objection.

20 THE WITNESS: I -- I think in general, I
21 could say that's true, but I -- I want to qualify
22 it -- again, I don't want to spend too much time
23 qualifying these -- these questions. But as a
24 clinician who only had access to Celexa at that

1 point, I don't think it would have been
2 unreasonable -- not based on the data just from
3 Celexa in pediatric patients, but based on -- on
4 the -- the data in adult patients as well. Because I
5 think extrapolating from adults to children, when we
6 believe that it's essentially the same -- especially
7 in adolescents, that it's essentially the same
8 disease, is not -- is not unreasonable, and for that
9 reason; not because of -- of the single Celexa trial
10 in pediatric patients.

11 BY MR. WISNER:

12 Q Fair enough, Doctor. I guess -- I guess
13 I appreciate your candor about what a doctor's
14 decision to prescribe a drug for use in children, and
15 I don't want to get there.

16 I guess my question to you is more from
17 an academic FDA perspective. Until Study MD-32,
18 which is the positive study in Lexapro, was completed
19 in 2008, 2009, there was no definitive evidence that
20 these drugs were effective in treating children. Is
21 that fair to say?

22 MR. ROBERTS: Objection.

23 THE WITNESS: It -- it's fair to say, and
24 for the umpteenth time, we didn't approve the

1 supplement.

2 MR. WISNER: Yes, exactly. Okay, great.
3 Let's take a short break.

4 THE VIDEOGRAPHER: The time is 4:11 --
5 excuse me, 4:12. This is the end of disc No. 4. We
6 will go off the video record.

7 (Recess.)

8 THE VIDEOGRAPHER: This is the beginning
9 of disc No. 5 in the deposition of Dr. Thomas
10 Laughren. The time is 4:26 p.m. Back on the video
11 record.

12 MR. WISNER: Let's go off the record.

13 THE VIDEOGRAPHER: 4:26, off the record.
14 (Pause in the proceedings.)

15 THE VIDEOGRAPHER: The time is 4:27.
16 Back on the video record.

17 BY MR. WISNER:

18 Q All right, Doctor, we're going to skip
19 for now Exhibit 24. So we will just put a
20 placeholder sheet for 24, unless I end up using it
21 later.

22 (Exhibit No. 25 was marked for
23 identification.)

24 BY MR. WISNER:

1 Q I'm handing you what has been marked as
2 Exhibit 25 to your deposition.

3 This is a document entitled "Summary
4 Report for Protocol No. SCT-MD-15, a double-blind,
5 placebo-controlled evaluation of the safety and
6 efficacy of escitalopram in pediatric depression."

7 Do you see that, Doctor?

8 A I do.

9 Q Do you recognize this document?

10 A I -- I don't offhand recognize it. I
11 mean, I -- I do know which study MD-15 is,
12 escitalopram study.

13 Q And this appears to be the study report
14 for MD-15. Do you see that?

15 A Yes.

16 Q It's dated December 3rd, 2004?

17 A Yes.

18 Q So this would have been after the FDA
19 denied a pediatric indication for Celexa; is that
20 right?

21 A That's correct.

22 Q Okay. If you turn to page 45 in this
23 document.

24 A Okay.

1 Q You see there is a section that says
2 "Efficacy Analysis"?

3 A I do.

4 Q And then below that, you see it specifies
5 within that section the primary efficacy analysis?

6 A Yes.

7 Q All right. And it reads: "The primary
8 efficacy parameter was the change from baseline
9 visit to week 8 in CDRS-R score."

10 Do you see that?

11 A Okay. Yes.

12 Q Okay. So the primary endpoint for MD-15
13 appears to be nearly identical to the primary
14 endpoint for MD-18; is that right?

15 A That's correct.

16 Q And below that you see that there are
17 three-secondary efficacy endpoints.

18 Do you see that?

19 A I do.

20 Q The first one is CGI score at week 8, the
21 second one is change from baseline to week 8 in the
22 CGIS score, and the third one is change from baseline
23 to week 8 in the CGAS score.

24 A Yes.

1 Q All right. And then finally, if you turn
2 the page to page 46, there's actually another section
3 that says "Additional Efficacy Analysis."

4 Do you see that?

5 A Yes.

6 Q And it lists two additional efficacy
7 parameters.

8 Do you see that?

9 A Yes.

10 Q The first one is the CDRS-R response
11 rate. Do you see that?

12 A Right.

13 Q And it defines it appears -- I'm sorry,
14 that's at week 8, right?

15 A Correct.

16 Q And it defines response rate at less than
17 or equal to 28. Do you see that?

18 A Yes.

19 Q So my understanding of that is, if a
20 patient's CDR score was less than or equal to 28,
21 that would be considered a response.

22 A Correct.

23 Q Okay. And then the CGI-I response rate,
24 it says: "CGI-I, less than or equal to 2 at week 8."

1 Do you see that?

2 A I do.

3 Q What is your general understanding of the
4 difference between a secondary efficacy parameter and
5 an additional efficacy parameter?

6 A I -- I would have to look back to the
7 analysis plan to see if they -- if they defined any
8 of these, if these were included in the hypothesis
9 testing. I don't know how offhand.

10 Ordinarily, the only secondary measures
11 that -- that, say, the psychiatry division would
12 focus on would be those that are designated as key
13 secondary endpoints and are included in the
14 hypothesis testing. Any -- any other endpoints would
15 be considered exploratory.

16 Q Okay. Turn to page 100 in this document.
17 Do you see the Table 3.1?

18 A Yes.

19 Q It's very similar to MD-18. Table 3.1
20 lists the change in baseline and the CDRS-R at
21 week 8.

22 Do you see that?

23 A I do.

24 Q And the P-value represented there is

1 0.310. Do you see that?

2 A I do.

3 Q That's negative?

4 A It's not statistically significant,
5 correct.

6 Q Okay. It's not close enough, right?

7 A No.

8 Q Okay. Now, Table 3.2, which is on
9 page 101, do you see that?

10 A Yes.

11 Q And that lists the secondary efficacy
12 endpoint of CGI improvement at week 8.

13 Do you see that?

14 A Yes.

15 Q That has a P-value of 0.169?

16 A Yes.

17 Q Again, that's negative?

18 A Not statistically significant.

19 Q Okay. And generally, that's known as
20 being negative, right?

21 A Yes.

22 Q Okay. And then the next table, 3.3,
23 that's another secondary efficacy endpoint.

24 Do you see that?

1 A Yes.

2 Q Change from baseline in CGI severity at
3 week 8?

4 A Yes.

5 Q And that has a P-value of 0.057. Do you
6 see that?

7 A I do.

8 Q That's close to statistically
9 significant, but it's not there, is it, right?

10 A No.

11 Q Okay. Look at the next table, Table 3.4,
12 it has another secondary endpoint change from
13 baseline in CGAS at week 8.

14 Do you see that?

15 A I do.

16 Q And that has a P-value of 0.065.

17 Do you see that?

18 A I do.

19 Q And, again, that's not statistically
20 significant, is it?

21 A It doesn't meet that threshold, correct.

22 Q Okay. Let's move on to Table 3.5. This
23 lists the results of an additional efficacy
24 parameter.

1 Do you see that?

2 A I do.

3 Q It's the analysis of the CDRS-R response
4 rate at week 8.

5 A Yes.

6 Q A P-value of 0.317. Do you see that?

7 A I do.

8 Q That's also negative?

9 A It's, again, not statistically
10 significant.

11 Q All right. Table 3.6. This is the final
12 additional efficacy parameter. It's the analysis of
13 CGI-R response at week 8.

14 Do you see that?

15 A I do.

16 Q Again, it has a P-value of 0.144.

17 A Correct.

18 Q That was not statistically significant,
19 correct?

20 A Correct.

21 Q Okay. So to be clear then, based on
22 these tables, it appears that the primary efficacy
23 endpoint, the secondary efficacy endpoints, as well
24 as the additional efficacy parameters, they were all

1 negative, correct?

2 A I -- based -- based on what you've shown
3 me here, yes.

4 Q Okay. And in fact, it is your
5 understanding that MD-15 was considered a negative
6 study, right?

7 A Yes.

8 Q These results with all the endpoints
9 being negative at week 8 is consistent with that
10 conclusion.

11 A That's correct.

12 Q Okay. Do you think that MD-15 provides
13 scientifically valid evidentiary support for the use
14 of Celexa in use in children?

15 A No.

16 Q Do you think that it provides
17 scientifically based information -- sorry, do you
18 think it provides similar support -- scientific
19 support for the use of Lexapro in children?

20 A No.

21 MS. KIEHN: Objection.

22 BY MR. WISNER:

23 Q And to be clear, MD-15, that study
24 population included both children and adolescents; is

1 that right?

2 A I believe that's correct.

3 Q Okay. And same thing with Study MD-18,
4 that also had children and adolescents, right?

5 A Yes.

6 Q Now, you understand that Study 94404 was
7 just in adolescents. You know that, right?

8 A Correct.

9 (Exhibit No. 26 was marked for
10 identification.)

11 BY MR. WISNER:

12 Q I'm handing you what has been marked as
13 Exhibit 26.

14 All right. This is a letter from Russell
15 Katz at the FDA to Andrew Friedman at Forest.

16 Do you see that?

17 A I do.

18 Q Have you ever seen this letter before?

19 A (Perusing document.)

20 I don't -- I don't offhand remember it,
21 but -- it doesn't -- it doesn't surprise me that we
22 would have been asked that question and responded to
23 the company.

24 Q Okay. And if you look at the last page

1 of the document, it's electronically signed by
2 Russell Katz on November 16, 2004.

3 Do you see that?

4 A Yes.

5 Q All right. And just for my own
6 edification, what does it mean when there's an
7 electronic signature like that on an FDA document?

8 A Virtually all documents now, all letters
9 that go out are -- are signed electronically. FDA
10 has an electronic document system, and so, you know,
11 rather than signing a paper copy, which is what we
12 did in the old days, you go into that document
13 system, you know, find the -- you get a notification
14 that there is a letter waiting for you or some other
15 document or a review that you're expected to look at,
16 and if you agree with, sign off on and so forth.

17 And so that's just an acknowledgment
18 that -- that the decision to -- to sign the letter
19 was made on that day at that time.

20 Q Okay. Because it's electronically
21 signed, that doesn't make the document any less
22 valid, right?

23 A No. No. No. There isn't -- there isn't
24 going to be any -- any paper copy of -- of this

1 document. It's just -- it resides in that -- in that
2 system.

3 Q Okay, great.

4 All right. If you look at -- do you
5 recall independently if you had any role in preparing
6 this letter?

7 A I -- I don't offhand recall the
8 discussion. I'm sure that I was included in this
9 decision to -- to draft this letter, and I may have
10 written parts of it. I -- you know, I --

11 Q Okay.

12 A A letter like this has to be signed off
13 by the division director.

14 Q Okay. And at this point, though, 2004,
15 Dr. Katz was the division director?

16 A Yes.

17 Q Okay. Now, the letter -- if you look at
18 the third paragraph, you said -- it's the third
19 paragraph on the first page.

20 A On the first --

21 Q Yeah.

22 A On the first page.

23 Q It starts off with "we have reviewed."
24 Do you see that?

1 A Yes.

2 Q Okay. It says: "We have reviewed the
3 referenced material and have the following comments
4 and recommendations. For clarity, we've repeated
5 your questions with our response immediately
6 following the question."

7 Do you see that?

8 A Yes.

9 Q So it appears that this is a response to
10 a series of questions posed by Forest to the FDA; is
11 that right?

12 A That's correct.

13 Q Now, we noted a second ago that this was
14 dated November 16th, 2004, but the final study report
15 for MD-15 was dated December 2004.

16 Do you see that?

17 A Yes.

18 Q So it appears that the final study report
19 for MD-15 was not submitted to the FDA until after it
20 had received this letter from the FDA.

21 A Correct.

22 Q Okay. Now, bullet -- or paragraph
23 number 2, do you see it says, "Would a positive" --
24 do you see that?

1 A Yes.

2 Q All right. So it reads: "Would a
3 positive study with escitalopram using a conventional
4 acute treatment design, Study B, along with the
5 previous positive study of citalopram, Study
6 CIT-MD-18, be adequate to support an indication for
7 acute treatment in pediatric patients aged 12
8 through 17."

9 Do you see that?

10 A Yes.

11 Q So based on what I read here earlier,
12 this is the question that Forest posed to the FDA; is
13 that right?

14 A Yes.

15 Q Okay. And here's the response. It says:
16 "We believe that one additional positive acute
17 treatment study of adolescents in addition to Study
18 CIT-MD-18 would support a claim for the acute
19 treatment of adolescents with MDD. In this case, the
20 study designed to be similar enough to provide a
21 sense of replication. Again, we do not concur with
22 your position that the post hoc analysis of the
23 failed trial is supportive of efficacy from a
24 regulatory perspective."

1 Do you see that, Doctor?

2 A Yes.

3 Q What is your understanding of this idea
4 of sense of replication?

5 A Of sense?

6 Q Yeah, it says here: "In this case, the
7 study is designed to be similar enough to provide a
8 sense of replication."

9 A Oh, a sense of replication.

10 Q What does that mean?

11 A I -- I'm not sure what Dr. Katz means by
12 that in this context. But I think what he is saying
13 is that two studies of similar design in the same
14 population, and, you know, it's not -- it's not
15 included in this language, but obviously he is making
16 the judgment that -- that citalopram and escitalopram
17 from the standpoint of the active ingredient are the
18 same drug. So...

19 Q You mentioned that earlier, and I guess I
20 will just explore that with you now.

21 Is it your belief that Lexapro and Celexa
22 are essentially the same compound?

23 A They're not the same compound.

24 Q Okay.

1 A They're not the same compound. Celexa,
2 racemic citalopram, is a mix of
3 R-citalopram and S-citalopram. They have -- you
4 know, S-citalopram has an effect on the serotonin
5 transporter; R-citalopram does not. And there is a
6 lot of evidence to suggest that it's the S-citalopram
7 that is the active ingredient of racemic citalopram,
8 animal data and other data.

9 So that's the basis for the belief
10 that -- I agree that this is -- this is unusual in a
11 regulatory context to -- you know, to base an
12 approval on -- on two compounds that are not
13 identical drugs. There is no question, you know,
14 that this racemic mixture is not identical. In fact,
15 there is other data to suggest that -- that the
16 racemic mixture, probably because of the
17 R-citalopram, has some risks that the S-citalopram,
18 that that isomer by itself, does not have.

19 So, they're not the same compound except
20 from the standpoint of an effect on the serotonin
21 transporters.

22 Q All right. But you would agree, though,
23 that the S-citalopram compound of Celexa is what
24 drives its serotonin effect.

1 A Yes.

2 MS. KIEHN: Objection.

3 BY MR. WISNER:

4 Q And you believe obviously the same thing
5 with escitalopram itself, right?

6 MS. KIEHN: Objection.

7 THE WITNESS: Yes.

8 BY MR. WISNER:

9 Q Okay. Considering what you just said, do
10 you think it's appropriate that Forest should have
11 been allowed to have exclusivity over S-citalopram,
12 even though it essentially was just the effective
13 part of Celexa?

14 MS. KIEHN: Objection.

15 THE WITNESS: Again, as I -- excuse me.
16 As I -- as I said, there are important differences
17 between S-citalopram and racemic citalopram. Mostly
18 on the safety side. So they're not -- they're not
19 the same compound.

20 BY MR. WISNER:

21 Q Okay. Are you familiar, just by any
22 chance, with the phrase "evergreening"?

23 A No.

24 Q Okay. All right. So my understanding

1 based on the response from the FDA is that if Forest
2 could produce a positive double-blind,
3 placebo-controlled clinical trial with Lexapro in
4 children aged 12 to 17, it would then agree to
5 provide an indication for Lexapro for that age group.

6 A Yes, that's -- that is what it's saying.
7 I mean, of course, it would -- you know, it would
8 have to be reviewed. It's subject to review by FDA.
9 But in principle, yes, that is what this letter says.

10 Q And -- and this agreement that the FDA
11 made was done notwithstanding the fact that
12 Study MD-18 was a study that was not relegated solely
13 to adolescents, right?

14 A That -- that -- that's correct.

15 Q And that -- I'm sorry.

16 A However, as -- and, again, it's -- you
17 know, this was an exploratory post hoc analysis, but
18 I did show at least in my memo that -- that the
19 effect size was -- you know, the effects were
20 probably more driven by the adolescents than by the
21 children in that study.

22 Q Sure. And I -- I'm not saying that you
23 didn't do that, Doctor.

24 I guess my question, though, is

1 Study MD-18 had both younger children and adolescents
2 in there, right?

3 A But it was -- you know, it was considered
4 a positive study for that entire age group.

5 Q Okay.

6 A And so if you make the argument that you
7 have, you know, one drug that's -- that in that study
8 is shown effective in children and adolescents, and
9 you have another drug that's just studied in
10 adolescents, that's enough to approve the -- you
11 know, that drug, if you're willing to extrapolate
12 from -- from the Celexa data to Lexapro. That's the
13 argument.

14 Q I understand the argument. I guess my
15 question actually was really simply Study MD-18 had
16 both younger children and adolescents in it, right?

17 A Yes.

18 Q And Study 94404 was actually a study
19 specifically aimed at looking at adolescent
20 depression, right?

21 A Well, that's true.

22 Q And 94404 was negative, right?

23 A It -- it's true that it was negative.

24 However, it had some other problems in it that --

1 that 18 didn't have.

2 Q Fair enough. I'm just saying Study 94404
3 was specifically limited to adolescents, that's all.
4 Right?

5 A That's true.

6 Q And it was negative.

7 A It was negative.

8 Q Okay. Now, at this point when the FDA
9 has made this promise to give -- or, sorry, I
10 shouldn't say "promise."

11 When the FDA has entered into this
12 agreement that it will give an adolescent indication
13 for Lexapro after they've given a positive study for
14 adolescents with Lexapro, they did not have the final
15 study report for MD-15, did they?

16 MS. KIEHN: Objection.

17 THE WITNESS: It -- I mean, this -- this
18 suggests that we had something on -- on 15.

19 BY MR. WISNER:

20 Q The final study report suggests you
21 didn't have that document, correct?

22 A Right, but -- but obviously we -- and
23 again, I don't have the package in which these --
24 these questions were embedded. But Question 1

1 assumes that there was quite a bit of information on
2 MD-15 included in the -- in the package that was
3 reviewed as the basis for this letter. That's all
4 I'm saying.

5 Q Okay. If MD-18 was negative -- okay,
6 just assume that for a second -- would the FDA have
7 made this agreement?

8 MS. KIEHN: Objection.

9 THE WITNESS: No. I don't -- I don't
10 believe so. That would be my impression that -- that
11 we would not have -- have reached that agreement.

12 BY MR. WISNER:

13 Q All right. Now, you understand that at
14 some point Forest did in fact complete Study MD-32,
15 which studied Lexapro in adolescents, right?

16 A Correct.

17 Q And that study was positive, wasn't it?

18 A Yes.

19 Q And you understand that that study had a
20 particularly large sample size, right?

21 MS. KIEHN: Objection.

22 THE WITNESS: I -- again, I haven't -- I
23 haven't looked at 32 any time recently, so I -- I'm
24 assuming you're going to give me something here.

1 BY MR. WISNER:

2 Q Sure. I'm trying to figure out what to
3 give you.

4 All right. I'm actually going to hand --
5 I'm going to go out of order, but we're going to go
6 back to Exhibit 27, but I'm going to hand you
7 Exhibit 28 because that will help answer the question
8 I just asked you.

9 (Exhibit No. 28 was marked for
10 identification.)

11 BY MR. WISNER:

12 Q I'm handing you what is Exhibit 28 to
13 your deposition. It's actually not marked. Let me
14 see that for a second.

15 Oh, it is. Okay, we're good.

16 This appears to be a memorandum prepared
17 February 17th, 2009. Do you see that?

18 A Yes.

19 Q And this is a memorandum prepared by
20 Dr. -- is it -- Kin?

21 A Yes.

22 Q And he was team leader --

23 A She.

24 Q Sorry. She was a team leader at the

1 Division of Psychiatric Products, right?

2 A Yes.

3 Q So she actually held the position that
4 you once held.

5 A Correct.

6 Q And if you turn to page 3, Section 5.2,
7 there is a "Summary of Study Pertinent to Efficacy
8 Claim."

9 Do you see that?

10 A Yes.

11 Q And you see there is a discussion of
12 Study MD-32?

13 A Correct.

14 Q If you go down to the third paragraph in
15 that thing, it says: "This study was conducted at 40
16 study centers in the United States."

17 Do you see that?

18 A I do.

19 Q "A total of 584 patients were screened
20 for eligibility. 316 patients were randomized."

21 Do you see that?

22 A I do.

23 Q So 316 patients randomized into the
24 study, that is a considerably larger sample size than

1 in MD-18, right?

2 MS. KIEHN: Objection.

3 THE WITNESS: That's correct.

4 BY MR. WISNER:

5 Q And we discussed earlier that when you
6 increase the sample size in a clinical trial, what
7 would otherwise be statistically insignificant
8 differences between the placebo arm and the drug arm
9 can suddenly reach a statistically significant
10 P-value, correct?

11 MS. KIEHN: Objection.

12 THE WITNESS: There's no question that --
13 that the sample size will -- an increase in the
14 sample size can in some settings -- it doesn't
15 always, but it can reduce variance, and therefore,
16 you know, increase the chance of getting a
17 statistically significant P-value.

18 BY MR. WISNER:

19 Q Now, in Study MD-18, they actually did
20 children and adolescents, so there was only
21 approximately 80 adolescents in that study, right?

22 MS. KIEHN: Objection.

23 THE WITNESS: I'd have to go back and
24 look, but I -- but let's assume that it was evenly

1 split. I -- I don't know. I guess it was probably
2 about that.

3 BY MR. WISNER:

4 Q Okay. Well, let's not assume. Let's
5 quickly just look -- look at your memo. That will
6 have it on it.

7 A Do you know which exhibit number my memo
8 is?

9 Q Exhibit 3.

10 A Great.

11 Q And you see on the page where you break
12 down the -- the adolescents and the -- on page 3?

13 A Right. But I don't -- I don't --

14 Q Oh, you don't have the N on there.

15 A I don't have the N in there.

16 Q Okay. All right. Let's go to study --
17 let's go to Exhibit 8, which is the final study
18 report. And turn to page 101. I think that should
19 have it. Sorry, page 100.

20 A Okay.

21 Q So we have -- on Table 3.1, you have the
22 N for -- in the placebo group, you have 47 in
23 adolescents.

24 Do you see that?

1 A Yes. Yes.

2 Q And you have 44 for adolescents in the
3 citalopram group.

4 A Right. Yeah.

5 Q So that's roughly 90?

6 A Yes.

7 Q Okay. So in MD-18, the adolescent
8 population studied was roughly 90 patients, right?

9 A Right.

10 Q And here in Study MD-32, we're -- we've
11 rocketed it up to 316 patients. Do you see that?

12 MS. KIEHN: Objection.

13 THE WITNESS: Yes.

14 BY MR. WISNER:

15 Q Okay. All right. So let's go back to my
16 -- give me one second, Doctor.

17 (Exhibit No. 27 was marked for
18 identification.)

19 BY MR. WISNER:

20 Q All right. I'm going to hand you now
21 what's Exhibit 27. We will come back to Exhibit 28
22 in a minute.

23 MS. KIEHN: I think you handed out 27,
24 no?

1 MR. GRIFFIN: That was 28.

2 MR. WISNER: That was 28. We skipped one
3 for a second.

4 BY MR. WISNER:

5 Q This is Exhibit 27, Doctor.

6 All right. This is a document titled
7 "Clinical Review." Do you see that?

8 A I do.

9 Q And are you familiar with this document?

10 A I -- I mean, I haven't looked at it any
11 time recently, but --

12 Q Okay.

13 A -- I notice that it only has what appears
14 to be a couple of pages from it.

15 Q Sure.

16 So this is excerpts of the clinical
17 review conducted by Roberta Glass at the FDA in
18 response to Forest's adolescent submission for an
19 adolescent indication.

20 A Yes.

21 Q Okay. And it looks like -- there are
22 some dates on there. I just don't know if you can
23 tell me what they mean. It has a letter date of
24 May 22nd, '08.

1 Do you see that?

2 A Yes.

3 Q Do you know what that refers to?

4 A Literally the -- the date on the -- on
5 the cover letter for -- for the supplement.

6 Q Okay. So it's basically when it was
7 submitted?

8 A And the date -- well, the date that the
9 company listed on the cover letter. The stamped date
10 is when it's actually stamped into FDA.

11 Q All right.

12 A And then the goal date is -- it's ten --
13 ten months later. It's the standard, you know, time
14 frame for -- for doing a review of a supplement.

15 Q Okay. So it's fair to say then that they
16 submitted this application in May of 2008?

17 A Yes.

18 Q Okay. All right. If you turn the page,
19 we're on page 22. Do you see that?

20 A Yes.

21 Q Okay. And you see the section titled
22 "Study 18"?

23 A Yes.

24 Q This is referring to -- it appears to be

1 referring to Dr. Glass's review of Study MD-18.

2 A Correct.

3 Q Okay. It reads -- in the second sentence
4 in that first paragraph, it reads: "Dr. Earl Hearst,
5 FDA clinical reviewer, reviewed this positive study
6 in addition to the negative Study 94404,
7 September 12th, 2002."

8 Do you see that?

9 A I do.

10 Q That's referring to Dr. Hearst's clinical
11 review, right?

12 A Correct.

13 Q Okay. And then it goes on to say --
14 well, I will stop right there.

15 It appears that Dr. Glass is, at least in
16 part, relying on Dr. Hearst's review of MD-18.

17 A Yes.

18 Q Okay. Now, it goes on to say: "Later it
19 was determined that Study 18 could" -- could -- I
20 think it should be "could be used," but it said
21 "Study 18 could used as one of the two positive
22 studies required to submit pediatric labeling for
23 escitalopram, an isomer of citalopram, in the
24 treatment of MDD. DPP letter of November 16, '04."

1 Do you see that?

2 A I do.

3 Q So that letter right there is actually
4 the one we just looked at a second ago.

5 A Yes.

6 Q All right. So it appears that Dr. Glass
7 is operating off of the fact that Study MD-18 was
8 positive and that they just had to look at whether or
9 not there was an additional positive study for
10 adolescents with Lexapro; is that right?

11 MS. KIEHN: Objection.

12 THE WITNESS: That's correct.

13 BY MR. WISNER:

14 Q All right. Look at the last paragraph on
15 this page. It reads: "The study is positive for the
16 effi- -- for the primary efficacy variable of change
17 from baseline of the CDRS-R total score P equals
18 0.038."

19 Do you see that?

20 A I do.

21 Q Now, we know that that's referring to the
22 results of the primary efficacy endpoint including
23 those nine patients that were unblinded, correct?

24 MS. KIEHN: Objection.

1 THE WITNESS: That's correct.

2 BY MR. WISNER:

3 Q All right. It goes on to say: "As it
4 can be seen from Table 6.1.3.4, there is a greater
5 improvement for the adolescent group than the
6 children group when comparing the differences to
7 placebo. As Dr. Laughren notes in his memo of
8 September 16th, 2002, quote: It appears that the
9 positive results for this trial are coming largely
10 from the adolescent subgroup."

11 Do you see that?

12 A I do.

13 Q It appears that Dr. Glass is relying on
14 your exploratory analysis of the different effects
15 observed in the pediatric and adolescent subgroup in
16 your memo of September 16th, 2002.

17 A That's correct.

18 Q And indeed, she has pasted the results on
19 the next page. It says "Summary of Primary Efficacy
20 Variable for Study 18 by Age Subgroups," and it
21 says -- literally says: "Extracted from memorandum
22 by Laughren, September 16, 2002."

23 Do you see that?

24 A I do.

1 Q You see that she has copied and pasted
2 that portion of your memorandum into here, correct?

3 MS. KIEHN: Objection.

4 THE WITNESS: She has given
5 acknowledgment as well.

6 BY MR. WISNER:

7 Q Abso- -- oh, sorry, I wasn't suggesting
8 that that was nefarious. She's relied on your prior
9 work here, right?

10 A Yes.

11 Q It does not appear that she did a
12 comprehensive clinical review of MD-18 at this point;
13 is that right?

14 MS. KIEHN: Objection.

15 THE WITNESS: That's likely the case,
16 yes.

17 BY MR. WISNER:

18 Q Now, earlier when we were discussing your
19 memorandum of September 16th, 2002, do you recall
20 that there had been an agreement not to conduct a
21 statistical analysis of the efficacy data?

22 A Yes.

23 Q Do you know if a statistical analysis of
24 the efficacy data was done at this point?

1 A Since one is not in the -- in the file
2 that you've been able to obtain, I'm assuming that it
3 was not done.

4 Q Yeah. Is that typical for a pivotal
5 trial that's going to be used to support indication
6 to have just not been given any statistical review?

7 MS. KIEHN: Objection.

8 THE WITNESS: It's prob- -- it's probably
9 not typical.

10 BY MR. WISNER:

11 Q And you said earlier one of the reasons
12 that you do a statistical review, although it's
13 redundant, is to sort of hash out the various effects
14 you're seeing in the data, right?

15 MS. KIEHN: Objection.

16 THE WITNESS: Generally, a statistical
17 review -- it does a couple of things. I mean it --
18 very often the statistical reviewer will have the
19 original actual dataset electronically and can do
20 some additional exploratory analyses looking at --
21 you know, breaking it down by gender and age and
22 ethnicity and that sort of thing. It can also
23 confirm the analyses that are done by the sponsor.

24 BY MR. WISNER:

1 Q Do you think that probably would have
2 been helpful, particularly since you're using a
3 particular subgroup of an exploratory analyses that
4 you did in your review of the study?

5 MS. KIEHN: Objection.

6 THE WITNESS: In -- in retrospect, I
7 think I -- I would have preferred that.

8 BY MR. WISNER:

9 Q Okay. All right. Let's turn back to
10 Exhibit 28, which is the one I handed you a minute
11 ago.

12 A Okay.

13 Q This is the -- the memorandum by Dr. Kin?

14 A Yes.

15 Q And she was Dr. Glass's supervisor,
16 correct?

17 A That's correct.

18 Q Okay. So this is sort of her memorandum
19 kind of overseeing the clinical reviews that were
20 done by, for example, Dr. Glass.

21 A Correct.

22 Q Okay. The subject of the memorandum is
23 "Recommendation of approval action for Lexapro
24 (escitalopram) for the acute and maintenance

1 treatment of major depressive disorder, MDD, in
2 adolescents."

3 Do you see that?

4 A Yes.

5 Q Okay. So this appears to be a memorandum
6 from Dr. Kin where she is recommending the approval
7 of Lexapro for use in adolescents. Is that right?

8 A That's correct.

9 Q Okay. Turn to page 2.

10 Do you see the section that says
11 "Overview of Studies Pertinent to Efficacy"?

12 A Yes.

13 Q All right. It reads: "To fulfill the
14 requirement of positive results from two
15 placebo-controlled studies to support efficacy of
16 pediatric MDD for escitalopram, the Division has
17 agreed to accept one positive pivotal study in
18 citalopram Study CIT-MD-18," or Study 18, "and one
19 positive study in escitalopram study SCT-MD-32,
20 Study 32."

21 Did I read that correctly?

22 A Yes.

23 Q And that's the agreement we again
24 discussed previously?

1 A That's correct.

2 Q It's the same agreement that was
3 mentioned in Dr. Glass's review, right?

4 A Correct.

5 Q Would it be fair to say that they had
6 marching orders at this point in their review that
7 Study MD-18 was positive, just look at 32 and tell us
8 if that's also positive?

9 MS. KIEHN: Objection.

10 THE WITNESS: I -- I don't -- I don't
11 know that I would call that marching orders.

12 BY MR. WISNER:

13 Q Fair enough.

14 A I think there was -- there was that
15 understanding that, you know, we had already looked
16 at -- at 18 and made a judgment that it was a
17 positive study. I mean, certainly no one instructed
18 them not to look at 18.

19 Q Sure.

20 A I --

21 Q I appreciate that, Doctor, and I didn't
22 mean to suggest they didn't look at it. But I was
23 just saying that they appeared at least to have been
24 relying upon the agreement that the FDA reached with

1 Forest in 2004.

2 A I think that's fair.

3 Q Okay. And if you look at page 4, there's
4 a section that says "Study CIT-MD-18."

5 Do you see that?

6 A Yes.

7 Q And this goes on for about three short
8 paragraphs.

9 Do you see that?

10 A Yes.

11 Q All right. Bear with me, Doctor, one
12 second.

13 I'm actually -- sorry, I'm mixed up
14 because I'm on the wrong page. Look at page 3 of
15 document -- do you see the paragraph below the
16 summary that starts off with "Study 18 is an
17 eight-week" -- do you see that?

18 Third paragraph from the top, "Study 18
19 is an eight-week" --

20 A Oh, correct.

21 Q Do you see that?

22 A Yes.

23 Q All right. It says: "Study 18 is an
24 eight-week double-blind, placebo-controlled,

1 flexible-dose citalopram, 20 to 40 milligrams a day,
2 study in children 7 to 11 years and adolescents 12 to
3 17 years. I would refer to the clinical review by
4 Dr. Hearst dated December 12, 2002, and the
5 memorandum by Dr. Thomas Laughren dated December 16,
6 2002, regarding their reviews of materials submitted
7 under supplemental NDA for citalopram on April 18,
8 2002. I will briefly summarize their interpretation
9 of results from Study 18 in Section 5123 below."

10 Do you see that?

11 A I do.

12 Q So it appears that Dr. Kin is relying
13 heavily, if not exclusively, on Dr. Hearst and
14 yourself's analysis of Study MD-18.

15 MS. KIEHN: Objection.

16 THE WITNESS: That's correct. Now, of
17 course, this is the team leader review. It's not the
18 primary review.

19 BY MR. WISNER:

20 Q Sure.

21 A I don't have Dr. Hearst's complete
22 review, so I don't -- I don't know exactly what --
23 what she did with regard to Study 18.

24 Q Okay. I represent to you that what I've

1 shown you is pretty much it.

2 A Okay.

3 Q And so it appears that they largely
4 relied upon yours and Dr. Hearst's review.

5 MS. KIEHN: Objection.

6 THE WITNESS: It -- it does appear that
7 way.

8 BY MR. WISNER:

9 Q Okay. If you turn to page 5 now, sorry,
10 do you see the paragraph that says "This study was
11 positive" at the top -- third from the top in
12 paragraph 5 -- on page 5?

13 A Yes.

14 Q Okay. It says -- it says: "The study
15 was positive for the primary efficacy variable of
16 change from baseline of the CDRS-R score.
17 Citalopram, minus 21.7 plus 1.6; placebo, minus 16.5
18 plus 1.6; P equals 0.038."

19 Do you see that?

20 A I do.

21 Q Again, he is representing the results of
22 the primary efficacy endpoint regarding -- I'm sorry.
23 Sorry. Strike that. It's getting late.

24 He's referencing the efficacy endpoint

1 and the primary endpoint which included data from
2 those nine unblinded patients, right?

3 A She is, correct.

4 Q Sorry. She is. I keep saying that,
5 forgive me.

6 It goes on to say: "Please see Table 2
7 in Section 5.1.3 regarding summary of primary
8 efficacy results by age group for CID -- CIT-MD-18
9 LOCF data extracted from Dr. Laughren's memo dated
10 September 16, 2002."

11 Do you see that?

12 A I do.

13 Q So, once again, there he -- she is
14 referencing -- in fact, referencing the reader to
15 look at a table that was extracted from your memo; is
16 that right?

17 A That's correct.

18 Q All right. And then if you look at
19 Table 2, it's on the next page, page 6.

20 It says: "Summary of Primary Efficacy
21 Results by Age Group for Study CIT-MD-18 LOCF."

22 Do you see that?

23 A I do.

24 Q It says again, "Data extracted from

1 Dr. Laughren's memo, September 16, 2002."

2 Do you see that?

3 A I do.

4 Q Okay, great. So in that table there,
5 although it doesn't look identical to your table, it
6 has the same information, right?

7 A Yes.

8 Q Okay. So, again, it looks like not only
9 to Dr. Glass but Dr. Kin also inserted the table from
10 your exploratory analysis on MD-18 in this analysis.

11 A That's correct.

12 Q When you prepared your memo for CD -- for
13 MD-18, and you did this exploratory analysis dividing
14 the adolescents from the children, did you anticipate
15 that that being -- that was going to be used to
16 support an indication for a different drug in
17 adolescents?

18 MS. KIEHN: Objection.

19 THE WITNESS: I -- I doubt that I was
20 thinking ahead that far.

21 BY MR. WISNER:

22 Q Fair enough.

23 In retrospect, it seems that that's
24 exactly what happened.

1 A That's true. But -- but let me just --
2 just point out that we -- we made -- we reached a
3 conclusion based on Study 18 that it was a positive
4 study for both adolescents and children. And so
5 it's -- it's that part of it, it's the adolescent
6 part of that that is being incorporated into this
7 judgment that these two studies, Study 18 for Celexa
8 and Study 32 for Lexapro, were sufficient as a source
9 of evidence for the -- the effectiveness of Lexapro
10 in -- in adolescents.

11 (Exhibit No. 29 was marked for
12 identification.)

13 BY MR. WISNER:

14 Q I'm handing you what has been marked as
15 Exhibit 29 to your deposition.

16 Doctor, this is a letter actually from
17 you related to the supplemental application for
18 Lexapro for use in adolescents, correct?

19 A Yes.

20 Q And, unfortunately, I don't have the page
21 that says the date of this letter, but do you recall
22 that this was in early 2009?

23 A I -- I can't remember back to 2009 and --
24 but that sounds about right.

1 Q And so since you were the division
2 director, at the end of the day, whether or not
3 Lexapro would be approved for adolescents was your
4 decision.

5 A I was the -- the final signatory
6 authority on that.

7 Q So, to be clear, it's sort of an
8 interesting turn of events, but it looks like your
9 review of an exploratory variable for MD-18 for
10 adolescents was then relied upon, separate clinical
11 reviewers as well as another team leader, for an
12 application that you later on approved; is that
13 right?

14 MS. KIEHN: Objection.

15 THE WITNESS: Although that is true, let
16 me -- let me again just qualify this by pointing out
17 that we made a judgment back when we reviewed the
18 Celexa supplement that Study 18 was a source of
19 evidence for both adolescents and children. And I
20 did this exploratory analysis simply to point out
21 that, if anything, more of the effect appeared to be
22 coming from the adolescents than it did from the
23 children. But -- but overall, it was a source of
24 evidence for adolescents.

1 BY MR. WISNER:

2 Q Sure.

3 A Apart from my exploratory analysis.

4 So...

5 Q Okay. Now, you understand that Lexapro
6 was then approved in -- was approved for adolescent
7 use, correct?

8 A Correct.

9 Q Are you aware that prior to that -- and
10 if you're not aware, it's fine -- but are you aware
11 prior to that, Forest was promoting the use of
12 Lexapro for use in adolescents?

13 MS. KIEHN: Objection. That's false.

14 THE WITNESS: I don't -- I don't have
15 any -- any specific knowledge of that. I mean, I --
16 again, this -- this fact may have come up in my work
17 with Forest and I just don't remember it, but I -- I
18 in general did not consult with them on issues of
19 promotions. It was never my thing at FDA. It wasn't
20 within my authority to make judgments about promotion
21 when I was at FDA.

22 BY MR. WISNER:

23 Q Fair enough, Doctor. I appreciate that
24 answer. Let me ask you a slightly different

1 question.

2 If Forest was promoting the use of
3 Lexapro for use in adolescents prior to this
4 approval, based on your understanding, that was
5 against the law, correct?

6 MS. KIEHN: Objection. Calls for a legal
7 conclusion.

8 THE WITNESS: Again, it's not -- not my
9 area of expertise, but -- but my impression is
10 that -- that you can't promote for an indication
11 that's -- that's not approved. So...

12 BY MR. WISNER:

13 Q Now, I've shown you a lot of documents
14 today that suggest that some of the patients were
15 unblinded in Study MD-18, right?

16 MS. KIEHN: Objection.

17 THE WITNESS: That's -- that's certainly
18 a possibility.

19 BY MR. WISNER:

20 Q And I've also shown you some documents
21 which suggest that Forest didn't properly disclose
22 that fact to the FDA in its submissions, correct?

23 MS. KIEHN: Objection.

24 THE WITNESS: It -- it certainly would

1 have been my preference that -- that Forest be more
2 transparent with FDA about the issue of unblinding.
3 I don't believe in the end that would have made any
4 difference in our judgment, as I've explained, but --
5 but I do -- I do feel that drug companies should be
6 fully transparent with FDA in what they provide to
7 them about the -- you know, the conduct of a study.

8 BY MR. WISNER:

9 Q Now, considering that they weren't
10 transparent about that issue, do you think -- and
11 also in consideration of the fact that Study MD-18
12 never had a statistical analysis of the efficacy
13 data, do you think that it would be appropriate for
14 the FDA to take another look at this data just to
15 make sure that in fact Study 18 was -- was positive
16 as Forest has represented?

17 MS. KIEHN: Objection.

18 THE WITNESS: It -- it isn't my judgment
19 at this point.

20 BY MR. WISNER:

21 Q Sure.

22 A So, I mean I -- that -- that's for FDA to
23 decide at this point. I mean, I -- I feel fairly
24 confident about our decision to approve Lexapro. I

1 was obviously involved in that. I -- I feel that was
2 probably the -- the right decision. Whether or not
3 FDA -- and I also told you that, in retrospect, I
4 would have had a statistical review done on -- on 18.

5 But my overall view is that it probably
6 would not have made a difference. We probably still
7 would have -- would have reached that same judgment.
8 And it's -- it's up to FDA to decide whether or not,
9 you know, based on this -- on this, you know, new
10 information, which I think is probably new
11 information from FDA because I wasn't aware of it at
12 the time. But it's not my call.

13 Q Okay, great.

14 MR. WISNER: Let's take a break.

15 THE VIDEOGRAPHER: The time is 5:14. We
16 will go off the video record.

17 (Recess.)

18 THE VIDEOGRAPHER: The time is 5:23.
19 Back on the video record.

20 BY MR. WISNER:

21 Q I want to talk briefly again about
22 Study MD-18. And, you know, we know that all the
23 secondary prespecified endpoints were negative,
24 right?

1 A That's my recollection, yes.

2 Q And we know that the OC analysis on the
3 primary endpoint was negative, right?

4 A That's correct.

5 Q We know that the treatment by age group
6 interaction term was also negative, right?

7 A Yes.

8 Q And we know that when these patients that
9 were unblinded are excluded from the efficacy
10 analysis, the P-value on the only positive endpoint
11 peaks just above 0.05, right?

12 MS. KIEHN: Objection.

13 THE WITNESS: That's correct.

14 BY MR. WISNER:

15 Q You'd agree with me that in light of all
16 those secondary and additional analysis of the data
17 that -- and considering the fact that these nine
18 unblended -- unblinded patients had an effect on the
19 P-value as such, would you agree with me that
20 Study MD-18 was not a clear and convincing positive
21 study?

22 MS. KIEHN: Objection.

23 THE WITNESS: I -- I don't agree with
24 that. I -- I do consider Study 18 a source of

1 evidence for the efficacy of, you know, of Celexa.
2 You know, the -- the effect size is not huge. You
3 know, it's -- it's a low effect size by -- by usual
4 standards.

5 I'm not that concerned about the change
6 in the P-value in the sensitivity analysis, an
7 analysis which reduces the power of the study and
8 still comes very close to being statistically
9 significant, and in my view is not the primary
10 P-value to focus on for the study.

11 So I don't -- I don't think that -- I
12 don't think that the argument that the potential
13 unblinding or actual unblinding, if that's what
14 actually happened -- I don't think we'll ever know
15 what actually happened there -- I don't -- I don't
16 think that undercuts the overall finding for the
17 study. That's just -- that's my view.

18 BY MR. WISNER:

19 Q I mean if you were to make that
20 determination, you'd have to ultimately conclude that
21 you were wrong, right?

22 MS. KIEHN: Objection.

23 THE WITNESS: I -- I'm not -- I'm not
24 opposed to changing my mind. I have -- there have

1 been many occasions when I changed my mind when --
2 when I was at FDA. There was an NDA that we -- we
3 turned it down, and this is for iloperidone. You
4 know, the company challenged it and came back in with
5 some additional analyses, and -- and they were able
6 to persuade me that -- that I was wrong, and -- and I
7 recommended approval, and Bob Temple agreed with me,
8 and we ultimately approved it.

9 So there have been situations where I --
10 I agreed with an argument that I was wrong and
11 reversed myself. That certainly isn't the only
12 circumstance. I -- I just don't see this as one of
13 those circumstances.

14 BY MR. WISNER:

15 Q If MD-18 was in fact negative, would you
16 ever have approved Lexapro for use in adolescents?

17 MS. KIEHN: Objection.

18 THE WITNESS: I mean, if -- if -- if you
19 couldn't rely on 18 as a source of evidence, then you
20 would've only had one source of evidence for Lexapro.
21 So the answer is this is speculation, but I -- I
22 would not have recommended approving it.

23 BY MR. WISNER:

24 Q You're the one who ultimately did approve

1 it, right?

2 A Because I -- I considered Study 18 a
3 reasonable source of evidence.

4 Q No, I know. And I'm just saying it's not
5 speculation because you're actually the one who
6 ultimately signed off finally on Lexapro's approval
7 for adolescents, right?

8 A Yes.

9 MS. KIEHN: Objection.

10 THE WITNESS: Yes.

11 BY MR. WISNER:

12 Q And you're saying you wouldn't have
13 approved it if there was only one study, positive
14 Study 32, right?

15 MS. KIEHN: Objection.

16 THE WITNESS: That's correct.

17 BY MR. WISNER:

18 Q Do you agree, though, Doctor, that a
19 reasonable regulatory person at the FDA could come to
20 a different conclusion about the positive results of
21 MD-18?

22 MS. KIEHN: Objection.

23 THE WITNESS: It -- this is always a
24 matter of judgment. So the answer would be, yes,

- 1 different people looking at the same dataset can
- 2 reach a different conclusion.

3 BY MR. WISNER:

4 Q Are you aware that there has been a
5 peer-reviewed publication last year discussing the
6 results of MD-18?

7 MS. KIEHN: Objection.

8 THE WITNESS: I -- I have -- I have not
9 been following the literature in that particular
10 area, so...

11 BY MR. WISNER:

12 Q So you have not seen any peer-reviewed
13 journal article coming to the conclusion, having
14 looked at the data without the unblinded patients,
15 that it was negative; is that correct?

16 MS. KIEHN: Objection.

17 THE WITNESS: I -- I don't recall seeing
18 that. If there is such a paper, I haven't seen it.

19 BY MR. WISNER:

20 Q Okay, great. But we do agree, and I
21 think this has been established and I just want to
22 make sure we're on the same page, that until
23 Study MD-32 was completed and reviewed by the FDA,
24 prior to that, with Study 94404 being negative for

1 primary and secondary endpoints, Study MD-15 being
2 negative for primary and secondary endpoints, and
3 Study MD-18 being negative on the secondary endpoints
4 as well as the OC analysis of the primary endpoint,
5 at that point there was not sufficient evidence to
6 conclude that either Celexa or Lexapro were
7 definitely effective in pediatric populations.

8 MS. KIEHN: Objection.

9 THE WITNESS: And that's reflected in the
10 fact that we did not approve the -- the supplement
11 for Celexa, and we didn't even consider the
12 supplement for Lexapro until they had a positive
13 study.

14 BY MR. WISNER:

15 Q So the answer is "yes"?

16 MS. KIEHN: Objection.

17 THE WITNESS: The answer is yes.

18 MR. WISNER: Okay. I pass the witness.

19 EXAMINATION BY COUNSEL FOR DEFENDANTS

20 BY MS. KIEHN:

21 Q Good afternoon, Dr. Laughren. I have a
22 few questions.

23 You referred a few minutes ago to the
24 information that Mr. Wisner had presented to you as

1 new information.

2 Do you recall that?

3 A Yes.

4 Q What specifically were you referring to
5 when you said "new information"?

6 A I -- I wasn't aware, you know, based on
7 the -- on the pediatric supplement for Celexa that --
8 that patients were actually given tablets that had
9 the brand name Celexa on them. That's my
10 understanding of -- of what actually happened.

11 Rather than my -- my understanding, and I
12 believe the understanding of our review team, was
13 that there might have been a different color for the
14 tablets that -- for patients who got active drug and
15 for those who got placebo. And that was -- that
16 would have been of less concern to us in terms of
17 unblinding.

18 And so -- so the -- you know, the
19 information that patients were actually, as I
20 understand it, provided tablets that had the brand
21 name Celexa on them is -- is further evidence of
22 potential unblinding that comes much closer to being
23 actual unblinding.

24 And so I think it would have been better

1 for Forest to -- to provide that information in the
2 supplement. Again, I -- I don't think that would
3 have made a difference because, as I've said,
4 blinding is something that you -- that you strive for
5 but you often don't achieve, and is not as critical
6 an element in the validity of a study as
7 randomization.

8 And often I think in trials, we -- we
9 don't achieve it, whether or not there is this kind
10 of problem. And in fact, as I pointed out, there are
11 trials in psychiatry that were explicitly open label,
12 and FDA relied on as a source of evidence for a new
13 claim. So...

14 Q Do you know for a fact that the tablets
15 had the name Celexa imprinted on them?

16 A Unfortunately, I don't think we were ever
17 provided with enough information to even make that
18 judgment. I mean, that -- that's the problem. The
19 only -- the only thing that, based on my memo and the
20 supplement, that we were informed of is that there
21 was a different color of the tablets for patients who
22 got active drug than those who got placebo.

23 Q But your testimony that the new
24 information you received today was that the tablets

1 bore the brand name Celexa, that was based
2 exclusively on things that Mr. Wisner showed you or
3 implied to you, correct?

4 A That's correct. That is absolutely
5 correct.

6 Q Okay. I'm going to hand you --

7 MS. KIEHN: What's the next -- what's the
8 next exhibit number?

9 MR. WISNER: 30.

10 (Exhibit No. 30 was marked for
11 identification.)

12 BY MS. KIEHN:

13 Q I've handed you what's been marked as
14 Exhibit 30. I will represent to you that this is an
15 exhibit that was introduced by Mr. Wisner at another
16 deposition in this matter.

17 Have you ever seen a branded
18 antidepressant tablet?

19 A I can't say that I have.

20 Q Do you know whether branded
21 antidepressant tablets typically have the brand name
22 imprinted on them?

23 A Typically not, no.

24 Q Does this image of Celexa tablet contain

1 the name Celexa anywhere?

2 A It -- it doesn't. However, it does -- it
3 does include the strength of -- of the tablet. And
4 that's -- that's different than simply a tablet that
5 has a slightly different color than the inactive
6 tablet.

7 Q And why is it different?

8 A It -- it refers -- it refers to a
9 strength, and -- again, I don't know, I don't know if
10 this actually unblinded patients.

11 All I'm saying is that, from my
12 standpoint, it would have been preferable if this
13 information had been included in the supplement.

14 Q And what information are you referring
15 to?

16 A The -- the actual nature of the error.

17 Q So what was imprinted on the tablets?

18 A What was imprinted on the tablet.

19 Q Okay. I'm going to hand you what is
20 being marked as Exhibit 31.

21 (Exhibit No. 31 was marked for
22 identification.)

23 BY MS. KIEHN:

24 Q Earlier today Mr. Wisner showed you some

1 deposition testimony of Dr. William Heydorn. Do you
2 recall that?

3 A Yes.

4 Q This is an additional excerpt.
5 I think I gave you my marked copy.

6 A Oh.

7 Q Does it have a mark on it?

8 A Yes.

9 Q Well, it's just directing you to the --
10 to the relevant section.

11 MR. ROBERTS: Here is another copy.

12 MS. KIEHN: Wait, we got to put this
13 thing on it.

14 MR. WISNER: Why don't you just do a new
15 one.

16 MS. KIEHN: All right.

17 (Exhibit No. 31 was remarked for
18 identification.)

19 THE WITNESS: Just put this in the --
20 over here, okay.

21 BY MS. KIEHN:

22 Q If you can turn to page 314.

23 A Okay.

24 Q At the top, I'm going to read some

1 testimony into the record.

2 "Q. Dr. Heydorn, you've answered a
3 number of questions regarding some
4 patients who participated in MD-18
5 who were potentially unblinded
6 today. Correct?

7 "A. Yes.

8 "Q. You don't actually know
9 whether those patients were in fact
10 unblinded, do you?

11 "A. No, I do not.

12 "Q. To the extent in your
13 testimony you referred to, quote,
14 unblinded patients, you don't
15 actually know that those patients
16 were unblinded, correct?

17 "A. No, I do not.

18 "Q. To the extent you adopted
19 Mr. Baum's use of the term
20 'unblinded patients,' you also don't
21 know that those patients were in
22 fact unblinded. Correct?

23 "A. No, I do not."

24 Do you see that?

1 A I do.

2 Q I'm going to hand you what we are marking
3 as Exhibit 32.

4 (Exhibit No. 32 was marked for
5 identification.)

6 BY MS. KIEHN:

7 Q Exhibit 32 are excerpts from the
8 deposition of Charles Flicker.

9 Do you recall Mr. Wisner showing you
10 some excerpts from Mr. Flicker's deposition earlier
11 today?

12 A I do.

13 Q Please turn to page 203. Starting at
14 line 12, I'm going to read some testimony in:

15 "Q. You don't think that the blind
16 was unmistakably violated for these
17 nine patients?

18 "A. No.

19 "MR. ROBERTS: Objection.

20 "BY MR. BAUM: You don't think that
21 the blind was compromised for these
22 nine patients?

23 "MR. ROBERTS: Objection. He
24 testified he doesn't recall the

1 dispensing error.

2 "THE WITNESS: I think it was
3 potentially compromised. It seems
4 to me perfectly possible that none
5 of those nine patients had any hint
6 whatsoever of what their treatment
7 group was.

8 "Q. But the investigators knew,
9 right?

10 "MR. ROBERTS: Objection.
11 Mischaracterizes testimony, no
12 foundation.

13 "THE WITNESS: I don't know."
14 Do you see that?

15 A I do.

16 Q So these two Forest witnesses have
17 testified under oath they do not in fact know whether
18 the patients were unblinded, correct?

19 A Correct.

20 Q And you testified earlier that on page 63
21 of the study report, all nine patients -- strike
22 that.

23 You testified earlier that on page 63 of
24 the study report, the report suggested all nine

1 patients received pink tablets.

2 Do you remember that?

3 A I -- I stated that?

4 Q Yeah, we can go -- do you want to go back
5 and look?

6 A Yes.

7 Q Okay. Exhibit 8.

8 A I don't -- I tried to keep track of these
9 things.

10 MR. WISNER: It's one of the thicker
11 ones. If that helps. I don't know.

12 THE WITNESS: It must have gotten
13 misplaced somehow.

14 MR. WISNER: It's right there
15 (indicating).

16 THE WITNESS: Oh. Okay. Sorry.

17 Okay, I've got it.

18 BY MS. KIEHN:

19 Q Okay. Page 63. So this is the MD-18
20 study report.

21 A Okay.

22 Q So Mr. Wisner had directed you to the
23 language that stated: "Nine patients -- I won't read
24 the numbers in -- "were mistakenly dispensed one week

1 of medication with potentially unblinding
2 information," open paren, "tablets had an incorrect
3 color coating," close paren.

4 Do you see that?

5 A Yes.

6 Q And under questioning, you had testified
7 that that language suggested to you that all nine
8 patients received pink tablets; is that correct?

9 A I -- I may have. I guess I -- I
10 misunderstood from this statement that -- I had
11 thought from what I was told that the -- the
12 incorrect color coating applied to the active
13 medication and not to the -- and not to the placebo
14 medication.

15 Is that incorrect.

16 MS. KIEHN: Do you mind my answering
17 or -- I think the documents you've been shown --

18 MR. WISNER: Honestly, I don't think you
19 can answer that because I don't know if there is an
20 answer to the question, so --

21 MS. KIEHN: I think there is an answer.

22 MR. WISNER: But I don't think it's
23 correct.

24 BY MS. KIEHN:

1 Q Do you recall that Dr. Tiseo's facts
2 described the tablets as the active drug had been
3 mistakenly packaged?

4 A Yes.

5 Q Do you recall that?

6 A Yes.

7 Q Okay.

8 A But this says that -- that all tab- --
9 the tablets had an incorrect color coating. It sort
10 of implies that -- that all nine patients had tablets
11 with an incorrect color coating.

12 Q It's possible because that's correct --
13 incorrect; is that right?

14 A I mean, if -- if some of the patients
15 had -- had the correctly packaged placebo, then it --
16 then it wouldn't have been all nine patients. But
17 that's --

18 Q Okay. I'm going to hand you what we are
19 marking as Exhibit 33.

20 (Exhibit No. 33 was marked for
21 identification.)

22 BY MS. KIEHN:

23 Q So Exhibit 33 is an e-mail from Andrew
24 Friedman to Gregory Dubitsky.

1 Do you see that?

2 A Yes.

3 Q And you are in the cc line; is that
4 correct? You see it?

5 A Yes. Yes.

6 Q And the date is July 26, 2004, correct?

7 A Correct.

8 Q And Andrew Friedman writes: "Dear
9 Dr. Dubitsky: Attached please find the requested
10 information. I will submit the official response
11 along with a cover letter tomorrow; however, I wanted
12 to get it to you as soon as possible. If you have
13 any further questions or comments, please do not
14 hesitate to contact me."

15 If you look down below, the e-mail he was
16 responding to was from Dr. Dubitsky sent on July 17,
17 2004.

18 Do you see that.

19 A Yes.

20 Q And you are cc'd again, correct?

21 A Yes, I am.

22 Q And Dr. Dubitsky writes: "Hello,
23 Dr. Friedman. I am the FDA medical officer reviewing
24 your May 4, 2004 submission which included the

1 protocols and study reports for studies CIT-MD-18 and
2 94404. There are a few additional pieces of
3 information I need to request from you."

4 Do you see that?

5 A I do.

6 Q If you turn to number 3 on the next page,
7 Dr. Dubitsky writes: "The study report for CIT-MD-18
8 discusses nine patients who possibly became unblinded
9 during treatment. Please provide a breakdown of
10 these patients by treatment group as well as the
11 breakdown of protocol violators in this trial by
12 group and type of violation as for 94404."

13 Do you see that?

14 A I do.

15 Q Do you recall this e-mail chain?

16 A Unfortunately, no.

17 Q If you can turn to page 9, please.

18 A Okay.

19 Q So at the top under FDA Request No. 3,
20 this repeats what Dr. Dubitsky had included in his
21 e-mail.

22 And then below, Forest's Response No. 3
23 indicates: "The breakdown of patients who possibly
24 became unblinded during treatment is provided in

1 panel 7."

2 And if you look at that table there, do
3 you see that there were five patients in the active
4 citalopram group and four in the placebo group?

5 A Yes.

6 Q And do you see a note there for Patient
7 505, that that patient did not receive study
8 medication?

9 A Correct.

10 Q So would this suggest that in fact only
11 four patients received pink tablets.

12 A And so the -- the placebo patients in
13 this -- in this panel received the -- the placebo
14 preparation which was given to all patients in the
15 trial with no markings on it whatsoever?

16 Q Correct. As far as we know.

17 MR. WISNER: Objection. Move to strike
18 that as testimony by the attorney. It's not
19 established, Doctor.

20 You can ask your question.

21 THE WITNESS: I mean this is why I said
22 earlier that -- that I don't -- I don't think we know
23 here whether or not there was -- and to what extent
24 there was unblinding.

1 All I -- all I was saying is that my --
2 my preference as -- as an FDA reviewer would have
3 been that -- that some more of this information would
4 have been provided in the supplement, rather than
5 just saying that -- implying that there was a -- that
6 the placebo and the active tablets could be
7 distinguished on the basis of color. It appears that
8 it was more than just color. That it was the actual
9 commercial formulation of -- of Celexa that was
10 provided to patients.

11 I mean, it's possible -- it's possible --
12 well, I don't -- I'd have to look at the exclusion
13 criteria for the study. It's unlikely actually that
14 the patients, that these patients would have -- would
15 have had prior exposure to -- to Celexa.

16 I'm just saying that -- that in general,
17 I think FDA would provide to have -- to have all the
18 information that a sponsor has about the conduct of a
19 trial in making its judgment. I don't think it would
20 have made any difference in this case, but -- that's
21 all I'm saying.

22 BY MS. KIEHN:

23 Q Okay. And you said you don't think it
24 would have made any difference in this case, correct?

1 A Well, again, that -- that has to do
2 with -- with the -- with the fact that we did the
3 sensitivity analysis, and with the reduced power, the
4 P-value moved up, but it -- it didn't -- I don't
5 think it had a material effect on the overall
6 judgment about that being a positive study. That's
7 just my view.

8 Q One moment.

9 I'm going to hand you what is -- we are
10 marking as Exhibit 34.

11 (Exhibit No. 34 was marked for
12 identification.)

13 BY MS. KIEHN:

14 Q Now, earlier Mr. Wisner showed you
15 Exhibit 15, which was an e-mail with an attachment.
16 This is the same e-mail but with the e-mails that
17 came after it in the chain.

18 So if you look at page 2, the e-mail from
19 Joan Barton sent December 6, 2000, that was the
20 e-mail that Mr. Wisner showed you earlier.

21 Does that look familiar?

22 A Yes.

23 Q So I would like you to take a look at the
24 e-mail just above, which if you look at the bottom of

1 page 1 is an e-mail from Jane Wu to John Barton, cc
2 Joan Howard, James Jin, Paul Tiseo, Charles Flicker,
3 Carlos Cobles and Edward Lakatos dated December 8,
4 2000.

5 Do you see that?

6 A I do.

7 Q And Mr. Wisner represented to you earlier
8 that Jane Wu was one of the senior statisticians on
9 the MD-18 study.

10 Do you recall that?

11 A I vaguely recall that.

12 Q So if you flip the page, Jane writes:
13 "Joan" -- and let me just step back a minute and
14 refresh you that Joan's original e-mail was asking
15 whether the issue with the packaging would alter the
16 total number of child or adolescent patients to be
17 randomized.

18 So Jane responds: "I don't think this
19 should alter the total number of patients to be
20 randomized in either group, but if we could enroll a
21 few more patients without jeopardizing the timeline,
22 it is not going to hurt us. By the intent to treat
23 principle, we have to include them in the analyses
24 anyway."

1 Do you see that?

2 A I do.

3 Q So the senior statistician on MD-18 is
4 indicating here that the primary efficacy analysis
5 will be conducted consistent with the study protocol,
6 correct?

7 MR. WISNER: Objection. Misstates the
8 document.

9 THE WITNESS: Well, that -- that's why
10 I -- I asked earlier if -- if there was any actual
11 change in the analysis plan, and it doesn't sound
12 like there was. Because the analysis that was in the
13 study report included the original -- included all
14 patients. That was my impression.

15 BY MS. KIEHN:

16 Q And Jane sent this e-mail before Forest
17 had the results of MD-18, correct? December 2000?

18 A Yes.

19 Q Dr. Laughren, when you were at the FDA,
20 were you involved in the review and approval of
21 package inserts?

22 A Yes.

23 Q What's the purpose of an FDA review of a
24 package insert?

1 A To make sure that the information is --
2 is, number one, accurate and complete enough to
3 inform prescribers about the appropriate use of a --
4 of a product.

5 Q Is one purpose also to make a
6 determination that the label is not false or
7 misleading in any particular --

8 A Well, that is the under- -- I'm sorry,
9 that is the underlying principle behind our review of
10 labeling, to make sure that it's not false and
11 misleading, but as part of that, we look at things
12 like whether or not it's complete enough, whether or
13 not it -- it's accurate, it provides accurate
14 information, and, you know, allows prescribers to
15 appropriately use a product. But false and
16 misleading is the underlying principle coming from
17 the law.

18 Q And we talked about earlier Lexapro was
19 FDA approved for adolescent depression in March 2009,
20 correct?

21 A That sounds right.

22 Q And you were involved in the decision to
23 approve Lexapro for adolescent depression, correct?

24 A That's correct.

1 Q Were you also involved in the review and
2 approval of the Lexapro package insert?

3 A Yes.

4 Q All right. I'm going to hand you what we
5 are marking as defendant's -- or just Exhibit 35.

6 (Exhibit No. 35 was marked for
7 identification.)

8 BY MS. KIEHN:

9 Q So I'm handing you the Lexapro package
10 insert, which I will represent to you was printed off
11 of the FDA's website and has a date of 2012.

12 Do you recognize this?

13 A It -- it looks like the Lexapro package
14 insert.

15 Q If you can please turn to --

16 MR. WISNER: Hey, Kristin.

17 MS. KIEHN: Yes, sir.

18 MR. WISNER: This has a bunch of missing
19 dates on it and stuff. Is this a draft package
20 insert?

21 MS. KIEHN: This is printed off the FDA
22 website, correct?

23 MR. ROBERTS: Yeah.

24 MR. WISNER: You understand that the --

1 the final package insert is actually created by the
2 sponsor, not FDA.

3 MS. KIEHN: But do you understand that
4 the approved package inserts are all on the FDA
5 website?

6 MR. WISNER: I understand, but this isn't
7 the actual package insert. This is the FDA's
8 approval of the package insert.

9 MS. KIEHN: Are you suggesting that the
10 actual one differs from this?

11 MR. WISNER: I hope it's not different.
12 You guys will be in trouble if it is. But I just
13 want to point out that this isn't the actual package
14 insert. I'm not saying that the substance is in any
15 way different. There are dates here, for example,
16 that need to be filled in.

17 If you look at the back, it has --

18 THE WITNESS: Yeah.

19 MR. WISNER: -- a copyright of 20XX --

20 THE WITNESS: Right.

21 MR. WISNER: -- Forest Laboratories. The
22 final page. And on the front it has recent major
23 changes and it has month/month, year/year/year/year.
24 I don't think substantively it makes a difference,

1 but to keep the record clear.

2 MS. KIEHN: Oh, you only have one --
3 well, I happen to have a copy of the package insert
4 dated 2009 printed off of the FDA website. However,
5 I only have one copy.

6 MR. WISNER: Okay.

7 MS. KIEHN: So we will mark that as --

8 MR. WISNER: 36.

9 MS. KIEHN: -- Exhibit 36 in response to
10 Mr. Wisner's objection. Let me locate the
11 relevant --

12 MR. WISNER: Don't -- don't write on it.

13 MS. KIEHN: Can I come over?

14 MR. WISNER: Sorry, can I just look at it
15 two seconds before you hand it to the witness?

16 MS. KIEHN: Yeah, I think we just have to
17 both come over. You want -- can we go off the
18 record?

19 MR. WISNER: Let's go off the record.

20 THE VIDEOGRAPHER: The time is 5:55. We
21 will go off of the video record.

22 (Recess.)

23 (Exhibit No. 36 to be subsequently
24 marked for identification.)

1 THE VIDEOGRAPHER: The time is 5:59.

2 Back on the video record.

3 BY MS. KIEHN:

4 Q Dr. Laughren, if you can look at page 21
5 of Exhibit 35. I think you're there already,
6 correct?

7 A Yes, I'm there.

8 Q You see the section titled "14, Clinical
9 Studies; 14.1, Major Depressive Disorder"?

10 A I do.

11 Q And then the heading "Adolescents"?

12 A I do.

13 Q I direct your attention to the second
14 paragraph, which I'm going to read into the record.

15 "The efficacy of Lexapro in the acute
16 treatment of major depressive disorder in adolescents
17 was established in part on the basis of extrapolation
18 from the eight-week flexible-dose, placebo-controlled
19 study with racemic citalopram, 20 to 40 milligrams
20 per day. In this outpatient study in children and
21 adolescents, 7 to 17 years of age, who met DSM-IV
22 criteria for major depressive disorder, citalopram
23 treatment showed statistically significant greater
24 mean improvement from baseline compared to placebo on

1 the CDRS-R. The positive results from this trial
2 largely came from the adolescent subgroup."

3 Do you see that?

4 A I do.

5 Q You were involved in the approval of that
6 language, correct?

7 A That's correct.

8 Q So you determined that that language is
9 neither false nor misleading; is that correct?

10 A That's true.

11 Q Is that still your view today?

12 A Yes.

13 Q You concluded that Study MD-18 was a
14 positive study, correct?

15 A That's correct.

16 Q Does that remain your view?

17 A It does.

18 Q In your opinion, the decision as to
19 whether an efficacy study is a positive or negative
20 study a decision that is appropriately made by the
21 FDA?

22 A I do.

23 Q That's the role of the FDA, right?

24 A That is our job, to look at the data in

1 support of a -- of a new claim and then make a
2 judgment about that.

3 Q Because if it's a close call, the
4 decision should be made by the scientific experts at
5 the FDA and not by plaintiff's attorneys and juries;
6 is that correct?

7 MR. WISNER: Objection. Move to strike
8 as argumentative and misstates the facts.

9 THE WITNESS: It -- it's true that --
10 that basically the law, I believe, gives FDA
11 authority to make those judgments.

12 BY MS. KIEHN:

13 Q And that's proper because the FDA has the
14 scientific expertise to do so; is that correct?

15 A Right. Correct.

16 Q Would it be fair to say that protocol
17 violations are relatively common in a clinical study?

18 A They are.

19 Q In your experience, does a protocol
20 violation automatically invalidate the results of a
21 study?

22 A No.

23 Q That would depend on the nature of the
24 protocol violation, correct?

1 A It -- it would depend on -- on the nature
2 of the protocol -- the protocol violation, but as you
3 point out, it would be very difficult to find a
4 clinical trial that did not have some protocol
5 violations.

6 Q In the opinion -- sorry, in the opinion
7 of the FDA, was CIT-MD-18 a double-blind, randomized,
8 placebo-controlled study?

9 MR. WISNER: Objection. This witness
10 does not speak for the FDA.

11 THE WITNESS: When I was at FDA, it was
12 my judgment that it met those criteria.

13 BY MS. KIEHN:

14 Q Was it also your judgment that CIT-MD-18
15 was an adequate and well controlled study?

16 A That was my judgment at the time, yes.

17 Q Do you continue to believe that MD-18 was
18 a double-blind, randomized, placebo-controlled study,
19 notwithstanding anything plaintiff's counsel has
20 shown you today?

21 A I continue to believe that -- that
22 overall it still met those criteria.

23 Q One moment.

24 When you reviewed the study report with

1 Mr. Wisner, you saw that Forest provided the primary
2 efficacy analysis that included the allegedly
3 unblinded patients and the post hoc secondary
4 analysis that excluded those patients, correct?

5 A That's correct.

6 Q So FDA had both of those analyses in
7 front of it when the agency was reviewing the
8 application.

9 A That's true.

10 Q So the FDA was fully aware that excluding
11 the allegedly unblinded patients, that the P-value on
12 the primary efficacy analysis changed from 0.038 to
13 0.052, correct?

14 A That's correct.

15 Q I'm going to hand you what we're marking
16 as Exhibit 37.

17 MS. KIEHN: 36?

18 (A discussion was held off the record.)

19 (Exhibit No. 37 was marked for
20 identification.)

21 MR. WISNER: This is Exhibit 37?

22 MS. KIEHN: Correct.

23 BY MS. KIEHN:

24 Q Dr. Laughren, I'm handing you what's been

1 marked as Exhibit 37.

2 A Okay.

3 Q That's the new document we just handed
4 you.

5 A Right. I don't have a 36, so that's --

6 Q Is that -- that's not 37 that she just
7 handed you?

8 A This is 37.

9 Q Okay. So you have that before you?

10 A I do have 37 before me, correct.

11 MR. WISNER: And just for the record,
12 Exhibit, I think, 36 --

13 MS. KIEHN: -- was the 2009 Lexapro
14 package insert.

15 MR. WISNER: Okay. And I believe you're
16 going to -- we agreed off camera, but we agreed that
17 you are going to submit a clean copy of that for the
18 court reporter, correct?

19 MS. KIEHN: Correct.

20 MR. WISNER: Okay.

21 THE WITNESS: Okay. Got you.

22 BY MS. KIEHN:

23 Q Exhibit 37 is excerpts from a deposition
24 of James Jin, Ph.D. Do you see that at the very

1 bottom?

2 A Yes.

3 Q The date is October 21st, 2016. Do you
4 see that?

5 A I do.

6 Q I will represent to you that Mr. -- or
7 Dr. Jin was one of the statisticians on Study MD-18.
8 If you turn to page 464.

9 A Okay.

10 Q I'm going to read into the record at the
11 very top:

12 "Q. Mr. Jin, do you personally
13 know whether all of the nine
14 patients received pink pills?

15 "A. Not personally."

16 Skip down to line 15:

17 "Q. In your opinion, did any
18 protocol violations in MD-18 impact
19 the validity of your statistical
20 analyses?

21 "A. I think the study result's
22 still valid.

23 "Q. In your opinion, did any
24 protocol violations in MD-18 impact

1 the validity of the study's positive
2 results in the primary efficacy
3 analysis?

4 "A. No."

5 Turning the page to page 465:

6 "Q. Do you personally know whether
7 the nine patients were actually
8 unblinded?

9 "A. No.

10 "Q. Assuming they were unblinded,
11 would that change how you conducted
12 the primary efficacy analysis?

13 "A. No. The ITT is still ITT.

14 "Q. Assuming that they were
15 unblinded, would that change the
16 result of the primary efficacy
17 analysis?

18 "A. ITT analysis result would not
19 be changed.

20 "Q. The study would still be
21 positive from a statistical
22 standpoint?

23 "A. The primary analysis, yes.

24 Mm-hmm.

1 "Q. Do you have any concerns that
2 MD-18 was analyzed incorrectly from
3 a statistical standpoint?

4 "A. No.

5 "Q. Do you have any doubt that
6 MD-18 was a positive study?

7 "A. No."

8 You would agree with Dr. Jin's testimony,
9 wouldn't you?

10 A I -- I largely agree with it. The one
11 difference that I just want to point out that -- just
12 to emphasize that the way you explored the question
13 of whether or not the primary analysis would have
14 been impacted by the potentially unblinded patients
15 was to do the exploratory analysis and see what
16 effect that had on the P-value. And in my view, that
17 basically confirmed the impression that it did not
18 have a major impact on the -- on the primary
19 analysis. So...

20 Q I believe you testified earlier that
21 Study 94404 had some problems. Do you remember that?

22 A If -- if I recall correctly, the
23 responder analysis in 94404 showed that the responder
24 rate in the two groups, in placebo and drug, was

1 approximately 60 percent, which is extraordinarily
2 high for a response rate in a -- in a depression
3 trial.

4 And there's a lot of data now looking
5 at -- at the ability of a depression trial to
6 distinguish drug from placebo being essentially
7 inverse related to the response rate. And when you
8 get up around 60 percent, you're -- you're getting
9 close to the ceiling, and a study like that has very
10 little chance of distinguishing drug from placebo.

11 So I think from that standpoint, it
12 raises questions about the assay sensitivity of
13 94404. That was really my major concern about that
14 study.

15 Q Are you aware of any other issues with
16 the study, with either the design or the conduct of
17 the study?

18 A I -- off the top of my head, no. The
19 design was -- was appropriate reasonably. The dose
20 was what it should have been. And it's been a long
21 time since I looked at that in detail, but that is
22 the one feature of that study that -- that always
23 stood out in my mind. In fact, I think the remission
24 rate was close to 50 percent in both groups. You

1 know, again, very unusual for a depression study.

2 Q In your opinion, are SSRIs effective in
3 treating pediatric depression?

4 A The -- the answer is yes. Of course,
5 only two SSRIs are approved for the treatment of
6 pediatric depression. But I -- I -- I think that the
7 data that we have in -- in principle supports that
8 conclusion. Again, we only have -- we only have
9 positive data for -- for two of them. Well, for
10 three if you include Celexa and Lexapro as different
11 drugs.

12 Q You testified a few minutes ago -- strike
13 that.

14 A few minutes ago, you agreed with
15 Mr. Wisner that there was not sufficient evidence to
16 definitively conclude that either Celexa or Lexapro
17 were definitively effective in pediatric populations
18 prior to 2009.

19 Do you recall that?

20 MR. WISNER: Objection.

21 THE WITNESS: I'm sorry. Repeat the
22 question.

23 BY MS. KIEHN:

24 Q So Mr. Wisner asked you if you agreed

1 with this statement, and you did: That there was not
2 sufficient evidence to definitely conclude that
3 either Celexa or Lexapro were definitively effective
4 in pediatric populations.

5 MR. WISNER: Objection.

6 BY MS. KIEHN:

7 Q Do you recall that?

8 A I -- I do.

9 Q Does that mean that neither drug was
10 effective in pediatric patients prior to 2009?

11 A No, it doesn't mean that. It means that
12 there is not sufficient evidence to reach a
13 conclusion that they are effective. It doesn't --
14 you know, the absence of evidence is not evidence of
15 absence.

16 And as I -- as I said -- I believe I said
17 this in my testimony, that it would not be
18 unreasonable for a thoughtful clinician to use either
19 one in treating pediatric depression based on
20 clinical judgment. But there was not enough
21 evidence -- there was not sufficient evidence for FDA
22 to reach a conclusion, a positive conclusion that
23 either drug was effective in pediatric depression.

24 Q And to your knowledge, were psychiatrists

1 prescribing Celexa and Lexapro for pediatric
2 patients --

3 MR. WISNER: Objection --

4 BY MS. KIEHN:

5 Q -- before 2009?

6 MR. WISNER: Objection. Lacks
7 foundation.

8 THE WITNESS: It -- it's -- you know, I
9 don't -- I don't have prescribing data to rely on in
10 making the statement, but it certainly was my
11 impression that they were both being prescribed.

12 BY MS. KIEHN:

13 Q So in your opinion, there is evidence
14 supporting the efficacy of both Celexa and Lexapro in
15 the treatment of pediatric depression; is that
16 correct?

17 MR. WISNER: Objection.

18 THE WITNESS: Let -- let me -- let me
19 rephrase that in a way that's acceptable to me.

20 There -- you know, based on FDA's review,
21 there is evidence that Lexapro is effective in
22 treating pediatric depression. I think, you know,
23 based on back extrapolation, one could likely reach
24 the same conclusion for Celexa, but in fairness, FDA

1 has not been asked to, nor have they looked at that
2 question.

3 BY MS. KIEHN:

4 Q But I believe you testified earlier that
5 MD-18 was evidence of efficacy for citalopram in
6 pediatric depression; is that correct?

7 A As -- as a standalone study, it
8 provided -- it didn't provide -- on its own, it
9 didn't provide evidence of the effectiveness of
10 Celexa in treating pediatric depression. What I --
11 what I -- based on what we had back in 2002, and
12 obviously that's reflected in FDA's decision not to
13 approve the supplement.

14 Q It didn't provide evidence of
15 effectiveness sufficient for FDA approval, correct?

16 A Correct.

17 Q But the MD-18 study itself does provide
18 some evidence of efficacy for Celexa in the treatment
19 of pediatric depression, correct?

20 MR. WISNER: I renew my objection.

21 THE WITNESS: It -- it's -- it's a
22 positive study in that population. And again, I --
23 in my -- and again, I'm not -- I'm not at FDA
24 anymore. In my judgment, it's not unreasonable for a

1 clinician to take some reassurance from that study in
2 making a decision to -- to use it in pediatric
3 depression. But that's a different question than,
4 you know, whether or not there is sufficient evidence
5 for a regulatory body like FDA to reach that
6 conclusion.

7 BY MS. KIEHN:

8 Q Is there anything that plaintiff's
9 counsel has shown you or said to you today that has
10 caused you to doubt any prior decision you made about
11 Celexa or Lexapro while you were at the FDA?

12 A No.

13 MS. KIEHN: Nothing further.

14 FURTHER EXAMINATION BY COUNSEL FOR PLAINTIFFS

15 BY MR. WISNER:

16 Q Doctor, a few follow-up questions. Let's
17 start off where you ended off on
18 cross-examination/redirect.

19 There has actually never been a positive
20 study for Lexapro in children under 12, correct?

21 A That's correct.

22 Q In fact, it was studied in MD-15 and it
23 was negative, right?

24 MS. KIEHN: Objection.

1 THE WITNESS: MD-15 was -- was a negative
2 study.

3 BY MR. WISNER:

4 Q So you would agree that even at where we
5 stand here today, there is insufficient evidence to
6 conclude that Lexapro is effective in pediatric
7 patients below 12 years old.

8 A That's correct.

9 Q And you would agree with me that when a
10 patient is going -- is getting older, between 12 and
11 as they're reaching their adolescence, their body
12 changes, right?

13 A That's correct.

14 Q They go through puberty.

15 A Yes.

16 Q And one of the explanations as to why
17 there might be a difference between children under 12
18 and adolescents over 12 in the results of depression
19 or the treatment of depression is that depression
20 manifests itself differently in children the way it
21 does in adolescents?

22 A It does have --

23 MS. KIEHN: Objection.

24 THE WITNESS: It does have a different

1 phenomenology in children compared to adolescents and
2 adults.

3 BY MR. WISNER:

4 Q Now, let's go back to Exhibit 8 briefly.
5 It's the final study report.

6 Hopefully, it's not too far buried in
7 there. It's probably in that pile (indicating).

8 A No, I got it right here.

9 Q Oh, you got it? Okay, great.

10 On page 63, you recall that defense
11 counsel, Ms. Kiehn, asked you some questions
12 regarding the first sentence in the second paragraph
13 there?

14 A Yes.

15 Q And it reads that: "Nine patients," and
16 it lists the patient numbers, "were mistakenly
17 dispensed one week of medication with potentially
18 unblinding information."

19 Do you see that?

20 A I do.

21 Q Now, there was some back and forth about
22 whether or not patients in the placebo arm got the
23 wrongly colored pills.

24 Do you recall that?

1 A I do.

2 Q You would agree that, at least the way
3 it's written here, it suggests that that in fact
4 happened.

5 MS. KIEHN: Objection.

6 THE WITNESS: I -- which -- which
7 happened?

8 BY MR. WISNER:

9 Q I'm sorry. The way it's written here, it
10 does sure look like that all nine patients received
11 the wrongly colored pill.

12 MS. KIEHN: Objection.

13 THE WITNESS: Um, that -- that's the way
14 I interpreted it when I -- when you showed it to me
15 previously.

16 BY MR. WISNER:

17 Q And if in fact that wasn't the case, this
18 would just be another example of the final study
19 report being inaccurate.

20 A Well, it --

21 MS. KIEHN: Objection.

22 THE WITNESS: I don't -- I wouldn't -- I
23 would characterize it more the way that the
24 characterization that you've used throughout the day

1 is inartfully written. How is that?

2 BY MR. WISNER:

3 Q Okay. That works.

4 Turn your attention to page 30 -- I'm
5 sorry, Exhibit 33. It's probably over there in that
6 pile. It's one of the defendant's exhibits.

7 A Yes.

8 Q Okay. This is an e-mail exchange from
9 Gregory Dubitsky at the FDA with people at Forest.
10 Do you see that?

11 A I -- I do.

12 Q And in this e-mail exchange in July of
13 2004, it appears that Gregory Dubitsky is asking for
14 clarification about the nature of the unblinding;
15 isn't that true?

16 A Yes.

17 Q Now, to be clear, this is dated July 17,
18 2004, right?

19 A Correct.

20 Q So this is -- this is long after your
21 memorandum and review of MD-18, correct?

22 A Correct.

23 Q And if you actually look at the answer,
24 it's on page 9 of 11 in the attachment --

1 A Yes, I have that.

2 Q -- Forest provides a response to the
3 inquiry, right?

4 A Correct.

5 Q Nowhere in that response does Forest
6 state that the blind was unmistakably violated.
7 Correct?

8 A There's simply -- to my understanding, in
9 that panel, simply providing the distribution of
10 treatment assignment, you know, for those -- for
11 those nine patients.

12 Q This sure would have been a great point
13 at which Forest could have disclosed what happened
14 with those unblinded patients since the FDA is
15 specifically asking about it.

16 MS. KIEHN: Objection. Misstates the
17 document.

18 THE WITNESS: I -- I -- again, my view
19 that I've expressed throughout the day is -- is in
20 general, I think -- I think it's -- it's appropriate
21 for drug companies to provide as complete information
22 as they can about what actually happened in the
23 conduct of a study.

24 BY MR. WISNER:

1 Q I agree, Doctor, and I'm just saying this
2 is yet another example where Forest had an
3 opportunity to do that with regards to these
4 unblinded patients.

5 A Let me -- let me read the question that
6 the FDA asked.

7 Q Sure.

8 A (Perusing document.)

9 I mean technically it's -- it's answering
10 the question that was asked. But, again, my -- my
11 view was -- was that more complete information on the
12 potential unblinding could have been provided in
13 the -- in the original supplement.

14 Q Now, Doctor, you agree that scientific
15 debate about science is an important part of the
16 scientific process.

17 MS. KIEHN: Objection.

18 THE WITNESS: In general, I -- I have to
19 support debate in science, yes.

20 BY MR. WISNER:

21 Q And you would agree that the FDA is not
22 the final authority when it comes to whether or not a
23 drug is effective or not, correct?

24 MS. KIEHN: Objection.

1 THE WITNESS: Congress has given FDA
2 legal authority to make that judgment.

3 BY MR. WISNER:

4 Q But it's not the final authority, right?

5 MS. KIEHN: Objection.

6 THE WITNESS: Well, it's -- FDA is the
7 final authority from the standpoint of whether or not
8 a product can be marketed and promoted for a
9 particular indication.

10 BY MR. WISNER:

11 Q Now, you have -- are you familiar with
12 the -- the sort of landmark Supreme Court decision
13 Wyeth v. Levine?

14 A You -- I mean I -- I've heard that.
15 You'll have -- you will have to fill me in.

16 Q Do you understand that the U.S. Supreme
17 Court has held that the content of the labeling, the
18 final responsibility rests with the drug manufacturer
19 at all times? Do you understand that?

20 MS. KIEHN: Objection. Mischaracterizes
21 the decision.

22 THE WITNESS: I -- I think, you know,
23 companies have an obligation to write a proposed
24 labeling that -- you know, that is consistent with

1 the available data about a drug. But FDA has the
2 final authority over -- over whether or not that
3 proposed labeling is acceptable.

4 BY MR. WISNER:

5 Q Absolutely. However, a drug
6 manufacturer, they write the label, right?

7 MS. KIEHN: Objection.

8 THE WITNESS: Well, it -- it -- it
9 depends. FDA, when a drug is first approved, has a
10 lot to do, probably more than most people understand,
11 about the actual language that goes into a label.
12 There's extensive editing typically of a -- of a
13 proposed labeling that comes with part of the NDA.

14 BY MR. WISNER:

15 Q Now, isn't it true, Doctor, that if there
16 is a falsehood or misrepresentation in the labeling,
17 it's the drug manufacturer's responsibility, not the
18 FDA's?

19 MS. KIEHN: Objection.

20 THE WITNESS: I -- I think -- again, and
21 this comes right out of the law, the expectation is
22 that companies will propose labeling that's not false
23 and misleading.

24 BY MR. WISNER:

1 Q But when it is, the responsibility lies
2 with the manufacturer, not the FDA, right?

3 MS. KIEHN: Objection.

4 THE WITNESS: I -- I think both share
5 responsibility for -- for, you know, making judgments
6 about -- because it's not a -- it's not a black and
7 white issue whether or not it's false or misleading.
8 You know, it's the kind of thing that is -- is
9 subject to debate.

10 BY MR. WISNER:

11 Q It's sort of like a disputed issue of
12 fact, right?

13 MS. KIEHN: Objection.

14 THE WITNESS: It -- it's -- it's a
15 dispute about how you interpret particular findings.

16 BY MR. WISNER:

17 Q Are you aware that the U.S. Supreme Court
18 has held that lawsuits which challenge labeling or
19 dig deeper into internal documents, kind of like
20 we've done today, actually help the FDA with its
21 mission of ensuring that drugs are safe and
22 effective?

23 A I -- I --

24 MS. KIEHN: Objection. Mischaracterizes

1 the decision.

2 THE WITNESS: I don't -- I don't question
3 that.

4 BY MR. WISNER:

5 Q I'm going to give you what I've marked as
6 Exhibit --

7 MR. WISNER: What are we at here?

8 MS. KIEHN: 38.

9 MR. ROBERTS: 38.

10 BY MR. WISNER:

11 Q I'm going to mark this as Exhibit 37-A.
12 Okay? This is additional testimony by Mr. Jin.

13 Do you recall that defense counsel read
14 to you portions of Dr. Jin's testimony?

15 A Should this be marked as 37-A?
16 (Exhibit No. 37-A was marked for
17 identification.)

18 BY MR. WISNER:

19 Q Thank you, Doctor.

20 So I've given you what has now actually
21 been marked as Exhibit 37-A. These are additional
22 excerpts of the deposition of James Jin.

23 Do you see that, Doctor?

24 A Yes.

1 Q All right. If you turn to page 181 --
2 well, before that, do you have Exhibit 37, the
3 exhibit that -- that counsel showed you?

4 A Here it is. Yeah. Yeah.

5 Q And you recall that she read portions of
6 this transcript starting on page 463. Do you see
7 that?

8 A Yes.

9 Q And you see that actually the questions
10 that Mr. Jin was answering were in response to
11 Ms. Kiehn's questions.

12 Do you see that?

13 A I -- I see that, yes.

14 Q I will represent to you that this
15 interchange occurred after a break, do you understand
16 that, in the deposition.

17 A Okay.

18 Q Okay. Let's look at what Dr. Jin said
19 before that break. Okay?

20 A Okay.

21 Q So if you look at page 181 in the
22 deposition transcript that I've handed you. It's
23 Exhibit 37-A. Page 181, starting on line 8:

24 "Q. Now, if you look at the P-value

1 over on the right midway, you see
2 it's 0.52?

3 "A. Yeah, I see that."

4 MS. KIEHN: 0.052.

5 MR. WISNER: Sorry. Did I say 0.52?

6 Good grief, sir.

7 THE WITNESS: You and I make the same
8 mistake.

9 MR. WISNER: I guess it's a common
10 typographical error. Let me try this again. It's
11 getting late.

12 BY MR. WISNER:

13 Q All right.

14 "Q. Now if you look at the P-value
15 over on the right midway, you see
16 it's 0.052.

17 "A. Yeah, I see that.

18 "Q. Was that a statistically
19 significant outcome?

20 "A. Not.

21 "Q. So it was negative, not in
22 favor of Celexa's efficacy, correct?

23 "MS. KIEHN: Objection.

24 "THE WITNESS: Yeah, I think

1 it's -- the P-value is not meet the
2 criteria for a 0.05."

3 Do you see that?

4 A I do.

5 Q All right. And I will just represent to
6 you that Mr. Jin does not speak English particularly
7 well, so that's why some of these -- the grammar
8 might seem a bit off. Okay?

9 A Okay.

10 Q All right. Now, if we turn to the next
11 page, page 219, it -- starting on line 6, it says:

12 "Q. So you don't care whether they
13 were unblinded or not?

14 "MS. KIEHN: Objection.

15 "THE WITNESS: I cannot say I
16 don't care, but we just -- we have
17 to exactly follow the definition.

18 "MR. BAUM:

19 "Q. With the patients in, with
20 the unblinded patients in, it
21 corrupted the data for the ITT
22 population, didn't it?

23 "MS. KIEHN: Objection.

24 "THE WITNESS: Has some impact,

1 yeah."

2 Do you see that?

3 A I do.

4 Q So it appears that Mr. Jin is conceding
5 that inclusion of these unblinded patients
6 potentially corrupted the data, didn't he?

7 MS. KIEHN: Objection.

8 THE WITNESS: That -- that is what he's
9 saying here, and -- and I've already expressed my
10 slightly alternative view of that.

11 BY MR. WISNER:

12 Q I understand.

13 A That the appropriate way to see whether
14 or not those potentially unblinded patients had an
15 impact on the -- the correct P-value for the study,
16 and I agree with him there that the ITT is -- is the
17 dataset to use to generate the P-value for the trial,
18 but the sensitivity analysis is the way to determine
19 whether or not there was a significant impact on --
20 on the P-value. And -- and that was done, and in my
21 judgment, it didn't have a -- an important impact.
22 So...

23 Q I appreciate your answer, Doctor. I'm
24 just saying, according to Mr. Jin --

1 A Yes.

2 Q -- it corrupted the data?

3 A I'm sorry. Yes.

4 MS. KIEHN: Objection. Mischaracterizes
5 the testimony.

6 BY MR. WISNER:

7 Q That's a "yes," Doctor?

8 A I'm sorry?

9 Q That's a "yes," Doctor? I'm sorry, I
10 didn't hear it. She objected.

11 A I mean in reading and interpreting his
12 answers here, he seems to be implying that.

13 Q Okay. He also testified earlier on
14 page 181, right, that he believed, as the
15 statistician conducting the analysis, the sensitivity
16 analysis that we were discussing, he believed that it
17 was negative, correct?

18 MS. KIEHN: Objection.

19 THE WITNESS: I'm sorry.

20 BY MR. WISNER:

21 Q Sorry. On page 181, it's the first
22 portion that we read.

23 A Oh, okay.

24 Q Sorry.

1 A Yes. That's correct, he does say that.

2 Q So you agree then that it appears that
3 Forest's lead statistician -- I'm sorry, Forest's
4 statistician on MD-18 appears to have agreed that the
5 sensitivity analysis showed that the study was
6 negative; is that right?

7 MS. KIEHN: Objection.

8 THE WITNESS: I -- I don't -- I don't
9 interpret what he is saying that way. Again, I can't
10 know what was in his mind when he was making the
11 statement, but the way I -- the way I read this is
12 that he's saying that technically a P-value of 0.052
13 does not meet the -- the standard, you know,
14 threshold of -- of 0.05.

15 Again, in my -- in my judgment, that's an
16 incorrect use of P-value. A sensitivity analysis
17 that has reduced power should not be held to that
18 same standard. That -- that's where we disagree.

19 BY MR. WISNER:

20 Q I got you, and I -- I understand you
21 don't agree and we've covered that several times.

22 I guess my question to you, Doctor, is it
23 says here:

24 "Q. So it was negative, not in

1 favor of Celexa's efficacy,
2 correct?"

3 And he responds:

4 "Yeah. I think it's -- the P-value
5 is not meet the criteria for 0.05."
6 Do you see that?

7 A That -- that's what he says.

8 Q So he is saying it's negative.

9 MS. KIEHN: Objection.

10 THE WITNESS: Yes.

11 MR. WISNER: Okay. No further questions.

12 FURTHER EXAMINATION BY COUNSEL FOR DEFENDANTS

13 BY MS. KIEHN:

14 Q Dr. Laughren, does Mr. Jin actually say
15 that the data were correct?

16 MR. WISNER: It's on the next page,
17 Doctor.

18 THE WITNESS: Well, I mean, at the top of
19 this page, the question is: "That's corrupted data,
20 though, isn't it?"

21 And the witness says: "There is some
22 data question, yeah, agreed. Mm-hmm."

23 So I don't -- I don't -- I don't know
24 quite how to interpret that -- that answer in

1 response to that question.

2 BY MS. KIEHN:

3 Q But Mr. Jin never says the data was
4 corrupted, correct?

5 A He says there is some data question.

6 Q He doesn't say it was corrupted.

7 A He does not -- he does not directly state
8 that the data are corrupt.

9 Q Do you believe that the data in MD-18
10 were corrupt?

11 A No. I -- I -- again, I believe the
12 correct P-value for that study is the 0.038, and I
13 believe it was proper to do the sensitivity analysis
14 to look to see whether or not there was any impact of
15 the data that were potentially unblinded. And -- and
16 the answer from that analysis is that it did not have
17 a -- in my view, a substantial impact, negative
18 impact on -- on the analysis. And so that's just my
19 judgment.

20 MS. KIEHN: One minute. I'm thinking.

21 MR. WISNER: People have families they
22 need to get home to, Ms. Kiehn.

23 MR. ROBERTS: You're here till Sunday.

24 MR. WISNER: I'm not talking about me. I

1 don't have a family. I'm too young of a lawyer for
2 that.

3 MS. KIEHN: No further questions.

4 MR. WISNER: Thank you, Doctor, for your
5 time.

6 THE WITNESS: Thank you.

7 MR. WISNER: That concludes the
8 deposition.

9 MS. KIEHN: Thanks, everybody.

10 MR. GRIFFIN: Thanks, all.

11 THE VIDEOGRAPHER: The time is 6:36 p.m.
12 This is the end of disc No. 5 and the end of the
13 video deposition. We will go off the video record.

14 (Signature having not been waived,
15 the deposition of THOMAS LAUGHREN,
16 M.D. was concluded at 6:36 p.m.)

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1 CERTIFICATE OF NOTARY PUBLIC

2 I, LESLIE A. TODD, the officer before whom
3 the foregoing deposition was taken, do hereby certify
4 that the witness whose testimony appears in the
5 foregoing deposition was duly sworn by me; that the
6 testimony of said witness was taken by me in
7 stenotypy and thereafter reduced to typewriting under
8 my direction; that said deposition is a true record
9 of the testimony given by said witness; that I am
10 neither counsel for, related to, nor employed by any
11 of the parties to the action in which this deposition
12 was taken; and, further, that I am not a relative or
13 employee of any counsel or attorney employed by the
14 parties hereto, nor financially or otherwise
15 interested in the outcome of this action.

16

17 Dated this 3rd day of February 2017.

18

19

LESLIE A. TODD

20

Notary Public in and for the
State of Maryland

21

22 My commission expires:

December 23, 2018

23

24

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4 PAGE LINE CHANGE

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ACKNOWLEDGMENT OF DEPONENT

I, _____, do
hereby certify that I have read the
foregoing pages, and that the same is
a correct transcription of the answers
given by me to the questions therein
propounded, except for the corrections or
changes in form or substance, if any,
noted in the attached Errata Sheet.

THOMAS LAUGHREN, M.D.

DATE

Subscribed and sworn
to before me this
_____ day of _____, 20____.
My commission expires:_____

Notary Public