IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

VIDEOTAPED DEPOSITION OF THOMAS LAUGHREN, M.D.
ROCKVILLE, MARYLAND
FRIDAY, JANUARY 27, 2017
9:08 A.M.

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

HILTON HOTEL
1750 Rockville Pike
Rockville, Maryland 20852

Pursuant to notice, before Leslie Anne Todd, Court Reporter and Notary Public in and for the State of Maryland, who officiated in administering the oath to the witness.

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C O N T E N T S

E X H I B I T S

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

P R O C E E D I N G S

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

Our deponent today is Dr. Thomas Laughren.

Counsel will be noted on the stenographic record.

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

THOMAS LAUGHREN, M.D.

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

EXAMINATION BY COUNSEL FOR PLAINTIFFS

BY MR. WISNER:

Q Good afternoon. My name is Brent Wisner --

A Good morning.

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

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

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

Q What is your current address?

A 4709 Kemper Street, Rockville, Maryland 28053.

Q Have you ever been deposed before?

A Yes.

Q How many times?

A Three.

Q And what were the circumstances of those depositions?

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

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

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

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

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

A Yes. Yes.

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

A Yes.

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

A Yes.

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

A Yes.

Q And that was for Pfizer; is that right?

A That's correct.

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

in after your time at the FDA?

A No.

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

A I -- I do.

Q What is your understanding of that oath?

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

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

Do you understand that?

A I do.

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

A I do.

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

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

A (The witness nods.)

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

A Oh, yes. Yes. Yes.

Q Okay, great.

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

A Yes.

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

A I understand.

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

You understand that?

A Yes.

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

You understand that?

A I understand.

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

A I understand.

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

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

A No.

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

A No.

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

A No.

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

current iteration, I think it's Allergan?

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

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

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

A But let me also clarify.

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

Q Okay, great.

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

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

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

A No.

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

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

Q And why did you stop doing it?

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

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

Q Was there any falling out with Forest?

A No.

Q Okay.

A No.

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

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

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

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

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

A Correct.

Q Celexa, that's the brand name for

citalopram, correct?

A Correct.

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

A That's correct.

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

A Yes.

Q And that's also an SSRI?

A That's correct.

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

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

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

A Roughly two hours, yes.

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

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

deposition was going forward and so forth.

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

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

Q That's fine.

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

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

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

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

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

you; is that right?

A That's right.

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

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

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

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

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

A Yes.

Q And was Mr. Ellison present?

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

Q Okay. What did you guys talk about?

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

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

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

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

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

A No.

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

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

Q And was that the Brown case?

A Yes.

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

A Just a small expert -- excerpt of it.

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

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

Q Do you recall if you looked at a legal filing with him?
A A legal filing?
Q Yeah, like a motion that had been filed in this case, specifically in regards to your deposition.
A I think -- I think I -- again, I -- I believe that's the case, but there were -- there were several documents. I mean, I --
Q Sure. And I just -- to the best of your recollection, so if you recall --
A I -- I think -- I think there was a legal document that -- that he showed me, yes.
Q And did you also review a legal document that was prepared by Forest?
A They -- no. I mean, Forest didn't send me any -- any documents to -- to look at.
Q Okay.
A I -- I got -- I got a subpoena to testify. That -- that's the document that I --
Q Okay. So you looked at the subpoena; is that right?
A Well, I was -- I was -- it was delivered to me.

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

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

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

Q Okay. Thank you.

Have you been given any instruction or direction from Forest about what you should or should not testify about today?

A No.

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

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

Q That's good to hear.

(Exhibit No. 1 was marked for identification.)

BY MR. WISNER:

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

Exhibit 1 to your deposition.

Give it one second for the copies to be distributed.

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

A That's correct.

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

A It appears to be, certainly.

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

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

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

A No.

Q Okay.

A No.

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

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

residency in psychiatry, also at the University of Wisconsin.

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

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

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

A I was, yes.

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

A Yes.

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

A I was.

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

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

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

MR. WISNER: I'm sorry.

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

BY MR. WISNER:

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

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

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

MR. WISNER: We're connected here.

Thank you for that correction, Ms. Kiehn.

BY MR. WISNER:

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

A There were no SSRIs at the time.

Oh, at the time I left the VA?

Q Yes.

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

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

A That's correct.

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

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

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

A Very much so, yes.

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

A That's correct.

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

Are you aware of those?

A Luvox.

Q Luvox.

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

with the approval or review of all of those SSRIs?

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

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

A Absolutely.

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

A Vilazodone. It's a --

Q Vilazodone.

A -- it's not a -- is not an SSRI. It's a much more complicated product. It has other -- it has some -- some serotonin reuptake activities, but it also has some other activities, 5-HT1A and so forth. It's not -- it's not considered an SSRI, although it has -- it has effects on the serotonin transporter which is characteristic of the SSRIs, but it's a more complex drug.

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

A That's correct.

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

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

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

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

When you were a clinical reviewer, were

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

A Yes.

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

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

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

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

A Yes.

Q Are you also familiar with something called an SNDA?

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

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

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

A Yes.

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

A That's correct.

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

A That's correct.

Q Did you also conduct clinical reviews yourself?

A I did some reviews myself as well.

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

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

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

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

A Yes. Yes.

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

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

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

A Yes.

Q -- for the application?

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

Q Now, the decision to ultimately approve

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

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

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

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

A That's correct.

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

A That's -- that's correct.

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

A Yes.

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

A Yes.

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

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

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

Q Are you familiar with Dr. Temple?

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

Q Okay.

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

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

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

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

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

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

A That's correct.

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

A 2012.

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

A The division of psychiatry -- psychiatric drug products.

Q Okay, great.

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

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

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

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

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

Q Why would you say that?

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

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

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

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

A No.
Q So you agree then that the FDA can make a mistake; is that right?
A Yes.
Q Do you believe that drug manufacturers need to be honest in their dealings with the FDA?
A Yes, they do.
Q And why do you believe that?
A Well, I mean, number one, it's required by -- as I understand the law, it's required by law. They have to -- they have to submit, you know, accurate and complete information on an application that, you know, is part of an NDA or IND. They have to give -- they have to give FDA everything.
Q Do you believe that there could be health consequences if they are -- if a drug sponsor is not truthful and honest in their disclosures to the FDA?
A Yeah, of course.
Q Do you believe it would ever be appropriate for a drug sponsor to mislead the FDA?
A No.
Q Do you believe it is acceptable in your opinion for a drug manufacturer to mischaracterize data from a clinical trial to make a result appear

positive?

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

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

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

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

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

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

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

MS. KIEHN: Objection.

THE WITNESS: I'm sorry?

BY MR. WISNER:

Q I will rephrase that question in a better way.

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

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

Q Are you familiar with something called the placebo effect?

A Oh, very much so.

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

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

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

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Yes.

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

A Yeah, yeah.

Q -- the therapeutic effect.
A Right. Right. Right. Right.
MS. KIEHN: Objection.
BY MR. WISNER:
Q Placebo pills are often referred to by -- in layman's terms as a sugar pill; is that right?
A Yeah.
Q In the context of treating depression specifically, can people who are given placebo pills experience improvement?
A Typically in a -- in a depression trial, you see a fairly substantial improvement. Say it's a two-arm trial where, you know, one group is assigned to the active drug, the drug of interest, and the other group is assigned to the placebo, you're right, they all get the same interaction with staff.
Typically what you see in a trial, in a depression trial is -- is a, you know, quite a substantial improvement on the depression ratings in both arms. In a successful trial, you see a greater improvement in those who get the active drug compared to those that get the inert substance.
But you're right, that both groups improve, you know, quite -- quite a lot in that -- in

that trial.

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

MS. KIEHN: Objection.

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

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

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

BY MR. WISNER:

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

A Yes.

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

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

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

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

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

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

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

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

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

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

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

trial as randomization.

Q Thank you for that answer, Doctor.

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

Q It's okay. Not a problem.

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

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

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

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

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

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

A It would be very unusual.

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

A Yeah.

MS. KIEHN: Objection.

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

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

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

BY MR. WISNER:

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

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

Q Fair enough.

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A That's true, yes.

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

A That's correct.

Q And in the context of -- of assessing a

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

A Yeah, that --

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Yes.

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

MS. KIEHN: Objection.

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

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Sure.

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

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

MS. KIEHN: Objection.

THE WITNESS: FDA would want to know

about -- about unblinding.

BY MR. WISNER:

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

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

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

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

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

A That's correct.

Q That's determined by the drug company.

A Right.

Q The FDA doesn't -- strike that.

Are you familiar with something called a

clinical trial protocol?

A Yes.

Q What is that?

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

Q And typically -- strike that.

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

A Yes.

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

A Yes.

Q Why are protocols used?

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

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

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

A Well, it --

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

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

A Yes.

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

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

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

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

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

Q Sure.

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

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

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

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

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

THE WITNESS: Okay.

BY MR. WISNER:

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

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

A Less than or equal to 0.05.

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

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

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

Q What is a primary endpoint in a clinical trial?

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

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

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

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

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

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

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

A In the analysis plan.

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

A Yes.

Q What is a protocol violation?

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

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

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

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

A No.

Q Could systemic protocol violations

invalidate a study?

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Okay.

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

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

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

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

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

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

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

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

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

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

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

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

HAM-D.

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

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

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

Q I recall, on "60 Minutes."

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

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

I guess my question, though, is are you

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

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

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

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

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

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

Q Yeah.

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Sure.

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

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

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

there were actually patients.

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

BY MR. WISNER:

Q Does the FDA audit the case report forms typically?

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Now, after that investigation and that

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Yes.

Q What is that?

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

Q Who prepares the final study report?

A The companies prepare the study report.

Q And they submit that to the FDA as part

of a -- a regulatory process or an application?

A As part of an application, yes.

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

A Yes.

Q Can you explain to the jury what that is.

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

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

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

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

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

A Yes.

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

A That's correct.

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

A That's true.

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

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

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

for the pediatric study protocols that they plan to do?

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

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

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

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

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

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Sure. I just mean relative to the

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

MS. KIEHN: Objection.

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

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

THE WITNESS: Okay.

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

(Recess.)

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

BY MR. WISNER:

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

Are you familiar with the phrase

"off-label promotion"?

A Yes.

Q What is your understanding of that phrase?

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

Q That would be off-label use, right?

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

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

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

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

A No.

(Exhibit No. 2 was marked for identification.)

BY MR. WISNER:

Q Okay. I'm handing you what has been

marked as Exhibit 2 to your deposition.

Have you ever seen this document before?

A I don't recall seeing it.

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

A Okay.

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

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

Did I generally read that correctly?

A Yes.

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

THE WITNESS: I -- I don't.

BY MR. WISNER:

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

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

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

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

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

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

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

A Yes.

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

criminal conduct to you at that time?

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

Q Absolutely, Doctor.

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

MS. KIEHN: Objection.

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

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

THE WITNESS: I understand that.

BY MR. WISNER:

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

A I don't --

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

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

A Yes.

Q And what do you recall your involvement being?

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

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

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

A That's correct.

MS. KIEHN: Objection.

(Exhibit No. 3 was marked for identification.)

BY MR. WISNER:

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

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

A Yes, I do.

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

A This -- that's correct.

Q To be clear, this document was authored by you while you were at the FDA?
A Yes.
Q And was it part of your duties at the FDA to prepare memorandums recommending the approval or non-approval of supplement applications?
A Yes.
Q And was this memorandum specifically prepared in the regular course of your work at the FDA?
A Yes.
Q Do you have any independent recollection of your preparation of this memorandum?
A No. No. It's a long time ago.
Q Okay. The memorandum is addressed to NDA 20-822/S-016. Do you see that?
A That's correct.
Q Can you explain what that -- that -- those numbers mean?
A The -- the NDA number is -- is the NDA for Celexa. The supplement is -- is the number. It means that this is supplement 16 to that NDA.
Q So it would be fair to interpret this as this was seeking an additional indication to a drug

that had already been approved by the FDA.

A That's correct.

MS. KIEHN: Objection.

BY MR. WISNER:

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

A That's correct.

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

Do you see that?

A Yes.

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

A That's correct.

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

A That's correct.

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

oversaw the review of the application.

A That's correct.

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

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

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

A That's true.

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

A That's correct.

Q And what were those two studies?

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

Q Throughout this deposition I'm going to

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

A That's fine.

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

A Yes.

Q It reads --

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

BY MR. WISNER:

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

You see that?

A Yes.

Q What is a chemistry review?

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

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

A That's correct.

Q And the pharmacology review, what is that?

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

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

A That's correct.

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

Do you see that?

A Yes.

Q Who is Dr. Hearst?

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

Q You were his supervisor, right?

A Yes.

Q And at some point there was a

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

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

Q Fair enough.

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

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

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

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

Q Okay. So --

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

Q Okay. Do you know when that was?

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

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

A Yes. Well, again, I became division

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

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

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

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

Does that mean there was only one primary review done?

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

somebody as well?

A Yes.

Q And as well as a pharmacology review?

A Right.

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

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

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

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

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

A Correct.

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

A That's correct.

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

Do you see that?

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

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

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

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

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

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

A Correct.

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

What is a statistics review?

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

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

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

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

protocol?

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

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

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

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

A No. No.

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

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

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

A Correct.

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

A Yes.

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

A That's correct.

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

Do you see that?

A Yes.

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

A Yes.

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

A That's correct.
Q And it says OC, that's referring to observed cases, right?
A Right.
Q Observed cases is different than last observation carried forward?
A That's correct.
Q Could you briefly explain to the jury your understanding of the difference between "observed cases," OC, and "last observation carried forward," or LOCF?
A An LOCF analysis uses data that are carried forward from the time that a patient drops out of a study. So, for example, if it's in -- you know, this was I think a 12-week study. Yes. So if a patient dropped out at eight weeks in a 12-week study, that last score, that last recording on the Kiddie-SADS would have been carried forward as if that patient continued to 12 weeks. Whereas, an observed cases analysis only includes the data on the patients who completed to 12 weeks.
Q Do you have an opinion one way or the other whether an OC analysis or an LOCF analysis is better?

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

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

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

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

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

A Yes.

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

A Yes.
Q Now, here you depicted the efficacy results for the primary endpoint for Study 94404, right?
A That's right.
Q And under the heading, it says "P-val versus placebo." Do you see that? In the table on the far right.
MS. KIEHN: P-value versus --
MR. WISNER: Yeah.
MS. KIEHN: -- P-val.
MR. WISNER: Yeah, I misspelled it in my outline. Sorry.
THE WITNESS: Oh, P-value --
BY MR. WISNER:
Q It says "P-value versus placebo," do you see that?
A P-value, yeah. Yes, yes.
Q And that's -- that's the P-value of the difference observed in the treatment group of Celexa and the placebo arm, correct?
A That's correct.
Q And that's not statistically significant, correct?

A That's correct.

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

Do you see that?

A That's correct.

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

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

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

Do you see that?

A That's correct.

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

MS. KIEHN: Objection.

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

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

BY MR. WISNER:

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

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

MR. ELLISON: Would you let him finish --

BY MR. WISNER:

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

A Sorry.

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

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

(Exhibit No. 4 was marked for identification.)

BY MR. WISNER:

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

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

Do you recognize this document?

A Not offhand.

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

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

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

A That's correct.

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

A That's correct.

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

positive results in them.

A That's correct.

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

A Okay.

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

A I see that.

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

A Yes.

Q Do you know what this section refers to?

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

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

A Correct.

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

A Yes.

Q Do you know who Paul Tiseo is?
A No.
Q Have you ever met Paul Tiseo?
A Not that I recall. I may have. I met thousands of people from companies. I may have met him. I just don't -- don't recall.
Q Sure. So you -- so you have no independent recollection of ever speaking or interacting with Dr. Tiseo?
A No.
Q Okay. Now, it says here that he's a medical monitor. Do you see that?
A I see that.
Q Do you know what that is?
A He's the, you know, the primary person at the company who has responsibility for overseeing the conduct of that -- that study.
Q Okay, great.
Now, if you go down here, you also see Charles Flicker, Ph.D. Do you see that?
A I see that.
Q And it says here he's the senior medical director, CNS.
A I see that.

Q Okay. Do you know Dr. Flicker?
A Same answer. Not -- not offhand, no.
Q So you don't have any independent recollection of ever meeting Dr. Flicker?
A I -- I don't.
Q Okay. Do you recall what role, by any chance, he played in this clinical trial?
A It -- it looks from his title that he was the, you know, the senior medical director in the CNS group at -- at Forest.
Q And then below that, you see Lawrence Olanoff. Do you see that?
A I do.
Q And he is also a physician as well.
A I see that.
Q Okay. Do you know Dr. Olanoff?
A I have -- I have met Dr. Olanoff.
Q In what capacity have you met Dr. Olanoff?
A At -- at FDA.
Q At FDA. Do you recall when you met him or how many times you met him?
A My -- my recollection is that he would show up at -- at meetings we had with -- with Forest.

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

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

A I -- I don't recall.

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q But you don't recall any conversations?

A I can't recall it.

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

A I don't.

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

A I could not answer that.

Q Okay. If you also look over to the

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

A Yes, I see that.

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

A Not offhand.

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

A No.

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

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

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

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

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

MS. KIEHN: Objection.

THE WITNESS: Very likely did.

BY MR. WISNER:

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

(Exhibit No. 5 was marked for identification.)

BY MR. WISNER:

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

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

Have you ever seen this transcript before?

A Not that I recall.

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

A Okay.

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

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

"A. Yes, that came under my

supervision."

Do you see that?

A I see that.

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

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

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

Do you see that?

A I see that.

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

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

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

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

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

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

"Q. Correct.

"A. Mary Mackle, Paul Tiseo, Bill Heydorn, Paul Butkerait" -- spelled B-U-T-K-E-R-A-I-T -- it continues: "Ralph Bobo, Joan Singh, and Anjana Bose."

Do you see that?

A I do.

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

A That appears that way.

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

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

Q Do you recall what he did at FDA?

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

I believe that he was a pharmacologist.

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

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

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

A No.

Q Okay.

(Exhibit No. 6 was marked for identification.)

BY MR. WISNER:

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

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

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

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

Have you ever seen this transcript before?

A Not that I recall.

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

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

"MR. ROBERTS: Objection.

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

BY MR. BAUM:

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

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

Do you see that?

A I do.

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

A Okay.

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

A I do.

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

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

Did I read that correctly?

A Yes.

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

A That appears to be what it is, yes.

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

A That's true.

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

A That's correct.

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

A That's true.

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

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

Did I read that correctly?

THE WITNESS: That's correct.

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

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

MS. KIEHN: You said "of baseline."

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

MS. KIEHN: "From baseline."

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

BY MR. WISNER:

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

A That is what the protocol states.

Q Okay, great. Please turn to page 328.

Do you see the section titled "Unblinding Procedures"?

A I do.

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

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

Q What does it mean for there to be unblinding?

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

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

BY MR. WISNER:

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

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

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

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

Q Okay. Now, going back to this section,

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

Do you see that?

A I see that.

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Now, Dr. Laughren --

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

It's talking about, you know: "The

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

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

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

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

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

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

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

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

A I -- I --

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

A I have not been told to say that.

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

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

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

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

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

A I do not --

MS. KIEHN: Objection.

THE WITNESS: I absolutely do not agree.

BY MR. WISNER:

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

A I'm sorry. I apologize.

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

MS. KIEHN: Objection.

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

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Could you ask the question again?

Q Absolutely.

If a patient was in fact unmistakenly unblinded, you agree in that circumstance they should

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

THE WITNESS: I will answer no.

BY MR. WISNER:

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

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

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

Q I understand --

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

Q And --

A Let me finish.

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

A I'm done.

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Sure.

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

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

Q Okay.

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

That's -- that's different.

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

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

When I say that this cup is unmistakenly white, that means that there is no question that this cup is white, right?

A Yes.

MS. KIEHN: Objection.

BY MR. WISNER:

Q Okay. If I tell you that the integrity of the blind was unmistakenly violated, that means there is no question that the integrity of the blind was unmistakenly violated -- was violated, right?

MS. KIEHN: Objection.

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

question. What was the question?

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Sure.

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

Q Okay.

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

that the data cannot be used in the analysis.

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Fair enough. But should they be used?

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Okay.

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

A Well --

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q I see.

A -- in my mind.

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

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

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

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Okay. If you turn to page 331.

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

A Yes.

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

Do you see that?

A I do.

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

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

BY MR. WISNER:

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

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

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

A That's my understanding, yes.

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

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

MS. KIEHN: Objection.

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

BY MR. WISNER:

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

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

Q Okay. Turn to page 334.

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

A I do.

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

A I do.

Q Do you know what a clinical trial manager is?

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

Q Okay. Do you know Joan Barton?

A Not that I recall.

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

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

A I do.

Q This chart lists the primary endpoint, correct?

A That's correct.

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

A That's correct.

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

0.05, right?

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q It is a statistically significant result.

A That's correct.

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

A Yes.

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

Do you see that?

A I do.

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

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

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

Q Is this actually the testimony you looked

at with your attorney in preparing for your testimony today?

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

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

(Exhibit No. 7 was marked for identification.)

BY MR. WISNER:

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

Do you recognize this document, Doctor?

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

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

A Yes.

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

A Yes.

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

A Yes.

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

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

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

A I believe that's correct.

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

A That's correct.

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

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

Q That's right, the small ones.

You got it?

A Got it.

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

But starting on line 300 -- page 300, line 13, it says:

"Focusing on Exhibit 6, page 3, about two-thirds of the way down on the page, there is a note from you. Do you see that?"

A I do.

Q Sorry. I was reading the transcript. So -- it's confusing. I'm actually going to read the whole testimony.

A Oh, sorry.

Q And then I will pause and ask the question, so you know when I'm actually asking the question.

A Okay. Sorry. Sorry.

Q All right. So I will just do it again.

"So focusing on Exhibit 6, page 3, about two-thirds of the way down the page, there's a note from you. Do you see that?"

"A. Yes.

"Q. And it says: 'There was a packaging error resulting in tablets being distinguishable for drug and placebo for nine patients, although still blinded.'"

I will stop right there. Doctor, that's the same sentence we just looked at in your memorandum --

A Correct.

Q -- correct?

A Correct.

Q So it appears that this testimony is referring specifically to that sentence.

A Correct.

Q All right. Going back to Exhibit 7, it continues:

"That is a representation of the reality that there was at the beginning of Study 18 trial a potentially unblinding event. Correct?

"A. Potentially, correct.

"Q. I mean that's what we're calling it. There was a potentially

unblinding event, correct?

"A. Yes. With an emphasis on 'potential.'

"Q. Yes, sir. We don't know one way or the other whether or not" -- oh, sorry.

"We don't know one way or the other whether it would have unblinded the study."

"MR. IPSARO: Objection.

Right.

BY MR. ANDREWS:

"Q. Right?

"A. Correct."

Do you see that?

A I do.

Q At this point when you testified, it was your understanding that the -- the dispensing error that occurred with these nine patients was a potential unblinding, correct?

MS. KIEHN: Objection.

THE WITNESS: Are you asking me a question or are you reading?

BY MR. WISNER:

Q I'm asking you the question now: That was your understanding, there was a potential unblinding?

A Yes.

Q And, in fact, you put emphasis on the fact that it was potential, correct?

A That --

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q All right. Going back to the exhibit, it says:

"Q. And then you say a reanalysis without these patients yielded a P-value of 0.52 in favor of citalopram, correct?

"A. Correct.

"Q. And 0.52 would not -- would be not statistically significant, correct?

"A. That's correct.

"Q. So in this potentially unblinding event, if these patients were removed, this would no longer

be a positive study?

"A. That's correct.

"Q. So the approval of Lexapro was based on -- for pediatric use was based on an escitalopram positive study and a citalopram positive study, where if you remove nine patients who were potentially unblinded, it was actually negative.

"A. If you remove the nine patients. We considered the issue and made a judgment that they should not be removed.

"Q. It seems like a lot of hoops to jump through to approve this drug for pediatric use.

"A. I didn't consider this a huge hoop. I considered this a nonissue. That there is no reason to believe that. The fact that tablets have a different color, any one patient would only get one color tablet."

Do you see that?

A I do.

Q Based on your previous testimony -- do you believe that the testimony provided in this deposition was true and accurate?

A The problem with this testimony is that the lawyer who was doing the deposition was assuming that the P-value for the sensitivity analysis was 0.5, when in fact it was 0.05.

I have -- there is a typo in my memo, and I know this because this is -- this is the testimony that Mr. Ellison and I, you know, went over when we met last week, and -- and I -- and this came up previously subsequent to this deposition that -- that I realized that -- that that's a typo. That is 0.052, which is statistically significant. And so the -- you know, the sensitivity analysis was statistically significant.

I mean, and -- and why -- why are you misrepresenting this to me as -- as being the correct P-value? You -- you know that.

Q Sorry, Doctor. I just read you the transcript of your testimony, and I asked you if it was true or accurate. I didn't misrepresent anything to you. So I take offense that you think that I did so.

My question was to you, is there anything that was truthful or accurate about this, and you specified that there was a typo, 0.52; is that right?

A That -- that's correct.

Q Okay.

A It's -- it's 0.052.

Q Now, you also just testified that a P-value of 0.052 is statistically significant; is that right?

A It's close enough.

Q I'm sorry, that wasn't my question.

Does a P-value of 0.052 meet the threshold of statistical significance, yes or no?

A Whether -- whether or not a -- a P-value meets that standard is a judgment. It is a judgment. Most people in looking at a P-value of 0.052 would round it to 0.05. And so in my -- in my view, that's close enough.

Q I'm sorry, Doctor. My question to you was not whether it's close enough.

My question to you and to this jury and under oath, and as someone who worked at the FDA for 29 years, a P-value of 0.052, does that meet the definition of "statistically significant" or not?

A It's close enough.

Q So you think it's close enough. Does it meet the value or not?

Doctor, a P-value -- for a P-value to be statistically significant, it has to be at 0.05 or lower, correct?

MS. KIEHN: Objection.

THE WITNESS: 0.052 in my mind, in my view and my judgment, and actually in the judgment of most people at FDA who evaluate clinical trials, is close enough.

BY MR. WISNER:

Q All right. I appreciate your answer. I'm going to ask the question again. I understand you want to say it's close enough, and I appreciate that, but that's not my question.

My question to you is, a P-value is statistically significant if it is at 0.05 or lower, correct?

MS. KIEHN: Objection.

THE WITNESS: That's -- that's one definition of statistical --

BY MR. WISNER:

Q That is the standard definition, Doctor,

isn't it?

MS. KIEHN: Objection.

THE WITNESS: We're not -- we're not going to agree on this. Because making a judgment -- again, this gets back to what I was saying earlier -- making a judgment about whether or not a package of data is sufficient to justify approving a drug is a judgment. It is based on the accumulated evidence, and -- and what -- what a thoughtful reviewer at FDA will conclude from that data about whether or not that drug is effective.

The difference between 0.052 and 0.050 is 2/1000ths.

BY MR. WISNER:

Q Doctor, I appreciate your answer. I move to strike all of it as nonresponsive.

Again, my question to you is not about the package. It's not even about Celexa. So if you could actually answer my question, we can get out of here a lot quicker.

MS. KIEHN: I think he has answered your question.

MR. WISNER: I appreciate your objection. Let me finish my question, and then you can issue

your objection, Ms. Kiehn.

BY MR. WISNER:

Q My question to you, Doctor, is: Isn't it true that the scientific standard for statistical significance is 0.05 or less? Yes or no, Doctor?

MS. KIEHN: Objection. Asked and answered.

THE WITNESS: I -- I believe I've answered the question to the best of my ability.

BY MR. WISNER:

Q Okay. I will reask the question, and you can give me the answer that you think answers the question.

Dr. Laughren, isn't it true that the scientific standard for statistical significance is a P-value of 0.05 or less?

MS. KIEHN: Objection. Asked and answered.

THE WITNESS: I -- I believe I've answered the question.

BY MR. WISNER:

Q What is your answer then?

A The answer --

MS. KIEHN: Objection.

THE WITNESS: The answer is that a P-value of 0.052 is statistically significant in my view.

BY MR. WISNER:

Q Doctor, that -- that wasn't my question, and -- that answer doesn't answer my question.

So my question is not about the P-value of 0.052. My question to you is actually about the scientific standard for statistical significance, and a P-value has to be at 0.05 or less to be, under the standard rubric of scientific investigation, a statistically significant outcome, correct?

MS. KIEHN: Objection. Asked and answered.

THE WITNESS: The -- the -- although the usual definition of "statistical significance" is the P-value of 0.05 or less, a judgment about whether or not a particular finding is statistically significant is -- is made by -- by individuals evaluating data. There is not any hard and fast rule that -- that a finding has to be 0.050000 or less to be statistically significant. It is a judgment.

BY MR. WISNER:

Q Now, Doctor, are you aware that Forest

has admitted under oath that a P-value of 0.052 is not statistically significant?

MS. KIEHN: Objection. That's false.

THE WITNESS: I -- I'm not -- I'm not aware of that. And honestly, I don't care what they think about it.

BY MR. WISNER:

Q Okay. You are aware that Forest has conceded that in fact if these unblinded patients were removed from the study, the study was negative. Are you aware of that?

MS. KIEHN: Objection.

THE WITNESS: I -- I'm not aware of that, and -- and honestly, I don't -- I don't agree with that.

BY MR. WISNER:

Q Okay. You previously testified that if these patients were removed from the clinical trial, the study was negative, didn't you?

MS. KIEHN: Objection.

THE WITNESS: I was -- I was -- I was misled in this case because the P-value listed here is not the correct P-value.

BY MR. WISNER:

Q I'm sorry you were misled because the man quoted your own sentence, right, Dr. Laughren?

MS. KIEHN: Objection.

THE WITNESS: You know, I -- I was not -- I was not provided with the complete data at -- at the time of this deposition. If I -- if I had had access to Dr. Hearst's review, I would have recognized immediately that -- that I had made a typo, that this -- that this is actually 0.052 and not 0.52.

BY MR. WISNER:

Q And, actually, at this point in your deposition back in 2013, when you were working for Forest as an expert consultant, you had your own memorandum in front of you, didn't you?

MS. KIEHN: Objection.

THE WITNESS: I had my memorandum. I did not have -- I -- I don't believe that I had the rest of the documents to basically, you know, verify what the correct P-value was.

BY MR. WISNER:

Q Okay. And so to verify what the truth is, you would need more than your own words; is that right?

MS. KIEHN: Objection.

THE WITNESS: I would need, you know, the full documents because I obviously made a -- made a typo.

BY MR. WISNER:

Q Okay. Now, in that sentence, before that, you said: "There was a packaging error in tablets being distinguishable for drug and placebo for nine patients, although still blinded."

It was your understanding that the patients, despite getting a different color tablet, were still blinded, correct?

MS. KIEHN: Objection.

THE WITNESS: I -- I'm assuming that I made that statement based on something that I had seen in -- in the supplement.

BY MR. WISNER:

Q Okay. So it was your understanding that the patients, despite receiving different color tablets, were still blinded, correct?

MS. KIEHN: Objection.

THE WITNESS: Well, that -- that was -- that was my assumption, correct.

BY MR. WISNER:

Q If in fact the patients were unmistakenly unblinded, that is not what you understood at the time that you wrote this memorandum, correct?

MS. KIEHN: Objection.

THE WITNESS: I -- I -- again, this goes back almost 15 years. I'm not sure what my state of mind was at the time that I -- that I wrote this memo. But my belief was based on what I've written here is that the patients were blinded.

BY MR. WISNER:

Q Okay.

(Exhibit No. 8 was marked for identification.)

BY MR. WISNER:

Q All right. I'm going to hand you what's marked as Exhibit 8 to your deposition.

This is a document titled "Study Report for Protocol No. CIT-MD-18." It is dated April 8, 2002.

Do you recognize this document, Doctor?

A Is this the same document that you gave me previously? Oh, study report. Okay. So this -- okay.

Q Do you recognize this document?

A I don't recognize it, but it looks like it's the full study report for Study 18.

Q Okay, great. And it's actually -- just so you know, it's portions of the final study report for MD-18. Okay?

A It's portions of the supplement?

Q Of the final report for MD-18.

A Oh, okay. Okay.

Q This is a 2,135-page document. I've only given you portions of it --

A Oh, okay. Fair -- fair enough.

Q -- to spare our scanning costs in this case.

This is the document that Forest submitted to the FDA to represent the results and conduct of Study MD-18, correct?

A So this -- this would have been part of the -- of the supplement that my memo was based on from the -- the April 18th, 2002 supplement.

Q Okay, great. Turn to page 63.

The second paragraph on page 63 reads or begins: "Nine patients, patients 105, 113, 114, 505, 506, 507, 509, 513, and 514, were mistakenly dispensed one week of medication with potentially

unblinding information. Tablets had an incorrect color coding."

Do you see that?

A I do.

Q This is consistent with what you wrote in your memorandum, correct?

MS. KIEHN: Objection.

THE WITNESS: It -- it appears to be.

BY MR. WISNER:

Q In fact, it was your testimony that simply because a patient received a different color tablet, there is no reason to understand that the patient or the investigator was unblinded; isn't that right?

A That's correct.

Q This sentence here that I just read you does not state that the integrity of the blind was unmistakenly violated, does it?

A No.

Q It didn't say that dispensing the incorrectly colored tablets would automatically unblind the study, does it?

A Correct.

Q Would you read those two sentences, the

unmistakenly unblinded and the automatically unblinded convey different occurrence than what's listed here in the final study.

MS. KIEHN: Objection.

THE WITNESS: Say that -- automatically unblinded.

BY MR. WISNER:

Q Sure. It does not say that the dispensing of the incorrectly colored tablets automatically unblinded the study. It does not say that, right?

A Correct.

Q Okay. You would agree that if it had said that the dispensing of these tablets automatically unblinded the study, that would be different than what it says here in the final study report.

MS. KIEHN: Objection.

THE WITNESS: What it says here is that -- that basically -- as I understand this, the coloring of the -- the coating of the tablets -- I would -- I would like to see the supplement that I reviewed that was the basis for this statement. That's what I would like to see. I don't -- I don't

know if this is a document that -- that we reviewed as -- as part of the supplement.

BY MR. WISNER:

Q I will represent to you this is the final study report that was submitted to FDA as part of its pediatric supplement. So this is a document that you would have reviewed as part of your consideration of -- of the pediatric indication, correct?

A Let me look through this. (Perusing document.)

It doesn't even have a table of contents.

Q I removed the table of contents to make the document more manageable in size. If you look on the bottom right-hand corner of each page, it's dated April 8, 2002.

A I see that.

Q And the supplement was submitted on April 18th, 2002, correct?

A Right.

Q So this suggests that this document was part of the package that was sent to you to review the pediatric submission for Celexa, correct?

A Correct.

Q So it's fair to say then that in your

consideration of the pediatric supplement submitted to FDA, this is a document you likely looked at.

A Likely.

Q Okay.

(Exhibit No. 9 was marked for identification.)

BY MR. WISNER:

Q All right. I'm going to hand you a document that's labeled Exhibit 9 to your deposition. We're going to come back to this several times, so keep it handy.

This is a document titled "Review and Evaluation of Clinical Data." Do you recognize this document?

A This looks like it's Dr. Hearst's review of -- of Supplement 16.

Q All right. And if you look at the last page, there is an electronic stamp that indicates this document was signed by Dr. Hearst electronically on September 12th, 2002. Do you see that?

A I -- I do.

Q Okay. And the date of your memo is subsequent to the date of this. Isn't that true?

A Correct.

Q All right. Would it be fair to say that in preparing your memo, you likely relied upon portions or some of Dr. Hearst's analysis in forming your memo?

MS. KIEHN: Objection.

THE WITNESS: That is probably true, but I -- as I mentioned earlier, I probably also looked at the -- at the actual supplement.

BY MR. WISNER:

Q Okay, great. Turn to page 8 in Dr. Hearst's review.

A Okay.

Q See, starting there on page 8 and continuing on for several pages, he conducts his review of the results of MD-18. You see that?

A I see that.

Q All right. Turn to page 11. Do you see the portion where he specifically is discussing the efficacy results of MD-18?

A I do.

Q All right. Do you see the paragraph that starts with the word "because"?

A I do.

Q That sentence reads: "Because of a drug

packaging error, the citalopram or placebo tablets initially dispensed to nine patients at three study centers were distinguishable in color, although otherwise blinded."

Do you see that?

A I do.

Q That is a verbatim copy and paste from the final study report, isn't it?

MS. KIEHN: Objection.

BY MR. WISNER:

Q Page 63, if you need to look at it to compare.

A Sorry. Where was the --

Q The sentence that begins -- the paragraph that begins "because of a drug packaging error," and then on page 63, it is the first sentence of the second paragraph on Exhibit 4 -- 8.

A Well, it's not -- you know, the phrase "although otherwise blinded" does -- does not appear -- I don't see that on page 63.

MS. KIEHN: Brent, they don't match.

THE WITNESS: It -- it's not -- it's not identical language.

BY MR. WISNER:

Q Oh, I'm sorry, Doctor. Let's go back to Exhibit 8. I'm having you look at the wrong section. I'm trying to skip portions in my outline. I apologize.

If you turn to page 44 in the final study report. If you look at the last paragraph there on page 44, do you see that? "No double-blind treatment," you see that?

A Right.

Q Okay. Now, this is the section titled "Blinding." Do you see that?

A I do.

Q And, actually, if you look at the second paragraph in that section, it discusses the tear-off procedure -- the tear-off panel procedure.

A I see that.

Q Okay. And in this section that relates to the tear-off panel procedure, look at the second paragraph in the -- sorry, the second sentence in the last paragraph on page 44.

It reads: "Because of a drug packaging error, the citalopram or placebo tablets initially dispensed to nine patients at three centers were distinguishable in color, although otherwise

unblinded. See Section 7.0?"

Do you see that?

A I do see that.

Q And that is a verbatim copy and paste which was in Dr. Hearst's medical review, correct?

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q Okay.

A That -- that does look like it's -- it's identical language.

Q Now, earlier you testified that the protocol section about unblinding procedures only applied to incidents involving the tear-off panel. You remember that?

A Well, in the -- in the protocol it -- it did.

Q Okay.

A I forget what page that was on. Oh, here it is on page 328.

Q Now -- thank you for referencing that.

Now, the fact that the blinding issue was discussed in Section 5.34 in the final study report where it discusses whether or not there was any

unblinding due to the tear-off panel, that it also discusses potential unblinding related to these nine patients who were subject to the dispensing error, doesn't that suggest that at least Forest understood that that section of the protocol applied to any form of unblinding in the study?

MS. KIEHN: Objection.

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

BY MR. WISNER:

Q Okay.

A I mean, you know, they -- they recognized that there was a potential problem because apparently, you know, the -- the coloring of the placebo and the active products were different and therefore allowed them to be distinguished. But that doesn't mean -- that doesn't mean that -- that patients were unblinded.

Q Okay, great.

MR. WISNER: Let's change tapes.

THE VIDEOGRAPHER: The time is 12:09 p.m. This is the end of disc No. 2. We will go off the video record.

(Recess.)

THE VIDEOGRAPHER: This is the beginning of disc No. 3 in the deposition of Dr. Thomas Laughren. The time is 12:21 p.m. Back on the video record.

BY MR. WISNER:

Q Okay. Doctor, previously we were discussing Dr. Hearst's clinical review and how it had a sentence that was copied and pasted in it from the final study report, do you recall?

MS. KIEHN: Objection.

THE WITNESS: I do.

BY MR. WISNER:

Q And that sentence that was copied and pasted specifically dealt with the nine patients that were dispensed the -- the incorrectly colored tablets?

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q The -- he goes on to say in his report -- now we're in Exhibit 9, I will let you turn to that so you're there. Are you in Exhibit 9, Dr. Hearst's report? Yeah, it's right in front of you, right there (indicating).

A Okay.

Q All right. After that sentence that was copied and pasted, it reads:

"A sponsor presents the results from the LOCF analysis for the change from baseline to week 8, excluding data from the nine patients from whom the study blind was potentially compromised."

Do you see that?

MS. KIEHN: Objection.

THE WITNESS: I do.

BY MR. WISNER:

Q "The results from the week 8 LOCF analysis comparing the mean change from baseline in CDRS-R in the citalopram and placebo groups was affected by the exclusion of those patients. The LSM difference decreased from 4.6 to 4.3, and the P-value increased from 0.033 to 0.052."

Do you see that?

A I do.

Q Now, Dr. Hearst does not state that -- that the P-value of 0.052 was statistically significant, does he?

A No.

Q He actually states that the analysis

changed the results, doesn't he?

MS. KIEHN: Objection.

THE WITNESS: Well, he -- he states that -- yes, he does state that, you know, that excluding those patients led to a decrease in the least squares' mean difference and increased the P-value.

BY MR. WISNER:

Q And the exclusion of those nine patients, according to him, changed the P-value from being 0.038 to 0.052. Do you see that?

A I do.

Q Now, you agree that 0.038 is -- is statistically significant?

A I do.

Q That is clearly statistically significant, right?

A Yes.

Q That is below 0.05, right?

A That's correct.

Q Now, 0.052, you testified already that that is statistically significant -- I believe you said it was close enough; is that right?

A I did.

Q Okay. But you agree that 0.052 is more than 0.050, right?

MS. KIEHN: Objection. Asked and answered.

THE WITNESS: I -- I do.

BY MR. WISNER:

Q Okay. It appears, based on the fact that Dr. Hearst copied and pasted a portion of the final study report into his own clinical review, that Dr. Hearst relied upon the statements made in the final study report.

MS. KIEHN: Objection.

THE WITNESS: It certainly appears that he read it.

BY MR. WISNER:

Q And do you recall whether or not you had any conversations with Dr. Hearst about this unblinding issue?

MS. KIEHN: Objection.

MS. WEINMAN: Objection.

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

BY MR. WISNER:

Q Okay. And I don't want to know any of the substance of any of those conversations, but if

you did have a conversation like that, would it have been documented anywhere?

MS. KIEHN: Objection.

THE WITNESS: Unlikely. I -- just to qualify, typically during a review process we would have had multiple discussions. There wouldn't have been any way to document every one of them.

BY MR. WISNER:

Q And when you say "discussion," you mean like in person, right?

A Yes.

Q And you would be sitting in each other's office and talking about stuff.

A Yes.

Q Okay. There was -- was there any sort of formalized way of communicating with one another internally within the FDA?

MS. KIEHN: Objection.

THE WITNESS: There were multiple ways of communicating. I mean, sometimes we had formal meetings, sometimes we just, you know, exchanged e-mails, sometimes you would stop down to someone's office.

BY MR. WISNER:

Q That was an inartfully worded question.

Is it customary practice -- and I don't know if it is, so I'm not suggesting that it is. I'm just asking?

Was there a customary practice within the FDA to make official recordings of meetings or discussions that happened solely internally within the agency?

A No.

Q Okay. In 2002, were you guys using e-mail?

A Yes.

(Exhibit No. 10 was marked for identification.)

BY MR. WISNER:

Q Okay. I'm handing you what has been marked as Exhibit 10 to your deposition.

Before we get into that document, actually, Doctor, I just want you to know I'm going to be showing you a bunch of documents that have been produced by Forest in this litigation. I'm not aware if you've seen any of them. I will ask you if you've seen any of them or have knowledge of them based on your interactions with counsel or Forest. I don't

want to know any privileged communications that you may have had with your counsel.

MR. WISNER: So if I am calling for that, please do object so we can properly instruct the witness.

BY MR. WISNER:

Q I've handed you a document that's been marked as Exhibit 10 to your deposition. This is a document that has been produced by Forest in this litigation. I will represent to you that this is a draft of a letter that was going to be sent to the FDA specifically relating to the dispensing error that we were just discussing. The typed text portion of the document was prepared by Dr. Paul Tiseo. The medical monitor of Study MD-18 and the handwriting portion of this document was written by Dr. Charles Flicker.

All right. The first paragraph of this document states: "The purpose of this letter is to inform the agency that an error was made during the packaging of the clinical supply to the above-noted study."

Do you see that?

A I do.

Q It is your understanding that in fact a packaging error did occur in the study, right?

A Yes.

Q Okay. The paragraph continues: "The error came to our attention following enrollment of the first few patients into the study. Two of our investigational sites called in to report that some of their patients were receiving white tablets and others were receiving pink tablets. These reports were passed on to Forest clinical packaging, where it was discovered that a number of bottles of," quote, "active," unquote, "medication were mistakenly packed with the pink-colored commercial Celexa tablets instead of the standard white citalopram tablets used for blinded clinical studies."

Did I read that correctly?

A Yes.

MS. KIEHN: I believe so.

MR. WISNER: Okay, great.

BY MR. WISNER:

Q So based on this letter, it appears that the dispensing error was discovered after two clinical investigators called Forest inquiring about why some of their patients were receiving white

tablets and some were receiving pink ones.

Do you see that?

A I do.

Q This letter also indicates that the pink-colored pills were actually the commercial branded Celexa tablets.

Do you see that?

A I do.

Q All right. The letter continues to say: "On March 2nd, all sites were notified of this error by telephone and by fax."

Do you see that?

A I do.

Q All right. We're going to take a look at that fax.

(Exhibit No. 11 was marked for identification.)

BY MR. WISNER:

Q I'm going to hand you what has been marked as Exhibit 11 to your deposition.

Like Exhibit 10, this is a document that has been produced by Forest in this litigation.

Have you seen this document before?

A I don't recall seeing it.

Q Okay. You don't recall seeing it with your attorney, by any chance, last Wednesday?

A I'm quite sure that we didn't see it that night.

Q All right. Please turn to the first page. This appears -- the first page appears to be an e-mail from Dr. Tiseo.

Do you see that?

A By the first page, you mean --

Q This page right here on the front (indicating).

A This page (indicating)?

Q Yes.

A This page. Okay.

Q This appears to be an e-mail from Dr. Tiseo. Do you see that?

A I do.

Q It's dated March 2nd, 2000. Do you see that?

A I -- I do.

Q The subject of the e-mail reads: "CIT-18 faxed to investigational sites."

You see that?

A I do.

Q In the e-mail Dr. Tiseo states: "For your information, a copy of the fax that went out to all the CIT-MD-18 pediatric investigational sites this morning is attached. All sites have been contacted by telephone and given verbal instructions on how to proceed with both drug treatment as well as their patients who have been screened and/or randomized. I would also like to thank everyone involved in this process for their input and their assistance in rectifying this situation in such a timely manner."

Did I read that mostly correctly?

A Yes.

Q All right. If you turn to the next page, you see that there is a -- what appears to be a facsimile that's attached.

Do you see that?

A I do.

Q And this facsimile is also dated March 2nd, 2000?

A I do.

Q And the subject line reads "CID -- CIT-MD-18 Citalopram Pediatric Depression Study." Right?

A I do -- yes.
Q And it states that it was actually sent by Dr. Tiseo?
A I see that.
Q All right.
The first paragraph of the fax states: "It has come to our attention that an error was made during the packaging of the clinical supplies for above-noted study. A number of bottles of," quote, "active," unquote, "medication were mistakenly packed with pink-colored commercial Celexa tablets, instead of the standard white citalopram tablets used for blinded clinical studies?"
Do you see that?
A I do.
Q It would appear then that this -- this facsimile is noted by the investigational sites that the pink pills that they have were actually commercial Celexa, isn't it?
MS. KIEHN: Objection.
THE WITNESS: It appears to -- to suggest that, yes.
BY MR. WISNER:
Q And previously when we looked at the

study report, it stated that nine patients were dispensed these incorrectly colored tablets, right?

MS. KIEHN: Objection.

BY MR. WISNER:

Q Do you want to take a look at the final study report?

It's on page 63 of the final study report, if you're looking for it.

MS. KIEHN: It's also on 44.

THE WITNESS: I'm confused by -- yeah, I have page 44.

BY MR. WISNER:

Q Yeah, turn to page 63 of that -- of the final study report. For the record, we're referring to Exhibit 8 here.

Do you see the second paragraph, the sentence --

A Right.

Q -- "nine patients were dispensed"? Do you see that?

A Yes.

Q Okay. So according to the final study report, these nine patients were actually dispensed at least one week of medication with potentially

unblinding information. Do you see that?

MS. KIEHN: Objection.

THE WITNESS: So, I mean, do we -- do we infer from this that all nine patients got the pink-colored tablets?

BY MR. WISNER:

Q Well, that's what the final study report says, doesn't it?

MS. KIEHN: Objection.

THE WITNESS: This -- this is the final study report.

BY MR. WISNER:

Q Are you on page 63 there?

I think you're in the wrong doc- -- oh, there you go. There you go. Page 63.

It says: "Nine patients," and it lists the patient numbers, "were mistakenly dispensed one week of medication with potentially unblinding information. The tablets had an incorrect color coding."

Do you see that?

A Yes.

Q Okay. So according to the final study report, these nine patients were dispensed this pink

medication. Do you see that?

A Okay.

MS. KIEHN: Objection.

BY MR. WISNER:

Q Right, that's what it says?

A That's what it says.

Q Okay. All right. Now, if you go back to the fax -- and keep the final study report handy if you want to reference it, but go back to the fax that we were looking at.

It reads: "As a result, dispensing these tablets would automatically unblind the study."

Do you see that?

A I -- I do. I do.

Q So according to this facsimile, dispensing this pink medication would automatically unblind the study. Isn't that right?

A Yeah, that's what it says.

Q And he is the medical monitor for MD-18?

A Yep.

Q Now, we know from the previous exhibit that Forest became aware of -- sorry. We know from the previous exhibit that Forest became aware of the dispensing error because the investigational sites

had actually called Forest and said, Hey, some of my patients are getting pink tablets, some of them are getting white. Right?

MS. KIEHN: Objection.

THE WITNESS: Correct.

BY MR. WISNER:

Q And this facsimile is telling the investigational site that the pink tablets are actually branded commercial Celexa.

Do you see that?

A I do.

Q Wouldn't that by definition have unblinded the investigator?

MS. KIEHN: Objection.

THE WITNESS: I -- it -- if -- if the tablet said "Celexa R" on it, yes, it would have unblinded the investigator.

BY MR. WISNER:

Q And, in fact, the investigator has now potentially received this facsimile saying, Hey, those pink tablets that you have, they're actually commercial Celexa.

Isn't that what this fax is saying?

A That's what the fax appears to say.

Q And it's saying, Listen, if you dispense this medication, you've automatically unblinded the study.

Isn't that what it says?

MS. KIEHN: Objection.

THE WITNESS: Certainly for the investigator.

BY MR. WISNER:

Q Okay. All right. If you turn to the third page of -- I'm sorry, the last page -- I'm sorry. Turn to the third page of the facsimile.

Do you -- do you see the section up there at the top that says "IRB"?

A Yes.

Q What is an IRB?

A Institutional Review Board.

Q And what does an IRB do in relation to a clinical trial?

A An IRB is -- is a group that -- that looks at the -- at the trial primarily from the -- from the standpoint of its -- of the ethics of the trial with regard to the patient --

Q Okay.

A -- patient safety and -- and ethical

aspects of the trial.

Q And the IRB, they're -- they're independent, of course, from the FDA, right?

A Independent of the FDA and the company.

Q Okay. It reads: "Although this is not a patient safety issue, we recommend that you inform your IRB of the mistake in packaging. A brief letter is attached for your use explaining in detail the reason for the medication recall."

Do you see that?

A I do.

Q And if you actually look at the next page, there is -- it looks like to be a form letter that appears to be that attachment for the IRB. Do you see that?

A I see that.

Q All right. And if you look at the second paragraph in that letter, the second sentence starts with "a number." Do you see that?

MS. KIEHN: Say that again.

MR. WISNER: So the second --

MS. KIEHN: The first paragraph.

BY MR. WISNER:

Q Sorry, the first substantive paragraph,

but -- sure. You see the paragraph that starts off with "we have"?

A Yes.

Q All right. The second sentence in that paragraph says: "The number of bottles of active medication" --

A That's -- that's --

Q I guess they both start with "we have." That's confusing. All right.

MR. ELLISON: Yeah. ^ Check.

BY MR. WISNER:

Q All right. So the first --

MS. KIEHN: The top paragraph.

BY MR. WISNER:

Q -- paragraph, it says: "We have been informed" --

A Do I have the right document?

Q Yeah, you do. The paragraph that begins "we have been informed." Do you see that?

A Yes, I do.

Q So the second sentence in that paragraph.

A I got you. Okay.

Q My mistake.

It says: "A number of bottles of active

medication were mistakenly packaged with the pink-colored commercial Celexa tablets instead of the standard white citalopram tablets used for blinded clinical studies."

You see that?

A I see that.

Q That's consistent with what we read earlier in the facsimile, right?

A Yes.

Q And the next sentence reads: "As a result, dispensing these tablets would automatically unblind the study."

Do you see that?

A I do.

Q And it reads: "The study will now be replaced with the appropriate white tablets to maintain the study blind."

Do you see that?

A I do.

Q So again --

MR. ROBERTS: "This medication will now be replaced."

MR. WISNER: What did I say?

MR. ROBERTS: You said, "The study will

now be replaced."

MR. WISNER: Sorry. Let me -- let me read it again so I -- clearly I'm riddled with illiteracy.

BY MR. WISNER:

Q It says: "This medication will now be replaced with the appropriate white tablets to maintain the study blind."

Do you see that?

A I do.

Q So, again, it looks like not only is Dr. Tiseo saying to the investigators that it would automatically unblind the study, but he is encouraging the investigators to inform the IRB that dispensing the medication would automatically unblind the study.

MS. KIEHN: Objection.

THE WITNESS: Yes, I see that.

BY MR. WISNER:

Q Okay. All right. Let's go back to Exhibit 10, which is the -- that single page draft letter that had the handwriting on it.

A Yes.

Q Okay. I want to look specifically at the

handwritten portion of the document, okay?

A Sure.

Q Now, this is the handwritten comments by Dr. Flicker, okay?

He writes: "Reconsider, no letter."

I will stop there for a second. Do you think it would have been appropriate for Forest to not have notified the FDA of this dispensing error?

MS. KIEHN: Objection.

THE WITNESS: No.

BY MR. WISNER:

Q Okay. You think they should have notified?

A Yes.

Q Okay. It continues to read: "Otherwise, I recommend much less narrative, more concise: Due to a packaging error, eight randomized patients at three investigational sites had access to potentially unblinding information. The drug has been repackaged and a full complement of 160 additional patients will be enrolled under standard double-blind conditions. For reporting purposes, the primary efficacy analysis will exclude the potentially unblinded patients and a secondary analysis including them will also be

conducted. These patients will be included in all safety analyses."

Do you see that?

A For the primary analysis will exclude the potentially unblinded patients (reading to himself).

Q Do you see that?

A Okay. I do see that.

Q So Dr. Flicker is recommending here that Forest will enroll a full complement of 160 patients under standard double-blind conditions, and then the primary efficacy analysis, they will exclude these patients that were subject to the dispensing error.

MS. KIEHN: Objection.

THE WITNESS: I mean, that's -- that's actually not what it says. And he's -- he's suggesting that the primary analysis should be the one that excludes the patients.

BY MR. WISNER:

Q Precisely. And he is saying -- yeah, I think we're on the same page here, Doctor. I'm sorry if I miss -- misworded that in some way.

He's suggesting that Forest is going to enroll a full complement of 160 patients under standard double-blind procedures. Do you see that?

MS. KIEHN: Objection.

THE WITNESS: That that was the original -- I mean, the original plan was to enroll 160 patients, correct?

BY MR. WISNER:

Q Yeah. So it looks like he's saying here that they tell the FDA, Listen, we're going to enroll a full complement of 160 patients under standard double-blind conditions, and for these nine patients that were subject to the dispensing error, we're going to exclude them from the primary efficacy analysis.

MS. KIEHN: Objection.

BY MR. WISNER:

Q That's what he's written here, right?

A That's -- that appears to be what it's -- what they're saying.

Q Okay, great.

(Exhibit No. 12 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what has been marked as Exhibit 12 to your deposition. This is another internal document that has been produced by Forest in

this litigation.

As you can see on the top there, there is an e-mail from Dr. Tiseo. It's addressed to Dr. Olanoff, Dr. Gergel, Amy Rubin and Anjana Bose as well as Tracey Varner, Julie Kilbane and Dr. Flicker.

Do you see that?

A I see that.

Q And the subject of the e-mail reads "Letter to FDA for CIT-18." Right?

A Yes.

Q And it's dated March 8th, 2000. Do you see that?

A I do.

Q So this is six days after the facsimile that was sent to the investigators, which was March 2nd.

A Yes.

Q In the e-mail Dr. Tiseo states: "Attached find the letter that Charlie and I put together for the purpose of informing the FDA of our packaging mishap in the citalopram pediatric study."

Do you see that?

A I do.

Q And if you see attached to the document is a letter or a document titled "Letter to FDA Draft." Do you see that?

A I'm sorry, which page are you on?

Q It's on the next page, attached to this document is a document that is titled "Letter to FDA Draft." You see that?

A Yes.

Q Also dated March 8th, 2000.

A I -- I see that.

Q Now, as we know from earlier, Dr. Olanoff, Dr. Gergel, and Dr. Flicker were all signatories to the study protocol for MD-18, right?

A Yes.

Q And we know that Dr. Flicker was the senior medical director at CNS and that Dr. Tiseo was the one overseeing the conduct of the study.

MS. KIEHN: Objection.

THE WITNESS: I see that, yes.

BY MR. WISNER:

Q Okay. Now, here is the -- the letter that was actually drafted.

It reads: "The purpose of this letter is to inform the agency that due to a clinical supplies

packaging error for the above-referenced trial, eight randomized patients at two investigational sites were dispensed medication that could have potentially unblinded the study. The drug for this study has since been repackaged and a full complement of 160 patients will be enrolled under standard double-blind conditions."

Do you see that?

A I do.

Q This appears to closely track Dr. Flicker's handwritten comments in the previous document we looked at, right?

A Yes.

Q The letter, however, no longer discloses how the investigators -- sorry. The letter no longer discloses how Forest learned about the dispensing error, does it?

A No.

Q It doesn't talk about how investigators had called Forest asking why some of their patients were getting pink pills and some were getting white, right?

A Correct.

Q All right. It goes on to read, the

second paragraph: "For reporting purposes, the primary efficacy analysis will exclude the eight potentially unblinded patients with a secondary analysis including them also to be conducted."

Do you see that?

A I do.

Q So that sentence read with the previous one about enrolling a full complement of 160 patients under standard double-blind conditions indicates that Forest intended to get a full cohort of patients that they would conduct a primary efficacy analysis on, correct?

MS. KIEHN: Objection.

THE WITNESS: Correct.

BY MR. WISNER:

Q And they planned to not include these patients who were subject to the dispensing error, at least in the primary efficacy analysis, right?

A Yes.

Q And that they would submit separately a secondary analysis which included these potentially unblinded patients.

Do you see that?

A I do.

Q Now, a minute ago, you said that the cardinal thing that's important for a clinical trials validity is that the randomization be maintained, right?

A Yes.

Q Now, if they're planning to enroll a full complement of 160 randomized patients, focusing just on those newly randomized patients wouldn't compromise the validity of the study, would it?

MS. KIEHN: Objection.

THE WITNESS: Say -- say again.

BY MR. WISNER:

Q So they plan to randomize 160 new patients into the study under standard double-blind conditions, right?

A Yes.

Q If they were to focus exclusively on that 160 newly randomized cohort, that wouldn't affect the validity of the randomization of the study, would it?

MS. KIEHN: Objection.

THE WITNESS: Well, they're not -- it looks like for the primary analysis that they're proposing, they would not include the -- and I'm

confused about eight versus nine, I thought it was nine patients. I don't know how we get from there to eight. But regardless, he is saying here that they're going to exclude those patients from the primary analysis.

BY MR. WISNER:

Q Precisely. And so I guess my question is, is if they did in fact do that, if they did enroll a full 160 patient cohort under proper fully standard double-blind randomized conditions, the issue of validity regarding randomization would still be kept intact, wouldn't it?

MS. KIEHN: Objection.

THE WITNESS: I -- the problem with that is, is that they're excluding eight randomized patients. And so from my standpoint, that should not be the primary analysis. The primary analysis should include all originally randomized patients. And an exploratory, a sensitivity analysis might be done that looks at -- at all randomized patients, less -- you know, excluding those who had had this -- this problem.

BY MR. WISNER:

Q Now, Forest's decision at this time to

exclude these patients who were subject to the dispensing error, patients that Dr. Tiseo said were automatically unblinded, that would be consistent with a practice of making sure that the patients' data that was analyzed was based on -- on -- was based on double-blind data, correct?

MS. KIEHN: Objection.

THE WITNESS: That -- that would -- that appears to be the intent.

BY MR. WISNER:

Q And in fact, that would be consistent with my reading of the study protocol, which says if there is an unblinding for any reason, the patient should be discontinued and no further efficacy assessments conducted.

MS. KIEHN: Objection.

THE WITNESS: That -- that -- that appears to be the case.

BY MR. WISNER:

Q So it appears, at least from what we see here, that Forest actually read the study protocol the way that I was suggesting it should be read, correct?

MS. KIEHN: Objection.

THE WITNESS: That -- that appears to be the correct -- what I don't know is -- is the analysis that we saw in the study report, if the primary analysis that led to the P-value of 0.038 was this one that excluded the -- the eight unblinded patients.

BY MR. WISNER:

Q I promise you, Doctor, we will get there.

A Okay.

Q Okay, great.

(Exhibit No. 13 was marked for identification.)

BY MR. WISNER:

Q I'm handing you a document that has been marked as Exhibit 13 to your deposition.

This is another document that has been produced in the course of this litigation by Forest. As you can see, this document contains a series of e-mails.

Do you see that?

A Yes.

Q All right. So the way you read e-mail chains is you've got to start from the back and move forward, okay?

So please turn to the last e-mail exchange in the document.

A Okay.

Q All right. That e-mail is dated March 8, 2000 and -- 2000, right?

A I -- yes, I see that.

Q And that's actually the e-mail we just looked at a second ago. Do you see that?

A Yes. Yes.

Q Okay. In response to that e-mail, do you see it -- it goes between page 1 through page 3, but there is a response from Amy Rubin dated March 9, 2000, at 8:56 a.m., and she writes an e-mail that is in response to Dr. Tiseo's e-mail.

Do you see that?

A So -- so the -- the e-mail on the first page, the first one is in response to the -- the last one?

Q No, no. If you look at -- on page 1 at the very bottom, it says, "Subject" -- you see that?

A Yes.

Q Okay. That is the e-mail, and it spans -- if you look, it goes on to page 2 --

A I see.

Q -- and on to page 3.
A I see. I see. That's the next one.
Q Yeah, that's the one that's in response to Dr. Tiseo's e-mail. Do you see that?
A Yes.
Q Okay. Now, Dr. Tiseo's e-mail, it says: "Please review and send your comments back to me within the next few days." Do you see that?
A Yes.
Q Okay. And if you look at the response from Amy Rubin, starting on the top of page 2, it says: "Paul, I have taken the liberty of editing your letter as follows. Please make any other" --
A I -- I'm sorry, where?
Q I'm sorry. The top of page 2.
A Okay.
Q Amy Rubin says: "Paul, I have taken the liberty of editing your letter as follows. Please make any other changes you feel are necessary."
You see that?
A Yes.
Q So it appears that she has taken up Dr. Tiseo's request that people review the proposed letter. Do you see that?

A Yes.

Q And then you see below that there appears to have been copy and pasted revisions or changes to the letter.

Do you see that?

A Yes.

Q And it reads here: "We are taking this opportunity to notify the division of a clinical supply packaging error for Study CIT-MD-18," open paren, "sites," several dashes, close paren.

Do you see that?

A I'm sorry?

Q Okay. So right under the word "Amy," there appears to have been copied and pasted her version of the letter in response to Dr. Tiseo.

A Yes.

Q Okay. So I just read you the first sentence.

A Okay.

Q Do you see that?

A Yes.

Q Okay. All right. It goes on to read: "Due to this error, medication was dispensed to eight randomized patients in a fashion that had the

potential to cause patient bias."

You see that?

A I do.

Q It goes on to read: "At no time was patient safety an issue. Upon notification of this error, Forest immediately requested that all study drug be accounted for and shipped back to Forest facilities. Upon receipt, the drug was correctly packaged and resent to the sites. Additionally, a fax was sent to the sites explaining the error, the corrective measures taken, and suggesting that although it was not a safety issue, that their IRBs be notified."

Do you see that?

A Yes.

Q And that's all consistent so far with the documents that we've reviewed, right?

MS. KIEHN: Objection.

THE WITNESS: Right.

BY MR. WISNER:

Q Now, it says here: "Upon -- upon receipt, the drug was correctly packaged and resent to the sites." You see that?

Let me just ask you a general question.

Based on what Ms. Rubin cites here, Forest had the investigational sites send all the incorrectly colored tablets to them.

Do you see that?

MS. KIEHN: Objection.

THE WITNESS: Right.

BY MR. WISNER:

Q So the patient was already randomized in the study and they were receiving pink tablets at that point.

A Right.

Q This suggests that they were now switched to white ones.

MS. KIEHN: Objection.

THE WITNESS: That's what it appears to suggest. They replaced the kits with ones that had white tablets rather than --

BY MR. WISNER:

Q If that happened to a patient that had already been randomized in the study, do you think that might have the potential to unblind the patient?

MS. KIEHN: Objection.

THE WITNESS: Well, it would certainly confuse the patient. Whether -- whether or not --

whether or not they were unblinded is another question, but it certainly would be confusing to them.

BY MR. WISNER:

Q Okay. All right. In response to this e-mail, so on page 1, you see that Dr. Flicker responds to Amy Rubin. You see that?

A Yes.

Q And this is dated March 14th, 2000. Do you see that?

A Right.

Q That's about five days after Amy Rubin's proposed edits.

A Yes.

Q And he writes: "Although," quote, "potential to cause bias," unquote, "is a masterful stroke of euphemism, I would be a little more up front about the fact that the integrity of the blind was unmistakenly violated."

You see that?

A I do.

Q It appears that Dr. Flicker has taken issue with Amy Rubin's editing of the letter to state "potential to cause bias," correct?

MS. KIEHN: Objection.

THE WITNESS: I see that, yes.

BY MR. WISNER:

Q According to Dr. Flicker, the phrase "potential to cause bias" in a letter to the FDA is "a masterful stroke of euphemism." You see that?

MS. KIEHN: Objection.

THE WITNESS: I do.

BY MR. WISNER:

Q According to Dr. Flicker, the phrase "potential to cause bias" is not being up front with the FDA; isn't that right?

MS. KIEHN: Objection.

THE WITNESS: That's what it says.

BY MR. WISNER:

Q According to Dr. Flicker, Forest should just be up front about the fact that the integrity of the blind was unmistakenly violated, right?

MS. KIEHN: Objection.

THE WITNESS: That's what it says.

BY MR. WISNER:

Q Now, we reviewed the final study report for MD-18. Nowhere in that study report that we reviewed, the portions that we looked at, did it

state that the integrity of the blind was unmistakenly violated, did it?

A No.

Q In fact, the final study report stated that they were otherwise blinded, didn't it?

A It -- it suggests that there was a potential for unblinding, but didn't acknowledge that -- that the investigators at least, if they received -- if they noticed that the tablets had the -- you know, the name "Celexa" on them and were commercial tablets, that the investigators at least would have -- would have been unblinded with regard to those patients.

Q Before we get to the next e-mail, does it concern you that the clinical medical director at the time, Dr. Flicker, believes that a letter that is being proposed to the FDA contains "a masterful stroke of euphemism"?

MS. KIEHN: Objection.

THE WITNESS: Yeah, no, that's -- that's concerning, I would say.

BY MR. WISNER:

Q Okay. Let's take a look at Mrs. Rubin's response. Do you see the -- the response right above

that that's dated March 15, 2000?

A I do.

Q This is the day after Dr. Flicker's e-mail. Do you see that?

A I do.

Q She states: "Thanks for the compliment. Part of my job is to create," quote, "masterful," unquote, "euphemisms to protect medical and marketing."

Do you see that?

A I do.

Q Now, I will represent to you Amy Rubin was in regulatory affairs for Forest.

Does it concern you that an employee for Forest whose job it is to interact with the FDA states that it's part of her job to "create masterful euphemisms to protect medical and marketing"?

MS. KIEHN: Objection.

THE WITNESS: It -- it is objectionable. I mean, my -- my expectation of -- of companies is that they will be, you know, completely transparent with -- with the FDA about what happened in the conduct of a trial.

BY MR. WISNER:

Q Now, earlier in 2013 you were actually asked to be an expert for Forest, weren't you?
A An expert in -- in litigation, yes.
Q For the Brown case, correct?
A Yes.
Q And, actually, one of the --
THE VIDEOGRAPHER: Doctor, if you would, I think your phone is in your shirt pocket.
(A discussion was held off the record.)
THE VIDEOGRAPHER: Excuse me.
MR. WISNER: No problem.
BY MR. WISNER:
Q I'm sorry, Doctor, you were saying you believed that it's important for pharmaceutical companies to be straightforward and honest with the FDA, right?
A Yes.
Q And does it concern you -- and I'm sorry if I asked this question already, but I got distracted, so I just want to keep the record clear.
Does it concern you that Ms. Rubin, whose job it was to interact with the FDA, believes that it's her job to "create masterful euphemisms to protect medical and marketing"?

MS. KIEHN: Objection.

THE WITNESS: What -- what concerns me is -- is that -- you know, what was represented to FDA was not precisely what happened.

BY MR. WISNER:

Q Doctor, it kind of looks like Ms. Rubin here is bragging about misleading the FDA, doesn't it?

MS. KIEHN: Objection.

THE WITNESS: I -- it -- I must say I -- I find that kind of language objectionable. But, again, what I mostly object to is, is the fact that Forest apparently knew that -- that it wasn't just a difference in coloring. The tablets that were sent actually had the brand name on them. That appears to be what happened. It would have been more transparent to say that.

I'm not sure that it would have made a difference in this case, you know, based on the data that I've seen, but I think it would have been more up front to -- to be, you know, transparent with FDA.

BY MR. WISNER:

Q Now, I -- this is where I was going earlier and now I remember. In 2013, you were asked

to provide expert testimony for Forest in a pediatric suicide case involving Lexapro, correct?

A That's correct.

Q And one of the things that you were offered as an expert on was whether or not Study MD-18 was in fact positive for efficacy. Isn't that true?

A That's correct.

Q In preparing you to testify under oath and to put your reputation on the line, did Forest disclose these e-mails to you?

MS. KIEHN: Objection. I'm going to instruct the witness not to reveal any communications that you had with Forest counsel. So if you can answer that question independent of any communications you had with counsel, you can go ahead and answer.

MR. GRIFFIN: He's a disclosed expert, and you're instructing him not to answer --

MS. KIEHN: I am.

MR. GRIFFIN: -- about conversations with outside counsel?

MS. KIEHN: In this litigation, yes.

MR. WISNER: To be clear, Ms. Kiehn, I'm

asking about whether or not you showed him -- I'm sorry, I'm referring to counsel showed him a document in his capacity as an expert testimony. Is it your claim that a document relied on by an expert constitutes privileged communication?

MS. KIEHN: You didn't ask him about a document.

MR. WISNER: Well, okay.

MR. GRIFFIN: Read the question back.

MR. WISNER: Read the question --

MS. KIEHN: Well, you said disclosed these e-mails.

MR. WISNER: So can you please read the question back?

(Whereupon, the requested record was read.)

THE WITNESS: I don't -- I don't recall seeing these e-mails, but, again, that was coming up on almost four years. So -- but I don't recall seeing them.

BY MR. WISNER:

Q If you had seen the document where Ms. Rubin was talking about using masterful euphemisms to protect medical and marketing, that's

something you probably would have remembered?

MS. KIEHN: Objection.

THE WITNESS: I -- I -- I likely would have, but I honestly don't know whether or not I -- I saw it, but I don't think so.

BY MR. WISNER:

Q Let me ask you this, Doctor: Whether or not you did see them or not, do you think that before asking you to put your reputation on the line as an expert testifying on behalf of Forest, they should have shown you these e-mails?

MS. KIEHN: Objection.

THE WITNESS: I -- I would like to have seen everything.

(Exhibit No. 14 was marked for identification.)

BY MR. WISNER:

Q I'm handing you a document that is marked as Exhibit 14 to your deposition.

This appears to be a letter dated March 20th, 2000, from Tracey Varner, manager of Forest Regulatory Affairs, addressed to Russell Katz, director of the Division of Neuropharmacological Drug Products in the FDA.

Do you see that?

A Yes.

Q Have you ever seen this letter before?

A I -- I don't recall seeing it, but -- but, again, if the letter was sent in March of 2000, that's almost 17 years ago. So I -- even if I had seen it, I wouldn't have remembered it.

Q Okay. This appears to be the final draft of the letter that was actually sent to the FDA regarding the dispensing error, doesn't it?

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q And it -- it appears to have been stamped by the FDA received March 21st, 2000. Do you see that?

A Yes.

Q Do you recall who Dr. Katz is?

A Well, Dr. Katz was the division director.

Q He was your boss at the time?

A Yes.

Q Okay. And in fact, when Dr. Katz left or changed divisions, you replaced him, correct?

A Well, the division split into two

divisions, and so he remained as division director of the neurology division. I became the division director of the newly formed psychiatry division.

Q Okay. Now, the document reads: "We are taking this opportunity to notify the division of a clinical supply packaging error for Study CIT-MD-18. Due to this error, medication was dispensed to eight randomized patients in a fashion that had the potential to cause patient bias."

Do you see that?

A Yes.

Q So that language that Dr. Flicker called "a masterful stroke of euphemism," it made it into the letter, didn't it?

MS. KIEHN: Objection.

THE WITNESS: Well, this version of the letter was the one that was sent to FDA apparently.

BY MR. WISNER:

Q So -- exactly. So the language that Dr. Flicker said was "a masterful stroke of euphemism" and wasn't being up front with the FDA, that actually made it into the final letter sent to the FDA, didn't it?

MS. KIEHN: Objection.

THE WITNESS: This version of the letter is -- is the modified version, yes.

BY MR. WISNER:

Q Okay. Now, the second paragraph, which is just one sentence, it reads: "A full complement of 160 patients will be enrolled under standard double-blind conditions."

Do you see that?

A I do.

Q What is your understanding of the meaning of that sentence?

A As I recall, the original plan was to enroll 160 patients. This -- this suggests that -- to me, it -- it's a little bit unclear, but it suggests to me that -- that eight additional patients will be enrolled to bring the complement up to 160, you know, excluding those eight patients who had -- you know, had been exposed to the knowledge of -- of the actual tablet.

Q The next sentence --

A But, again, I'm not -- I'm not entirely clear about it. It's a little bit unclear to me exactly who was included in the primary analysis at this point.

Q Sure. The next sentence reads: "For reporting purposes, the primary efficacy analysis will exclude the eight potentially unblinded patients with a secondary analysis including them also to be conducted."

Do you see that?

A I do.

Q It appears that Ms. Varner is stating in this letter that Forest plans to exclude the patients from the primary efficacy analysis, doesn't she?

MS. KIEHN: Objection.

BY MR. WISNER:

Q Let me rephrase that.

It appears from this letter that Ms. Varner is telling Forest that they plan to exclude those eight potentially unblinded patients from the primary efficacy analysis?

A That -- that's what it says.

MS. KIEHN: Objection.

BY MR. WISNER:

Q And it says, instead, that Forest will include those potentially unblinded patients in a secondary analysis. Do you see that?

A I do.

Q Okay. It appears that Forest did the exact opposite when it finally issued its final study report, didn't it?

A Right. Because what -- if I'm looking at -- at my memo and -- and Dr. Hearst's review, our understanding was that the primary analysis included all patients, including, you know, those patients who were exposed to this medication error, and the sensitivity analysis excluded them, rather than the other way around.

Q So it just appears that between when Forest sent this letter and when it finally submitted its final study report, it did the exact opposite of what it said it would do in March of 2000.

A Well, if -- if -- what we saw in the study report was a primary analysis that included all patients, and then a sensitivity analysis that excluded those patients. In my view, that -- that is the correct thing to do.

Q I understand. But it's the exact opposite of what Forest --

A I -- I --

Q -- said it was going to do.

A Yes. Yes. But I -- you know -- and,

again, I don't -- I don't recall seeing this letter. I don't know that -- I mean, what happens with these letters is that, you know, they come into the file. It goes initially to -- to the primary reviewer, even if it's addressed to Dr. Katz, but I'm sure Dr. Katz didn't see this. I may have not seen it. Again, it's 17 years ago. I can't possibly know.

If I had seen this, I would -- I would likely have objected to this plan, you know, to exclude the eight patients from the primary analysis. But, you know, it looks like they eventually did what we ordinarily would have expected is to include all patients in the primary analysis.

Q Now, Doctor, at this point in March of 2000, when Forest is saying they're not going to include them in the primary analysis, Forest doesn't know the results of the study, does it?

MS. KIEHN: Objection.

THE WITNESS: They -- they could not have.

BY MR. WISNER:

Q Yeah.

When they submitted the final study report where they did include the results of the

unblinded patients in the primary efficacy analysis, they did know the results, didn't they?

MS. KIEHN: Objection.

THE WITNESS: That -- that's -- that's true.

MR. WISNER: All right. Let's take a break?

THE WITNESS: Well, let me -- let me qualify that. Let me qualify that.

BY MR. WISNER:

Q Sure.

A It's quite possible that when they further thought about this and talked about it with their statisticians, they changed their mind before breaking the blind and -- and decided that they should go with the original plan to include everybody.

I -- I can't -- I can't possibly know.

Q Fair enough. And that's a possibility, I grant you that, Doctor.

But I'm just saying what we do know is that in March of 2000, Forest has agreed to exclude those potentially unblinded patients from the primary efficacy analysis, correct?

MS. KIEHN: Objection.

THE WITNESS: Well, that's what this letter says.

BY MR. WISNER:

Q Okay.

A I would like to see whether or not there was an amendment to the analysis plan reflecting that as well. Because the -- the analysis -- it appears that -- that the original analysis plan was -- was followed.

Q Okay. Fair enough, Doctor. I -- we can get into a lot -- that nuance later, we will after the break.

I guess my question, though, is as of March 2000, this letter is representing that Forest intends to exclude those potentially unblinded patients from its primary efficacy analysis.

A That -- that's what -- that's what this letter says, yes.

Q Okay. And we also know that in the final study report, they included those potentially unblinded patients in the primary efficacy analysis.

A Which -- which is -- which is what the original analysis plan very likely called for.

Q Sure.

And we know that in March of 2000 when they sent this letter, Forest didn't know the results of the study because it wasn't completed yet.

A They -- they couldn't possibly have known then.

Q Okay. And then -- I don't want to go down the rabbit hole. I'm trying to keep it simple, Doctor. And we know that when they submitted the final study report in April of 2002, they did know the results, right?

MS. KIEHN: Objection. Asked and answered.

THE WITNESS: Well, when they submitted the second report, but we don't know -- what we don't know is when the decision was made to go back to the original analysis plan.

BY MR. WISNER:

Q Sure.

A When they made --

Q Yeah, whether or not they made that decision knowing the results or not, we don't know that. Is that what you're saying?

A That's what I'm saying.

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

MS. KIEHN: Lunch break?

MR. WISNER: Yeah.

THE VIDEOGRAPHER: The time is 1:09 p.m. We will go off the video record.

(Lunch recess.)

THE VIDEOGRAPHER: The time is 2:06 p.m. We're back on the video record.

(Exhibit No. 15 was marked for identification.)

BY MR. WISNER:

Q Hi, Doctor.

A Hi.

Q I'm handing you a document that has been marked as Exhibit 15 to your deposition. This is an e-mail from Joan Barton to Dr. Tiseo, Dr. Flicker, Joan Howard, Jane Wu and Carlos Cobles dated December 6, 2000.

Have you ever seen this document before?

A I don't recall seeing it.

Q Okay. You recall earlier that we -- we discussed that Ms. Barton was the clinical trial manager. Do you recall?

A Yes.

Q It reads: "Attached is a table showing which patients were randomized when the problem was discovered that the study drug was unblinded. A total of six adolescents and three children had already been randomized. Please let me know if this will alter the total number of child or adolescent patients to be randomized for this trial."

Do you see that?

A Yes.

Q This is dated in December of 2000. Do you see that?

A Yes.

Q So this is about seven months, eight months after the dispensing error occurred; is that right?

A Yes.

Q And you know at this point in the trial they had not unblinded the results yet, right?

A Right.

Q She states here: "The problem was discovered that the study drug was unblinded."

Do you see that?

A Yes.

Q She doesn't state that it was potentially unblinded, right?
A Correct.
Q Or that it had the potential to cause patient bias, does she?
A No.
Q It also says that a total of six adolescents and three children had been randomized.
Is it fair to say that based on that statement, it looks like the majority of the dispensing error occurred in patients in the adolescent arm?
MS. KIEHN: Objection.
THE WITNESS: Well, two to one.
BY MR. WISNER:
Q Yeah. Six to three, right?
A Yeah.
Q Okay. All right. If you turn the page, this is the attached table that she referenced in her e-mail.
Do you see that?
A Yes.
Q And it states that this is CIT-MD-18 study drug packaging error, site tracking March 1st,

2000.

Do you see that?

A Yes.

Q This suggests that Forest became aware of the dispensing error at least as of March 1st, 2000. Do you see that?

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q And it lists here all the various investigator sites. Do you see that?

A Yes.

Q And it appears that the dispensing error occurred in patients in the Busner, Harmon and Wagner investigational sites.

Do you see that?

A Yes.

Q Do you know Dr. Busner?

A I've heard the name. I don't -- I don't even know if it's a him or a her.

Q Okay. Fair enough.

Do you know Dr. Harmon?

A Again, the name is familiar, but I -- I don't -- I don't.

Q Well, you sure know Dr. Wagner, right?

MS. KIEHN: Objection.

THE WITNESS: Well, I know -- I know the name. I don't -- I don't know her personally. I know -- I mean, she's, you know, well known, but...

BY MR. WISNER:

Q Sure. And Dr. Wagner is known for her work specifically in pediatric depression, right?

A Correct.

Q It appears based on this chart that four of the nine patients subject to the dispensing error occurred at her site.

Do you see that?

A Yes.

(Exhibit No. 16 was marked for identification.)

BY MR. WISNER:

Q I'm handing you a document that's been premarked as Exhibit 16 to your deposition.

Let's keep them in order.

A Okay.

Q I will help you out here.

A Okay.

Q Let's get them all in order.

A Okay.
Q Exhibit 14, do you have it right here?
A Sorry. Yes.
Q That one right there (indicating)?
A This is my -- this is my -- oh, this one here.
Q Yeah. I'm just going to put them all together so they're all in order.
A Okay. All right. This is 7.
Q Okay. All right. I think I got them mostly in order.
A And here is 7.
Q Okay, great.
Okay. I just handed -- I'm going to hand you -- I just handed you Exhibit 16. There you go.
All right. These are a series of documents, e-mail exchanges that were produced by Forest in this litigation ranging from August 9th, 2001, through August 10th, 2001. The first e-mail appears to have been sent by Jane Wu to Dr. Tiseo and Dr. Flicker on August 9th, 2001.
Do you see that?
A Yes.
Q Okay. I will represent to you that

Jane Wu was one of the lead statisticians on Study MD-18 within Forest.

Her e-mail reads: "Paul, Charlie, we will meet with you to talk about the results of CIT-18 in the R&D conference room at 9:30 to 10:30 a.m., August 10th."

Do you see that?

A I do.

Q Now, if you see the next e-mail, she appears to have forwarded that e-mail to James Jin and Qiong Wang.

Do you see that?

A Yes.

Q I think it's Qiong Wang.

Okay. I will represent to you also that Mr. Jin and Ms. Wang were both biostatis- -- biostatisticians working at -- at Forest on MD-18.

This e-mail from Ms. Wu to Mr. Jin and Ms. Wang appears to have been sent shortly after midnight.

Do you see that?

A Yes.

Q And it reads: "We need to generate Tables 4.1A and 4.1B for ITT population, excluding

the nine patients who were unblinded at the beginning of the study. Can you please tell Qiong who they are and try to get the results before 9:30 Friday morning."

Do you see that?

A I do.

Q Ms. Wu has characterized these patients as being unblinded at the beginning of the study.

Do you see that?

A I do.

Q She does not say "potentially unblinded." Do you see that?

A Yes.

Q And she references Tables 4.1A and 4.1B, right?

A Yes.

Q And she appears to be trying to obtain Tables 4.1A and 1B without the nine unblend -- unblinded patients included; isn't that right?

A Correct.

Q And she appears to be doing this in anticipation of a meeting, quote, about the results of CIT-18, right?

A Correct.

Q All right. So please turn to Exhibit 8, which is the final study report. It should be in order now.

All right. If you could please turn to page 108.

This is a document, it has the title "Table 4.1A." Do you see that?

A I do.

Q And this is Table 4.1A as it was submitted to the FDA, right?

A Okay.

Q All right. The title of it is "Change From Baseline By Visit for CDRS-R."

Do you see that?

A I do.

Q And it specifies that this is an LOCF analysis?

A Yes.

Q And it has the by week results of that primary efficacy point from week 1 to week 8.

Do you see that? It goes on to the next page.

A Oh, okay.

Q Do you see that?

A I do.
Q Okay. It appears that in the final study report the nine patients that were subject to the dispensing error were actually included in Table 4.1A, doesn't it?
MS. KIEHN: Objection.
THE WITNESS: Right.
BY MR. WISNER:
Q And that's different than what Ms. Wu has asked them to do in preparation for a meeting about the study results in August; isn't that right?
MS. KIEHN: Objection.
THE WITNESS: Well, I mean, she -- she asked for tables. She doesn't say what Table 4.1A is supposed to do here in the e-mail.
BY MR. WISNER:
Q Well, fair enough.
If we look at the final study report, Table 4.1A is the primary efficacy endpoint by week, right?
A What I -- what I don't know is what Tables 4.1A and 4.1B, how they -- how they differ.
Q Oh, we will get into the difference between 4.1A and 4.1B in one second.

A So -- so your understanding of 4.1A from this is that it excludes or does not exclude?

Q The final study report it does not exclude. Do you see that? If you look at --

MS. KIEHN: I don't think he can tell that by looking at it.

BY MR. WISNER:

Q Well, if you look at week 8, the P-value --

A Well, the P-value is -- is the P-value that was reported in the study report --

Q Exactly.

A -- for the primary analysis, presumably including all patients, including those nine patients or eight patients, whatever.

Q All right. Do you know whether or not those eight patients were included?

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

Q Okay. Let me show you something that might help you figure that out.

Turn to page -- page 70 in the final study report.

A Okay.

Q If you look underneath the chart that's graphing the study results --

A 85 and 89. N equals 85 and N equals 89, those are the numbers that were included in this analysis set that generated the P-value of 0.038.

Q There you go. So the 85 and 89 -- and that's a good way of doing it. And if you look at Table 4.1A, those are the corresponding entries.

A Okay. Okay. So -- so it includes those -- those patients.

Q Precisely.

Okay. So it appears then that Jane Wu is requesting in August in anticipation of a meeting to discuss the efficacy results -- well, let's back up. Okay. Let's back up.

On Exhibit 16, you see that this e-mail she sends is at -- on August 10th, 2001.

A Yes.

Q Okay. In this e-mail --

A Well, uh --

Q From Jane Wu on the top.

A Okay, correct.

Q So it's August 10, 2001, and that's the one that's just after midnight.

A Right.
Q And this is in anticipation of a meeting at 9:30 Friday morning, right?
A Right.
Q Okay. And in this e-mail she is asking to generate these tables excluding the nine patients --
A Right.
Q -- that were, quote, unblinded at the beginning of the study, right?
A Right. Correct.
Q Okay. Now, if you look at the final study report, on page 108 --
A Okay.
Q -- this is Table 4.1A.
Do you see that?
A Right.
Q And if you look at the top right, there is actually a date, August -- October 30th, 2001, right?
A Right.
Q So this was generated, it appears, after that meeting on August 10th, right?
A Yes.

Q Okay. So in the meeting she had asked to generate this table excluding the nine patients, but in this table that's represented to the FDA, those patients are included, aren't they?

A Yes.

Q Okay. Now, if you turn to the next table, 4.1B, which is on page 110 of the same exhibit.

A Okay.

Q And this represents the same endpoint, but instead of using the LOCF, it's using observed cases. Do you see that?

A Okay. Got you.

Q Do you see that, Doctor?

A I do. I do.

Q Okay. And if you actually look at week 8, the final week in the study, which was the prespecified endpoint, the P-value is 0.167, right?

A Correct.

Q And you agree with me that a P-value of 0.167 is not statistically significant.

A Correct.

MS. KIEHN: Objection.

BY MR. WISNER:

Q It's not a -- it's not close enough, right?

A It's not close enough.

Q Okay. All right.

(Exhibit No. 17 was marked for identification.)

BY MR. WISNER:

Q Okay. I'm handing you a document that's Exhibit 17 to your deposition.

This is another document that has been produced by Forest in this litigation containing an e-mail from Joan Howard to a large number of individuals dated September 14th, 2001.

Dr. Laughren, if you look at the recipient line in that e-mail -- it's not Joan Barton, it's Joan Howard. It's a different person. If you look at the recipient line, you will see in the recipient line Dr. Flicker, Dr. Tiseo, Jane Wu, James Jin, William Heydorn and Ms. Barton, right?

A Yes.

Q Okay. At the bottom of the e-mail, Ms. Howard writes: "Attached are minutes from the meeting held August 21st."

Do you see that?

A Yes.

Q Okay, great. And if you turn the page, there's a document attached to this titled "Forest Laboratories, Inc.'s Citalopram Clinical Team Meeting, Minutes of Meeting, August 21, 2001."

Do you see that?

A Right.

Q All right. So this appears to be the minutes of -- of a meeting that happened in August of 2000 -- August 21st of 2001, right?

A Correct.

Q And this also appears to have been after that meeting of August 10th, 2001, correct?

A Right.

Q Okay. And if you look at the -- the highlight section, there is a section that says "CIT-MD-18." Do you see the -- see that, "CIT-MD-18"?

A Correct.

Q And it says: "Databases locked and headline results available. Timing of pediatric submission needs to be determined. Final report is contracted out to Pharmanet."

Do you see that?

A Yes.

Q All right. So it appears by at least this point in August of 2001 that the database has been in fact locked and that they had the results of the study.

A Correct.

Q All right. Are you familiar with a company called Pharmanet?

A I -- I've heard the name. It's a -- it's one of many companies that I believe provides services to -- to drug companies. I don't know if they do primarily data analysis or what they do, but I -- I have heard the name. I honestly don't know exactly what they do.

Q Okay. It appears here that they've contracted out to Pharmanet to help prepare the final study report; is that right?

A Yes.

Q Is it -- have you heard of something called a contract research organization?

A Yes. Yes.

Q Is Pharmanet a contract research organization?

A I -- I -- based -- based on what's

characterized here, they probably would -- would fall under that general rubric of a contract research organization. Contract research organizations assist companies in various ways, often in the conduct of a trial and other things. So I --

Q Is it unusual in your experience for a company like Forest to contract with a CRO to help prepare a final study report?

A I just don't know the answer to that. I...

Q Okay. Do you have any opinion about whether or not it's appropriate for a drug company to use a contract research organization to prepare a report to be submitted in a regulatory filing?

A I don't have an opinion one way or the other.

Q Okay. In the submit -- in the submitting of a final study report to the FDA, do you think it's -- the fact that a contract research organization was used to prepare it should have been disclosed?

A I -- I -- I don't -- I don't -- you know, I don't have an opinion about that. I -- you know, the assumption is that however -- however the study

is conducted, however the data are analyzed, however the study report is put together, that it has -- it has to follow, you know, certain basic standards. And whether that's done within the company or whether it's contracted out, I -- I don't -- I don't know that FDA has a particular concern about that. I...

Q At the end of the day, though, the accuracy and content of a final study report, the buck stops with the drug sponsor submitting it, right?

A Yeah, no, they --

MS. KIEHN: Objection.

THE WITNESS: They take -- they have to take responsibility for the final product that they're submitting.

BY MR. WISNER:

Q Great.

(Exhibit No. 18 was marked for identification.)

BY MR. WISNER:

Q I'm handing you a document, it's Exhibit 18 to your deposition.

This document contains excerpts of a deposition taken of William Heydorn on August 29th,

2007, in the In re Forest Laboratories, Inc. Securities litigation.

By any chance, have you ever seen this deposition before?

A No, I don't. I don't -- I don't recall seeing it.

Q Okay. If you could turn to page 42 of the deposition. It shouldn't be too many pages in there. It's just the excerpts.

Are you there, Doctor?

A I am there.

Q Okay. Starting on line 16, it reads:

"Q. Did you have any role in the creation of the study report for CIT-MD-18?

"A. Yes.

"Q. And what was your role?

"A. I was the primary author on the study report for CIT-MD-18.

"Q. When you say 'primary author,' what did that entail?

"A. I was the individual responsible for ensuring that the study report was written and

completed as accurate and was completed on time and was available when needed for submission to the FDA."

Did I read that correctly?

A Yes.

Q Okay. If you turn to page 47 in that same exhibit, line 4. Are you there?

A Yes.

Q Okay.

"Q. And what did the department work on with regards to submitting information to the FDA?

"A. So the department was responsible for writing up the clinical study report, and that was my primary -- I took on that role personally as my primary responsibility. We subcontracted that to a third party to generate the first draft of the study report, and then I worked closely with the third party and with Dr. Flicker to complete the study report, making

sure it was accurate and completely summarized the available data for submission to the FDA."

Do you see that?

A I do.

Q All right. So based on the testimony I just read you, it appears that Dr. Heydorn was the primary author of the final study report for MD-18, right?

A Correct.

MS. KIEHN: Objection.

THE WITNESS: Correct.

BY MR. WISNER:

Q It also appears, and it's consistent with the document we just looked at, that Dr. Heydorn worked with a third party to help generate the first draft of the study report, right?

MS. KIEHN: Objection.

THE WITNESS: Correct.

(Exhibit No. 19 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what has been marked as Exhibit 19 to your deposition.

Again, this is a document that has been produced in the course of this litigation. This appears to be an e-mail sent from Dr. Heydorn to several individuals dated October 4th, 2001.

Do you see that?

A Yes.

Q Okay. Copied on this e-mail are Dr. Flicker, James Jin and Jane Wu, right?

A Correct.

Q And the subject of the e-mail is, quote: Notes from Conference Call, October 4th. Do you see that?

A Yes.

Q In the body of the e-mail, it reads: "Attached are my notes from our conference call today."

Do you see that?

A I do.

Q Now, if you turn the page, there's an attachment, and the attachment is titled "Notes from Conference Call with Pharmanet, October 4th, 2001." Do you see that?

A I do.

Q And it appears that from Forest,

Dr. Flicker, Dr. Heydorn, James Jin and Jane Wu were participants for Forest, right?

A Yes.

Q And it appears to have two participants from Pharmanet.

Do you see that?

A Yes.

Q I don't know how to say their names, but do you -- do you recognize those individuals from Pharmanet?

A No.

Q Okay. This document appears to contain the notes of a conference call that Forest had with Pharmanet regarding Study MD-18, doesn't it?

A Yeah --

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q All right. Now, if you look down at point 11, it's the second to the bottom.

A Yes.

Q It states: "Dosing error. Some citalopram tables" -- and I will tell you that Dr. Heydorn has subsequently testified that that

should read "tablets," so I'm going to read it that way -- "There was a dosing error. Some citalopram tablets were not blinded. The nine patients who received unblinded medication were included in the main analysis. A secondary post hoc analysis of the ITT subpopulation was done. Refer to these analyses briefly in the methods and results, and reference the reader to the appendix table."

Do you see that?

A I do.

Q That appears to be what they ultimately did in the final study report, correct?

MS. KIEHN: Objection.

THE WITNESS: Correct. That's what it appears that that's indicating, yes.

BY MR. WISNER:

Q Okay. Notably, he says that the nine patients who received the unblinded medication were included in the main analysis. It does not state that the patients were potentially unblinded, does it?

MS. KIEHN: Objection.

THE WITNESS: It -- it says they received unblinded medication.

BY MR. WISNER:

Q So it appears, at least at this point when they're meeting with Pharmanet in October of 2001, Forest had made the decision to renege on its statement to the FDA that it would not include the potentially unblinded patients in the prior efficacy analysis, correct?

MS. KIEHN: Objection.

THE WITNESS: I don't know that that's correct. I don't know based on what you've given me whether or not there was a change in the analysis plan consistent with what was written in that -- in that e-mail that -- that basically that memo or whatever it was to the FDA, a letter -- I forget whether it was a letter or an e-mail or what it was, it was probably a letter -- in which they said that the primary analysis would -- would not include them.

BY MR. WISNER:

Q Sure.

And I guess my question is, it appears by this point in October of 2001, Forest had made the decision to not do what it said it would do in that letter, correct?

MS. KIEHN: Objection.

THE WITNESS: That -- that appears to be the case. Yes.

(Exhibit No. 20 was marked for identification.)

BY MR. WISNER:

Q All right. Coming at you fast here, Doctor. I'm handing you what has been marked as Exhibit 20 to your deposition.

Thank you.

All right. These are the excerpts of a deposition taken of William Heydorn taken on -- the deposition of William Heydorn taken in this litigation, in this case on October 14th, 2016. Okay?

A Okay.

Q Have you ever seen this deposition transcript before?

A I don't -- I don't believe so, no.

Q All right. During the course of Dr. Heydorn's deposition we showed him many of the documents that I've shown you today about the unblinding and the e-mail correspondence, and he provided testimony. And considering he was the primary author on the report, I would like to show

you what he had to say, okay?

MS. KIEHN: Objection. You're testifying.

BY MR. WISNER:

Q Okay?

A Yes.

Q I'm just telling you that's what I'm going to do. Just telling you what I'm doing.

All right. So let's start off with page 87, and these are just excerpts so they -- they should all be pretty much one after the other.

A Okay.

Q On page 87, it reads: "So" -- on line 19, it reads:

"So with the dispensing error patients excluded from the MD-18 primary efficacy outcome measure, Celexa failed to -- failed to significantly outperform placebo in treating pediatric depression. Right?

"MR. ABRAHAM: Objection.

"THE WITNESS: "That appears to be the case.

BY MR. BAUM:

"Q. Would it an important substantial diff-" -- sorry.

"Q. That would be an important substantial difference, wouldn't it?

"MR. ABRAHAM: Objection.

"THE WITNESS: Yes."

According to Dr. Heydorn, excluding those nine patients rendered the results of the study no longer statistically significant.

Do you see that.

MS. KIEHN: Objection.

THE WITNESS: I -- I see that's what he says, yes.

BY MR. WISNER:

Q And he also agrees that that shift in statistical significant on the primary endpoint was an important and substantial difference.

Do you see that?

MS. KIEHN: Objection.

THE WITNESS: I -- I see that's what he said, yes.

BY MR. WISNER:

Q Okay. Turn to page 109. I'm sorry, turn

to page 107.

A 107. Okay.

Q On line 13:

"Q. So if these eight patients or nine patients who were unblinded or if the investigators working with them were unblinded, the efficacy scores for those individuals should not have been included in the primary outcome measure, correct?

"MR. ABRAHAM: Objection.

"THE WITNESS: Yeah. Apparently from the wording in the protocol, if they were indeed unblinded."

Do you see that?

A I do.

Q So according to Dr. Heydorn, who ultimately actually wrote the final study report, if these patients were unblinded, they should have been excluded from the primary efficacy analysis.

Do you see that?

MS. KIEHN: Objection.

THE WITNESS: That -- that -- that's what he says, yes.

BY MR. WISNER:

Q Okay. Now, if you could turn to page 157. We're going to skip a few pages. We'll come back to them later.

Are you on page 157, Doctor?

A Yes.

Q All right. Starting on the first line, it reads:

"Q. Well, if they received the pink tablets and they're being told just now that they were active medication, those patients were given active medication, correct?

"MR. ABRAHAM: Objection.

"THE WITNESS: Yes, I would assume so, yeah.

"MR. BAUM:

"Q. And the investigators would know that.

"MR. ABRAHAM: Objection.

"MR. BAUM:

"Q. They would know which patients reached them, right?

"MR. ABRAHAM: Objection.

"THE WITNESS: I would have no direct knowledge, but I would assume so.

"Q. So they were unblinded as well, correct?

"MR. ABRAHAM: Objection.

"THE WITNESS: With respect to those patients, I would assume so."

Do you see that?

A I do.

Q So it appears that Dr. Heydorn is concurring with what you said earlier that if the investigator knew that the pink pills being distributed to a patient were in fact Celexa, that would unblind the study with regards to that investigator, right?

MS. KIEHN: Objection. Misstates prior testimony.

THE WITNESS: The -- I mean, the problem is what I -- the problem is that I don't know the actual operational details of -- of what happened. I don't know if -- you know, who provided the kit to the patient. It -- it -- it may have been, you know, a different person certainly than the investigator.

I -- I don't -- I mean the problem is we're making a lot of assumptions here about -- I mean, I understand that the tablets were pink and they presumably had the Celexa brand on them, which certainly, you know, would be expected to unblind the patients if -- if they looked at that.

Whether or not the investigator -- whether or not the person who ultimately did the rating on that patient was unblinded, I don't know that from this.

BY MR. WISNER:

Q Fair enough.

But we do know that Dr. Flicker, who was a director -- medical director at Forest overseeing this trial, stated that the integrity of the blind was unmistakenly violated, right?

MS. KIEHN: Objection.

THE WITNESS: I -- yes.

BY MR. WISNER:

Q And we do know that Dr. Tiseo, the guy overseeing the conduct of the trial, he said that dispensing these medications would automatically unblind the study, right?

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q So at least according to Dr. Heydorn, Dr. Tiseo, as well as Dr. Flicker, they at least seem to have read these documents and came to the conclusion that there was an unblinding, right?

MS. KIEHN: Objection.

THE WITNESS: Well, the -- I agree that's what was said. Again, the problem is they may -- they may have meant that it was unblinded with regard to the patients. It doesn't necessarily mean that the patient doing the rating on that patient was unblinded. That's -- that's the distinction I want to make.

BY MR. WISNER:

Q I understand that, but let's -- let's use a little bit of common sense here, right. The investigators who are doing these analyses raise an issue that some of them -- their patients that they're doing this with are having white -- white pills and some are getting pink, right?

MS. KIEHN: Objection.

THE WITNESS: I agree.

BY MR. WISNER:

Q And they bring this attention to Forest, and then Forest sends them a memo explaining the whole situation, right?

A I agree.

Q And that memo says, Listen, you know, these pink tablets that you're dispensing, they're actually branded Celexa.

Do you see that?

MS. KIEHN: Objection.

THE WITNESS: I see that.

BY MR. WISNER:

Q Okay. So while I agree there's an assumption being made here, it's a pretty reasonable assumption that in response to that facsimile from Forest, the investigators -- the investigation site said, Hey, guys, those pink pills, by the way, we got the solution, it turns out that's the drug.

MS. KIEHN: Objection.

THE WITNESS: Those findings certainly raise a concern. I will -- I will agree with you there.

BY MR. WISNER:

Q Okay. Now, on page 202, it's the next one over, line 13, it reads:

"Q. Okay. If an investigator knows which patients are taking branded Celexa and which ones are taking white pills" --

A I'm sorry, which --

Q Oh, I'm sorry. We're on page 102, line 13.

A You mean 202, line 13. Okay.

Q Page 202, line 13. I apologize. It reads:

"Q. Okay. And if an investigator knows which patients are taking branded Celexa and which ones are taking white pills, doesn't that mean the integrity of the blind was un -- was mistakenly -- unmistakenly compromised?

"MR. ABRAHAM: Objection.

"THE WITNESS: It does raise questions about the integrity of the blind."

Do you see that?

A Yes.

Q And you would agree with that statement,

right?

A Yes.

Q Okay. All right. If you turn to the next page, page 218. All right. Starting on line 6 -- I'm going to read quite a bit here, so forgive me, but I will try to read it all correctly.

Starting at line 6, it reads:

"Q. Now, having seen this e-mail from Dr. Flicker and the fax from Dr. Tiseo, would you agree that the patients who are subject to the dispensing error were actually unblinded?

"MR. ABRAHAM: Objection.

"THE WITNESS: I don't know for a fact, but that's the implication from these letters, yes.

"MR. BAUM:

"Q. Does it concern you that the clinical medical director at the time, Dr. Flicker, believed that the letter being sent to the FDA contains a masterful stroke of euphemism?

"MR. ABRAHAM: Objection.

"THE WITNESS: I don't know what his frame of mind was when he wrote that.

"MR. BAUM:

"Q. But they had the obligation to be up front, truthful and honest with the FDA, correct?

"MR. ABRAHAM: Objection.

"THE WITNESS: Yes.

"MR. BAUM:

"Q. And this shows that they weren't, correct?

"MR. ABRAHAM: Objection.

"THE WITNESS: He apparently had some concerns about this, yes.

"MR. BAUM:

"Q. Well, it was more than just concerns. He said it was unmistakenly unblinded, and they said it had the potential for bias. That's a misrepresentation, isn't it?

"MR. ABRAHAM: Objection.

"THE WITNESS: It's a misrepresentation of what Charlie Flicker thought should be communicated to the FDA.

"MR. BAUM:

"Q. Did Dr. Flicker ever tell you directly that the integrity of the blind was unmistakenly violated because of the dispensing error?

"A. No."

All right. Now, if you turn to the next page, starting on page 229, line 2:

"Q. Now, when you helped draft the MD-18 study report, the MD-18 posters and the PowerPoints that were used for CME and the publication in the American Journal of Psychiatry in MD-18, were you aware that Forest personnel like Tiseo and Joan Barton and Charlie Flicker, viewed these patients as unblinded as opposed to potentially unblinded?

"MR. ABRAHAM: Objection.

"THE WITNESS: No, not to my knowledge -- not to my recollection.

"MR. BAUM.

"Q. Do you think academics and physicians exposed to the poster CME and the MD-18 journal article ought to have been apprised of the unblinding issue in order to fully weigh the pros and cons of prescribing Celexa or Lexapro to kids?

"MR. ABRAHAM: Objection.

"THE WITNESS: Probably, yes."

Do you see that, Doctor?

A I do.

Q Now, do you agree with Dr. Heydorn that this issue of the unblinding should have been disclosed by Forest in its publication of the results regarding Study MD-18?

MS. KIEHN: Objection.

THE WITNESS: I -- I -- I think in -- in full transparency, it should have been more fully disclosed both to FDA in the final study report and -- and it's reasonable, as -- as we did in our

reviews, to mention the potential unblinding in our reviews. So I -- I do agree with -- with that statement.

MR. WISNER: Thank you.

Let's take a break so he can change the tape.

THE VIDEOGRAPHER: The time is 2:41 p.m. This is the end of disc No. 3. We'll go off the video record.

(Recess.)

THE VIDEOGRAPHER: This is the beginning of disc No. 4 in the deposition of Dr. Thomas Laughren. The time is 2:48 p.m. Back on the video record.

BY MR. WISNER:

Q All right. Now, if you turn to page 307 in Exhibit 20, which is the deposition of Dr. Heydorn, do you see the line starting at 21, Doctor?

A I do.

Q All right. It reads:

"Q. Do you have any regrets about your involvement with the CIT-MD-18 based on what I've shown you today?

"A. I wish we had done things a little differently.

"Q. Like what?

"A. I wish I had known for certain whether the patients -- those nine patients were unblinded. But obviously I don't. You showed me a lot of documents today suggesting that people knew the patients were unblinded. I don't know for a fact that they knew that. All I know is what they wrote on the paper. I wish I was aware of the correspondence with the FDA.

"Q. Do you think based on what I've shown you today that Forest misled anyone about the results of MD-18?

"A. It probably should have been more forthcoming."

Now, I'm going to skip down to the question starting on line 24:

"Q. Would you have changed anything in the final study report?

"MR. ABRAHAM: Objection. Calls for speculation.

"THE WITNESS: If I were the only one involved in writing it, I probably would have written it somewhat differently."

Do you see that?

A Yes.

Q It appears based on Dr. Heydorn's testimony, he did not believe that the final study report was fully up front or forthcoming with the FDA; isn't that true?

MS. KIEHN: Objection.

THE WITNESS: That's what he's saying.

BY MR. WISNER:

Q And he's the man who actually was responsible for the final study report for Study MD-18, right?

MS. KIEHN: Objection.

THE WITNESS: He appears to have been, yes.

BY MR. WISNER:

Q Does it concern you that Dr. Heydorn, who was a former FDA employee himself, thinks that Forest

was not as forthcoming as it should have been with the FDA about its representation of the results from MD-18?

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q You would agree, Dr. Laughren, that I've shown you several documents today that suggest that at least people within Forest believed that these nine patients who were subject to the dispensing error were unblinded.

MS. KIEHN: Objection.

THE WITNESS: It appears that that is the conclusion that -- that some people reached.

BY MR. WISNER:

Q And you would agree with me that the final study report did not disclose unequivocally that these patients were unblinded, correct?

MS. KIEHN: Objection.

THE WITNESS: It -- it referred -- it referred to them as potentially unblinded. And -- and that is still a possibility, but probably less a probability than if they had just been different colored tablets without the brand name on them.

So I -- I think it would have been more transparent to include in the study report that additional information. I'm not sure that it would have made a difference here, but it -- I -- I do object to, you know, a company not being completely transparent with information that they have in reporting on the results of a study.

BY MR. WISNER:

Q Okay, Doctor, I would like to switch gears a little bit here, get off the unblinding issue for a quick second.

You recall that the secondary endpoints for MD-18 were the CGI improvement score and the change from baseline and CGI severity score, K-SADS-P depression module score and CJS -- CGAS score at week 8, correct?

A I don't recall that, but I'll take your word for it.

Q Okay. Do you recall that we looked at the secondary endpoints earlier in the protocol?

A I -- I do. I just don't recall exactly what was stated.

Q Okay. Let's turn to Exhibit 8, which is the final study report.

All right. If you turn to page 100.

Do you see page 100?

A Yes, I've got 100.

Q All right. This is Table 3.1 and this lists the primary efficacy endpoint, correct?

A Yes.

Q And this has the P-value of 0.038 at week 8, right?

A Right.

Q And you agree -- we've all agreed that that is a statistically significant result, right?

A Correct.

Q All right. If you turn the page to page 101, you have Table 3.2.

Do you see that?

A Yes.

Q And Table 3.2 is the secondary efficacy endpoint of CGI improvement after eight weeks.

Do you see that?

A Yes.

Q And that has a P-value of 0.257, right?

A That's correct.

Q That's not statistically significant?

A No, it's not.

Q Definitely not close enough, right?
A No.
Q Okay. You would agree that that secondary endpoint was negative?
A Right, correct.
Q Okay. Look at Table 3.3, which is the next one on page 102. This lists the change from baseline in CGI severity after eight weeks.
Do you see that?
A I -- I do.
Q And that's the LOCF analysis as well?
A Correct.
Q And that has a P-value of 0.226?
A Correct.
Q Also not statistically significant?
A True.
Q That's a negative secondary endpoint as well, right?
A That's correct.
Q All right. Let's turn to the next page to Table 3.4. This lists the secondary efficacy endpoint of change from baseline in CGAS after eight weeks.
Do you see that?

A I do.
Q And again, this has a P-value of 0.309 at week 8.
Do you see that?
A I do.
Q That's not statistically significant?
A No.
Q That secondary endpoint was also negative?
A Correct.
Q All right. Next page, page 104. This lists Table 3.5, which is the secondary endpoint of change from baseline in K-SADS-P depression module after eight weeks.
Do you see that?
A I do.
Q Again, this has a P-value of 0.105.
Do you see that?
A Right.
Q That is not statistically significant?
A Right.
Q That's negative, correct?
A Correct.
Q Okay. It appears then that all four

prespecified secondary endpoints were negative, correct?

MR. ROBERTS: Objection.

THE WITNESS: Right.

BY MR. WISNER:

Q Now, that doesn't make the study negative -- back up.

MR. WISNER: Did you just object?

MR. ROBERTS: I did.

MR. WISNER: Who's defending this deposition?

MS. KIEHN: It's okay. Go ahead.

MR. ROBERTS: She asked me to take over for a little while.

MR. WISNER: Oh.

MS. KIEHN: It's fine.

MR. WISNER: That's fine. Just give me a heads-up. I was suddenly surprised that you were speaking.

MR. ROBERTS: Okay. Sorry. She whispered it to me. You guys were going back and forth. I didn't want to --

MS. KIEHN: If it's all right -- if it's all right --

MR. ROBERTS: Yeah, yeah.
MS. KIEHN: -- he will go for a while.
MR. WISNER: That's fine.
Let's go off the record.
THE VIDEOGRAPHER: The time is 2:56 p.m. Go off the video record.
(Brief discussion off the record.)
THE VIDEOGRAPHER: 2:56, back on the video record.
BY MR. WISNER:
Q Now, Doctor, notwithstanding the fact that all the secondary endpoints were negative, the study is still considered positive because the only endpoint that really counts is the primary endpoint, correct?
MR. ROBERTS: Objection.
THE WITNESS: That's true.
BY MR. WISNER:
Q And so because it reached statistical significance, you concluded the ultimate, the study was positive, right?
A Yes.
Q Okay. Let's go back to Exhibit 19.
I told you earlier we'll do a lot of

jumping around here. I apologize.

A Okay.

Q This is the e-mail that had attached to it the pharmacy -- Pharmanet note conference notes. Do you see that?

A Yes.

Q Now, if you turn to the actual conference notes, look at the numbered paragraph 9. Okay?

A Okay.

Q It reads: "For the secondary efficacy measures, no significant difference at week 8 LOCF analysis."

Do you see that?

A Yes.

Q And that's consistent with the tables we just saw, right?

MR. ROBERTS: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q In those tables, all of the LOCF analysis for the secondary efficacy measures were negative, right?

MR. ROBERTS: Objection.

THE WITNESS: At week 8, yes.

BY MR. WISNER:

Q Okay. It then reads: "There were significant findings early on in treatment. Forest looking at individual patient listings to see if there were any clues as to why week 8 findings are not positive. For now emphasize the positive findings at earlier time points for the secondary efficacy variables."

Do you see that?

A I do.

Q Earlier you talked about how the final study report is the drug sponsor's opportunity to spin the data in the most positive light, right?

MR. ROBERTS: Objection.

THE WITNESS: Well, I -- I think it's fair to say that -- that most companies will put their best foot forward when they're presenting their data. And -- and that's why I say FDA reviewers often go directly to the datasets and don't bother with the company's interpretation of the findings.

BY MR. WISNER:

Q Now, here they're specifically saying because all of our secondary endpoints that we gave are negative, we should emphasize the positive

findings earlier in the study, right?

MR. ROBERTS: Objection.

THE WITNESS: I -- I see that, yes.

BY MR. WISNER:

Q All right. Let's look at the final study report. If you could turn to Exhibit 8.

A Oh, do I have 8?

Q Yeah, you got it there.

A Okay.

Q Turn to page 72.

A Okay.

Q Okay, great. Drawing your -- you see the section titled "Efficacy Conclusions"?

A I do.

Q And this is the section of the report where in a narrative format the sponsor discloses the overall conclusions of efficacy, right?

A Correct.

Q Now, you look at the second paragraph, the first sentence, it reads: "Significant differences less than 0.05 indicative of greater improvement in citalopram patients than placebo patients were also observed on the CGI-I, CGIS and CGAS."

Do you see that?

A I do.

Q I'm going to stop right there.

That does not say that every single secondary endpoint was negative at week 8, right?

A Correct.

Q And week 8, that's actually the protocol specified endpoint, isn't it?

MR. ROBERTS: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q Okay. All right. Let's turn to Exhibit 9, which is Dr. Hearst's clinical review.

Got it?

A I do.

Q Okay, great. Turn to page 11.

A Okay.

Q All right. Do you see the paragraph beginning "significant differences" that's there?

A Yes.

Q And this actually appears to be where Dr. Hearst is discussing the secondary endpoints, right?

A Okay.

Q He writes: "Significant differences, less than 0.05 indicative of greater improvement in citalopram patients than placebo patients, were also observed on the CGI-I, CGIS and CGAS."

Do you see that?

A Yes.

Q It looks like he copied and pasted that sentence again from the final study report, didn't he?

MR. ROBERTS: Objection.

THE WITNESS: However, he goes on to say --

BY MR. WISNER:

Q Sure, sure, we're going to go back to that in a second.

MS. KIEHN: Let him finish his answer.

MR. WISNER: That wasn't responsive to my question.

MS. KIEHN: I don't care.

THE WITNESS: No, you're right, that's what he -- it looks like. I mean, he is basically agreeing with, you know, their conclusion that if -- that they're -- you know, if you look at earlier timewise, it doesn't -- it doesn't actually say

that.

BY MR. WISNER:

Q Sure. But, just to be clear, though, that sentence that I just read to you in his report is a verbatim sentence from the "Efficacy Conclusions" in the final study report.

A Yes.

Q Okay. While you have the study report in front of you, let's read the rest of it.

It said: "Statistically significant effects were not found consistently across study time points for the secondary efficacy parameters as the primary efficacy parameter, but numerically greater improvement in the citalopram group was observed on every efficacy parameter on every clinical visit in both the LOCF and OC analysis. Results from the LOCF and OC analysis were similar."

Do you see that?

A Yes.

MR. ROBERTS: Wait. Where do you see "results" from -- which document are you referring to when you say "results"?

MR. WISNER: Doc -- Exhibit 8.

MR. ROBERTS: Oh, okay.

BY MR. WISNER:

Q So you see that, Doctor, in the final study?

A I -- I do.

Q Okay. Now, if you actually look at the Hearst medical review, he quotes verbatim the same thing with the exception of the last part that says "results."

Do you see that?

A Yes.

Q So it appears that Dr. Hearst copied and pasted almost an entire paragraph directly from the final study report into his medical review as it related to the secondary endpoints.

MR. ROBERTS: Objection.

THE WITNESS: Yes, it's -- it's identical.

BY MR. WISNER:

Q So a second ago you said typically medical reviewers don't even look at the study report, they go straight to the data. This does not appear to be one of those cases.

MR. ROBERTS: Objection.

THE WITNESS: Well, I -- I don't know,

you know, what -- what he -- what he looked at before he used this language.

So, again, I -- you know, we're making a lot of assumptions that he never actually looked at any of these data tables. I don't -- I don't know that.

BY MR. WISNER:

Q Fair enough.

Now, Doctor, in the course of your work at the FDA, do you recall copying and pasting language from a final study report into your medical review?

A No, I -- I -- I did not do that.

Q Why not?

A Because I preferred to reach my own conclusions.

Q Now, the way this is written in the final study report and transcribed into Dr. Hearst's review, that does appear to have been trying to emphasize the positive results to earlier time points and avoid discussion of the fact that all the secondary endpoints that we gave were negative, right?

MR. ROBERTS: Objection.

THE WITNESS: Well, I -- I don't want to assume motive. I -- I don't know what he had in mind when he did this.

BY MR. WISNER:

Q Fair enough.

Putting Dr. Hearst aside, I'm talking about Forest, we saw that they had a conference where they said they were going to emphasize this.

A Yes. Yes. No, it's -- it is consistent with -- with that view of focusing on the positive and not giving a complete picture.

Q And it appears that that spin that Forest put into the final study report made it into Dr. Hearst's report, correct?

MR. ROBERTS: Objection.

THE WITNESS: It -- it appears to have, yes.

BY MR. WISNER:

Q Okay. Let's go back to Exhibit 3, which is your memorandum.

All right. If you turn to page 3. Now, on page 3, just above the paragraph that says "comment," there is a sentence that reads: "Results also significantly favored citalopram over placebo on

most secondary outcomes."

Do you see that?

A Yes.

Q Now, you didn't state there that all the prespecified secondary endpoints were negative at week 8, right?

MR. ROBERTS: Objection.

THE WITNESS: Correct.

BY MR. WISNER:

Q You're referring here, I assume, to the earlier time points when there were statistically significant results in the secondary endpoints, correct?

MR. ROBERTS: Objection.

THE WITNESS: I -- again, I don't -- this was written a long time ago. I don't recall what would have been in my mind at the time that I wrote this, but it -- you're correct in saying that it doesn't -- it doesn't emphasize the fact that the eight-week results were all negative on the secondary endpoints.

BY MR. WISNER:

Q Now, I know you don't recall this, but is it possible that when you were drafting this memo,

you looked at the final study report, looked at Dr. Hearst, who you relied upon, and thought, Oh, most of the secondary endpoints must have been positive?

MR. ROBERTS: Objection.

THE WITNESS: I -- I would -- I would have to speculate about what -- what I was looking at at the time when I wrote this, and I -- I -- I prefer not to do that. I just -- I don't know.

BY MR. WISNER:

Q Okay. Would you agree with me, though, that it would be accurate to say all the protocol specified secondary endpoints for Study MD-18 were negative at week 8?

MR. ROBERTS: Objection.

THE WITNESS: That is -- that appears to be correct, yes.

BY MR. WISNER:

Q And would you agree with me that -- that you don't state that in your memo?

A I -- I do not state that in my memo.

Q And you would agree with me from what we've seen in Dr. Hearst's clinical review, he did not state that either.

A He did not appear -- appear to do that either.

Q Okay. So on the same page -- you have your memo in front of you, right?

A Yes.

Q Okay. You have broken down the efficacy results between children and adolescents. Do you see that?

A I do.

Q Now, you understand that Dr. Hearst didn't present data this way, right?

MR. ROBERTS: Objection.

THE WITNESS: I would have to look at --

BY MR. WISNER:

Q Please take a look and tell me if he did.

A (Perusing document.)

Can you direct me again to where on his --

Q Sure.

A -- his review the efficacy findings --

Q It's just on page 11, that's -- that's about it. That's the only reference to secondary endpoints or even primary endpoints for MD-18 that I've seen.

On page 11, do you see any reference to it?

A No. No, I don't. So he didn't break it down that way.

Q Okay. Do you know why you did?

A It's something that I -- that I generally do. I -- you know, I explore a little bit more. So...

Q Were you trying to somehow see if there was any indications from the data that might suggest that there are some positive results somewhere in the data?

MR. ROBERTS: Objection.

THE WITNESS: What -- what I was trying to do, because, again, you're dealing with a -- with a -- in pediatric years, a fairly wide range there of children and adolescents, and it's, in general, of interest to know -- because there have been many other cases where we have found some differences in the effect of a drug in children compared to adolescents. Adolescents tend to look more like adults.

So that -- that's -- that's why I broke it down that way.

BY MR. WISNER:

Q Okay.

A I mean if you look at the findings, it's not as if the findings are entirely coming from adolescents, but the effect size is -- is somewhat bigger in the adolescents. So in children, it's about, you know, about four units difference on this measure. In adolescents, it's closer to seven. So...

Q Now, in the -- in your memo you said: "The sponsor did not calculate P-values for these groups separately."

Do you see that?

MR. ROBERTS: Where is that?

THE WITNESS: Where do I say that?

Oh, right, right, right. Yeah, you ordinarily wouldn't do that in a -- in an exploratory -- it's -- it's an exploratory analysis. You're not testing a hypothesis. Ordinarily you don't generate a P-value unless you're specifically testing a hypothesis.

BY MR. WISNER:

Q Fair enough.

And so just based on what you said here,

do you know whether or not the differences observed here were statistically significant or not?

A I -- I don't. And again, from my standpoint, it -- it wouldn't be that important. Because a P-value, whether it met that usual threshold of statistical significance would not be particularly relevant for something that wasn't -- that wasn't being prespecified and tested.

I mean -- and you could do that. You could say if you make it on the overall analysis, then you get to -- you have another 0.05 to look first at -- at adolescents, and if you win there, then you get to look at -- but it wasn't done that way.

Q Okay. And that's all I was saying is the reason why there is no P-value is because that wasn't the hypothesis being tested, right?

MR. ROBERTS: Objection.

THE INTERPRETER: Right.

BY MR. WISNER:

Q Okay. Now -- all right.

Keep this all here, but can you pull out Exhibit 19, which is the e-mail with the pharma -- Pharmanet notes attached to it.

A Okay.
Q You got it?
A Yeah.
Q And that's Exhibit No. 19.
A Okay.
Q Now, if you go to the item number 7. Do you see that?
A I do.
Q It reads: "Note: The study was not powered to look at differences within the two subgroups, children and adolescents. The sample size was calculated based on the anticipated effect size for the primary efficacy variable."
Do you see that?
A Correct.
Q And that's consistent with what you just --
A Yes.
Q -- testified to, right?
A Yes.
Q The study wasn't specifically designed to look at adolescents in isolation or -- or even children in isolation.
A Correct.

Q Okay. All right. You can put that down.
Go back to the final study report, which is Exhibit 8, which is right here.
All right. If you turn to page 72.
A Okay.
Q You beat me.
MR. ROBERTS: We were there already.
BY MR. WISNER:
Q All right. You see the section that says "Treatment By Age Group Interaction"?
A Yes.
Q What is an interaction variable in a statistical analysis?
A It -- it's basically an indication that that -- that that variable, in this case age, you know, may -- may have an effect on the outcome. That's all it is. It's just a -- it's a -- it's a metric to measure whether or not there appears to be a -- a difference by age.
Q Okay.
A By that -- by that strata. You can stratify this, and you can stratify males versus females, by weight, whatever. You do a lot of different exploratory analyses, and they calculated

interaction terms by -- by age and --

Q Now, it says here in the second sentence in that section: "No significant treatment by age group interaction was found on the CDRS-R, CGI-I, CGI-S, CGAS or K-SADS-P."

You see that?

A I do.

Q So it appears that based on the statistical analysis represented in the final study report, there was no significant effect by the age of the treatment groups; is that right?

MR. ROBERTS: Objection.

THE WITNESS: Again, you know, these P-values for these interaction terms are -- are not very -- in my mind, not very useful. But...

BY MR. WISNER:

Q Fair enough.

But according to this, it's saying that there is no treatment by age group interaction, right?

MR. ROBERTS: Objection.

THE WITNESS: That -- that is what it says.

BY MR. WISNER:

Q And that's for the primary and all the secondary endpoints, right?

MR. ROBERTS: Objection.

THE WITNESS: Correct.

BY MR. WISNER:

Q Okay. Now, on that same page, if you look at the paragraph at the bottom, it says: "No treatment by age group interaction was observed, indicating that the magnitude of the treatment effect was similar in the child and adolescent subgroups."

Do you see that?

A I do.

Q Do you have any reason to dispute that conclusion?

A Well, "similar" is a -- is a somewhat vague term. I mean, obviously in my memo, I point out the difference in magnitude between the two different age groups.

Q Sure.

A So it's -- it's a matter of how you -- of how you interpret "similar." I mean, there is an effect in both strata by this crude nonstatistical approach to looking at it, just exploratory looking

at the numbers. Yes, if you calculate an interaction term, it's -- it doesn't have a significant P-value, but I just -- I think -- I prefer this way of looking at the data.

Q I understand.

A But personal preference.

Q If you look at page 243 in the final study report.

A Okay.

Q This is appendix Table 5. Do you see that?

A I do.

Q And this lists out the treatment by age group interaction terms, doesn't it?

A Right.

Q And it has the P-values all listed there. Do you see that?

A Yes.

Q For the primary as well as all the secondary endpoints. Do you see that?

A I -- I -- well, if you go on to 244, you mean? No, no.

Q CDRS-R, CGI --

A Are we looking at the same page?

Q Yeah, 243 in the table.
A Yeah.
Q Efficacy parameter on the left?
A Right.
Q And it lists all the primary as well as the secondary --
A Oh. No, no -- right. You're exactly right.
Q Okay, great. And all the P-values there, they're all not statistically significant, right?
A Yeah.
Q And you would agree with me that -- okay, great.
While we're here, just because we're here, if you turn to the next page, which is appendix Table 6.
A Okay.
Q As you see here, this is the change in baseline in the CDRS after eight weeks. Do you see that?
A Yes.
Q And this is the subpopulation. Do you see that?
If you look at the bottom, there's a

note, it says "Patients," and it lists all of them --

A Right. Right. Right.

Q -- the drug dispensing error excluded.

A Right.

Q Do you see that?

A Yes.

Q So this is actually the table that reflects the statistical analysis --

A Yes.

Q -- of the primary efficacy endpoint excluding --

A Excluding those patients.

Q That's right.

And the P-value there is 0.052, right?

A Correct.

Q Okay. Earlier we -- we discussed this a little bit. Do you recall that you participated in a symposium in 2013 that was meant to bring various stakeholders from around the country together to discuss the difference between clinical and statistical significance?

MR. ROBERTS: Objection.

THE WITNESS: I -- I think there was a -- a session at ISCTM. Is that the one that you're

referring to?
BY MR. WISNER:
Q I believe so, yes. Do you recall that meeting at all?
A I -- I participate in a lot of meetings. I -- you know, I -- I do vaguely recall it.
(Exhibit No. 21 was marked for identification.)
BY MR. WISNER:
Q All right. I'm going to hand you a document that's been marked as Exhibit 21.
A Okay.
Q This is a document, it's titled "Defining a Clinically Meaningful Effect for the Design Interpretation of Randomized Controlled Trials."
Do you see that?
A I do.
Q And it has a bunch of authors listed, and one of them is yourself, right?
A That's correct.
Q Would it be fair to say then that you reviewed this document before it was published with your name?
A Yes.

Q Okay. Now, if you look at the objective, and I think this will help crystallize your participation in it, it says: "This article captures the proceedings of a meeting aimed at defining clinically meaningful effects for use in randomized controlled trials for psychopharmacological agents?"

Do you see that?

A I do.

Q And if you turn the document and turn to page -- well, I guess 10-S at the bottom. It's in the red box on the bottom.

A Okay.

Q 10-S, do you see it?

A Got you.

Q Do you see the section that says "The FDA's perspective"?

A Right, right, right.

Q Do you see that?

A I do.

Q Would it be fair to say that you probably played a heavy role in drafting this portion?

A Right. Yes --

MR. ROBERTS: Objection.

THE WITNESS: -- that's very likely.

BY MR. WISNER:

Q Okay, great.

You can go back to the beginning. I'm going to go through a couple of sentences and ask you questions about them. We'll get to your -- the FDA section in a second.

But if you turn to page 5-S.

A Okay.

Q In the column to the far left, do you see the paragraph that begins "the effect"?

Do you see that?

A Yes.

Q It reads: "The effect of a treatment reflects the differential response among patience when treatment is given versus when treatment is not given, control over comparison condition, often placebo. Statistically significant effects are not necessarily clinically meaningful effects."

I'll stop right there.

A Yes.

Q Do you agree with that?

A In general, yes.

Q Okay. It continues: "While there is broad consensus as to how to establish statistical

significance, clinical significance remains elusive."

See that?

A I -- I do.

Q And you agree with that, right?

A I do agree with that.

Q Okay.

A But we were talking about that earlier.

Q Exactly.

It continues: "Many statistical methodologies have been put forth to measure the magnitude of a clinical effect," open paren, "an effect size," close paren. "One of the most frequently used effect size measures is Cohen's d."

Do you see that?

A I do.

Q Are you familiar with the Cohen's d or Cohen effect size?

A Yes.

Q Okay. Is that something that you would consider in assessing whether or not the results of a clinical trial are clinically meaningful?

A I -- I think -- I think it has value. I don't think it's perfect, and -- and FDA statisticians tend not to like it because it's, in

part, dependent on sample size. The standard deviation shrinks as you increase the sample size, and, of course, that's a denominator in the calculation for Cohen's c.

Q Yeah.

A So they -- they tend not -- not to use it, but I -- I do use it myself. I think it's -- it's useful, but it isn't perfect.

Q All right. It goes on to say: "A randomized controlled trial, RCT, Cohen's d is the difference between the treatment and control means divided by the assumed common standard deviation. It is a clinically interpretable effect size reflecting a degree of overlap between the patient responses in the treatment and control groups when the responses have normal distributions with equal variances."

Do you see that?

A Yes.

Q For the people here who do not have a degree in statistics, does that generally say that the Cohen effect size can be an effective measure for assessing clinical significance?

MR. ROBERTS: Objection.

THE WITNESS: It -- it's -- it's a useful

way of roughly assessing -- putting -- putting a numeric -- putting a metric on effect size by sort of standardizing it with the standard deviation. And so it's a way of making comparisons across different trials, across different diseases, across different, you know, outcome measures. It's -- it's sort of a standard -- and that's why, you know, we say, you know, an effect size of like 0.3, which is typical of what you get in a depression study, is pretty -- is pretty small. In other disorders like ADHD, you get much bigger effect sizes that are based -- based on Cohen's d. So...

BY MR. WISNER:

Q Sure. Are you familiar with something called the number needed to treat?

A Yes.

Q And what is that?

A So the number needed to treat is -- is a number that you can calculate if you're -- if you're, you know, basically using percentage of responders, proportion of responders as an outcome.

And so, say, if you have a trial where, you know, 75 percent of patients in a -- in a trial were assigned a drug have a, quote, response, however

you define "response," and 50 percent on placebo have a response. So then the -- you know, the difference between responders in the drug and placebo groups is -- is 25 percent. So the number needed to treat them is just the inverse of that, so it would be 4. Which is -- you know, by psychiatric standards is a -- is a pretty good number needed to treat. In most psychiatric trials it's -- it's more than that. It's more like 7 or 8.

So -- but, again, it's a rough measure of the -- of the -- sort of the clinical impact in the population of a particular treatment that has a -- an effect, but the question is how important is the effect in the population.

Q Is one way to express the concept of NNT -- you don't agree with me, you can tell me so -- but that if we have -- let's say the NNT number is 5, okay? That the number of patients that need to be treated with the drug such that you would see an outcome different than what you would see if you just gave placebo is 5?

MR. ROBERTS: Objection.

THE WITNESS: That -- that's correct. That is the -- the common sense interpretation of

that -- of that measure.

BY MR. WISNER:

Q Okay, great.

All right. Let's -- let's turn to the next page, page 6-S, under the "Payer's Perspective." Do you see that?

A I do.

Q All right. If you look down in the last paragraph there midway through the paragraph, you see the sentence that begins "today"? Do you see?

A Yes.

Q All right. It says: "Today P less than 0.05 is generally accepted to be statistically significant. Besides being an arbitrary limit, it does not necessarily align with clinical significance. Clinicians know well that results from an RCT, or randomized controlled trial, can be statistically significant without being clinically significant and vice versa."

Do you see that?

A I do.

Q Do you agree with that?

A In general, yes, that statistical significance by itself is -- is not necessarily a

good measure of how impactful a treatment will be in the -- in the population.

Q Okay, great. Now, if you turn the page to 7-S, the top of the paragraph, it says: "It may be more appropriate to speak of a clinically meaningful effect size, which has been defined as the smallest difference, i.e., effect size, that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects and costs, a change in the patient's management."

Do you see that?

A I do.

Q Have you ever -- have you ever heard of that concept of clinical significance?

A Yeah. I mean, I -- again, I was at this meeting, and I -- as you -- I am an author on this paper, so I -- I am familiar with -- with that notion.

Q Sure. Do you agree with that notion?

A I -- I -- I do agree that, in general, we need to be thinking more about how to develop treatments that have a real impact on patients' lives. And actually, FDA is -- is moving more in that direction too. There's a lot greater interest

now at FDA in looking at, for example, what are called PROs, patient reported outcomes, as an alternative to these standard instruments like the HAM-D and the MADRS and so forth that are typically used now in clinical trials.

Q And you're familiar that, for example, agencies in the United Kingdom have -- like the NICE organization, they -- they focus heavily on the idea of clinical significance --

A Yeah.

Q -- right?

MR. ROBERTS: Objection.

THE WITNESS: Yeah.

BY MR. WISNER:

Q And you believe that organizations like NICE are reputable organizations?

MR. ROBERTS: Objection.

THE WITNESS: I have -- I have a good deal of respect for NICE.

BY MR. WISNER:

Q Okay. All right. Well, let's turn to page 10-S in the section that says "FDA Perspective." Do you see that?

A I do.

Q And -- and do you think that you probably wrote this section?

MR. ROBERTS: Objection.

THE WITNESS: I -- I suspect I probably drafted the first version of it, yes.

BY MR. WISNER:

Q And it's probably fair to say that before you allowed a document to be published with the "FDA Perspective" as a header, you made sure to read through it and make sure it was accurate, right?

MR. ROBERTS: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q Okay.

A As -- as did my boss at the time.

Q Well, this -- well, that's a good question, actually. This says that this supplement was published in May/June of 2013.

A Oh, I -- yeah, right. This was after I left FDA, so...

Q Okay. So that's what I thought. This was after --

A No, no, I -- right.

Q Okay. That said, I am still sure you

wanted to make sure you didn't get in trouble with your boss or bosses at the FDA. All right.

A But -- knowing -- knowing Bob Temple, I would think that -- that he probably would agree with a lot of this.

Q Okay.

A But I -- I can't speak for Bob Temple.

Q Sure. Sure.

All right. Well, it says here under the "FDA Perspective," the first paragraph starts off: "The FDA looks for," quote, "substantial evidence," unquote, "that a drug will do what it's labeled to do, although it does not define 'substantial evidence.' There are no specific regulations defining minimum effect size or how to determine a clinical meaningful effect."

Do you see that?

A I do.

Q Is that your understanding?

A It -- it's true. I mean, you know, if you look at the law, it says to support efficacy, you have to have substantial evidence of effectiveness from adequate and well controlled trials. It doesn't say what -- you know, what "substantial" is. Either

in terms of the number of trials, although it does say trials, but in terms of the effect size in those trials, it doesn't -- doesn't really get into that. And the regulations don't really get into that much either.

Q Now, from my understanding of the law, and you can tell me your understanding insofar as you work with the FDA, but --

MR. ROBERTS: With the caveat that he is not a lawyer.

MR. WISNER: I'm sorry. I'm asking a question. Please don't interrupt me with testimony.

MR. ROBERTS: Okay.

BY MR. WISNER:

Q So let me ask my question again.

Now, Doctor, my understanding of the law is that unless the FDA makes a finding that there is a lack of substantial evidence, an NDA, at least with regards to efficacy, has to approve it.

MR. ROBERTS: Objection.

THE WITNESS: I think -- I think FDA is -- is obligated to, you know, approve an application unless it can find compelling reasons not to, if it has -- meets that minimum definition of

"substantial evidence."
BY MR. WISNER:
Q And my understanding generally, and this is obviously a generalization, but to meet the burden of substantial evidence of efficacy, a sponsor has to provide two positive clinical trials, right?
MR. ROBERTS: Objection.
THE WITNESS: That's general -- that's generally the way it's interpreted, yes.
BY MR. WISNER:
Q And that means, for example, you could have many more negative clinical trials, but so long as you have those two positive ones, you've met that minimum burden of substantial evidence, right?
MR. ROBERTS: Objection.
THE WITNESS: That -- that -- I mean, in -- in general, that is true. However, I can tell you that FDA does consider the total database of trials. In fact, you can -- you can do -- I don't want to take up too much time with this -- but you can use the binomial formula for calculating the probability of getting out of a set of, say, four trials -- I happen to know this probability by heart because it's such a common thing -- but if you have

four trials considered independent, so you can use the binomial formula, you get two that are significant of P less than 0.05 or less, and two that don't make it, the probability of getting that by chance is about four in a thousand.

So, it's still -- even if you have some negative trials, that's the point I'm making, it's so -- it's still quite a rare finding by chance to get those two positive. And that's why I think, you know, the drafters of the law, you know, were thinking in terms of replication, that you would like to have replication.

BY MR. WISNER:

Q Okay. We'll come back to that topic in just a few seconds actually, so I -- I appreciate you bringing that up.

A All right.

Q All right. Let's turn the page and look at page 11-S. Okay?

A Okay.

Q And then in the middle of the section there's a paragraph that says "Effect size." Do you see that?

A Yes.

Q All right. It says: "Effect size is usually measured by regulators as the difference between the drug and placebo mean change from baseline using a standard measure. Cohen's d would be the mean test group minus the mean control over standard deviation. While Cohen defined large, medium and small effects as d, 0.8, 0.5, and 0.2, respectively, an FDA rule of thumb is that an effect size is deemed large if it is greater than 0.8, small if it is less than 0.5, and moderate if it falls between those values."

Do you see that?

A I -- I do.

Q And is that your understanding of generally how the FDA views or labels the Cohen effect size?

A Yeah, I think --

MR. ROBERTS: Objection.

THE WITNESS: I think that's articulated somewhere in some FDA document, but I can't off the top of my head point to it. As I was saying, FDA statisticians tend not to think too highly of Cohen's as a measure of effect size, but clinicians at FDA view it somewhat differently. So...

BY MR. WISNER:

Q Okay. And just is it a rule of thumb, I'm just saying that it's greater than --

A And --

Q Sorry.

A I'm sorry.

Q If it's greater than 0.08, it's considered large, and if it's smaller than 0.5, it's considered small?

MR. ROBERTS: Objection.

THE WITNESS: I -- I think that's -- that's generally accepted.

BY MR. WISNER:

Q And this is, of course, based -- based on your experience working on psychiatric medications, right?

MR. ROBERTS: Objection.

THE WITNESS: And that's -- that is consistent with the way these numbers are used in the -- in the academic clinical community.

BY MR. WISNER:

Q Okay, great.

And then the next sentence reads: "On the NNT scale then, large would be smaller than 2,

small would be greater than 4, and moderate if it falls between those two values."

Do you see that?

A Yeah, I'm not sure in retrospect exactly where this comes from.

Q Well, do you agree with that?

A I -- I think it's -- it's a little -- a little bit severe in terms of a requirement for -- and I know that I'm an author on this paper. I'm not sure exactly where that came from, because it isn't -- it isn't consistent with the NNTs that you often see for psychiatric drugs.

Q But you would agree with me that the effect sizes in the NNTs that you commonly see in psychiatric drugs are generally pretty small, right?

MR. ROBERTS: Objection.

THE WITNESS: They're -- generally they are more above this.

BY MR. WISNER:

Q Okay.

A They're more like -- more like 6, 7, 8, even 10. So...

Q All right. The next paragraph -- sorry, the paragraph right from the bottom that starts "As

briefly." Do you see that?

A I do.

Q "As briefly described in the introduction above, the NNT value, how many people need to be treated with the new drug rather than placebo for one additional patient to benefit, can also be helpful to regulators."

Do you see that?

A Yes.

Q And you agree that the NNT number is something that's helpful to regulators?

A It's -- it's -- it's commonly used, and, you know, FDA is -- is now working on the concept of clinical meaningfulness in trying to come up with some -- some metrics to incorporate into the review process to -- to do something more specific on that -- on that issue.

Q Okay. Now, if you go through to the next paragraph -- well, the next -- the end of that paragraph in the next column.

Do you see that?

A Yes.

Q The sentence that begins "overall"?

A Right.

Q It reads: "Overall, the NNT is a meaningful, well respect -- well accepted, common sense measure, but its value depends on how 'response' is defined."

Do you see that?

A I'm sorry, where exactly are you?

Q Sure. Right there in that last paragraph, the sentence that leads "overall."

A Okay. Right, right, right.

Q All right. So it reads: "Overall, the NNT is a" --

A Yes.

Q -- "meaningful, well accepted, common sense measure, but its value depends on how 'response' is defined," right?

A Right.

Q And what you mean by "its value depends on how 'response' is defined," that means how the response rate is defined in the protocol for that clinical trial, right?

MR. ROBERTS: Objection.

THE WITNESS: Yes. For -- for example, typically a response is -- is -- it's a change of 50 percent reduction on, say, the HAMD or the CDRS-R

is considered a responder, but clearly it depends on how you define that.

BY MR. WISNER:

Q Yeah. But you don't define the response measure after the study is completed, right?

MR. ROBERTS: Objection.

THE WITNESS: Ordinarily, no. You would do it before.

BY MR. WISNER:

Q Okay. All right.

All right. Let's turn to page 13-S.

A Okay.

Q All right. This is a section that says: "Determining how effective a treatment will be for an individual patient" -- do you see that?

A I do.

Q All right. I'm going to skip the first paragraph and start with the second one that starts with "Paul." Do you see that?

A Mm-hmm.

Q All right. It reads: "Paul Meehl" -- am I saying that right?

A Yes.

Q Okay.

-- "held that all null hypothesis of randomness are false in that with a large enough sample size and sufficient number of RCTs, there will eventually result one or two or more values of P-value less than 0.05."

MR. ROBERTS: "One or two more values."

BY MR. WISNER.

Q "... result one or two more values of P-value less than 0.05." Do you see that, Doctor?

A I do.

Q Okay. It continues: "A P-value less than the conventional 0.05 means that the sample size was large enough to detect some deviation from the null hypothesis, not that the deviation was clinically significant or important. A nonstatistically significant result means that the sample size was not large enough and often reflects the adequacy of the study design in terms of sample size and units measured."

Do you see that?

A I do.

Q Do you agree with that?

A There's no question that, you know, that P-value is dependent on sample size. You can drive

the variance down as you increase the sample size to get a statistically significant finding that potentially may not be clinically meaningful. That is true.

Q And so in the context of a depression trial, if the difference between the placebo and the drug treatment -- let's say it was five points on the HAMD scale, okay?

A Yeah.

Q It's possible that if you had a sample size of 100 patients, you would not have a statistically significant result, but if you had a sample size of 500 patients, the same difference would be statistically significant; is that right?

A That's true.

MR. ROBERTS: Objection.

BY MR. WISNER:

Q And so in that --

MR. ROBERTS: Do you mind just waiting a second after he finishes the question so I have a chance to object.

THE WITNESS: Sorry. Sorry.

MR. WISNER: You don't have to object to everything, you know.

MR. ROBERTS: I don't object to everything --

MR. WISNER: Well, it's true --

MR. ROBERTS: -- but your questions are objectionable sometimes.

BY MR. WISNER:

Q All right, Doctor. So -- so you would agree then that, as a general matter, one of the ways to help ensure that any differences between the placebo group and the treatment group is actually statistically significant is just really increase the sample size, right?

MR. ROBERTS: Objection.

THE WITNESS: As -- as I said before, you can by driving up a sample size achieve statistical significance that -- that potentially, you know, may not be clinically meaningful.

BY MR. WISNER:

Q All right. Now, going back to this paragraph, I'm going to skip the next sentence and starts with the sentence that says "if two." Do you see that?

A Which column are you in?

Q We're in the same area, it's the same

paragraph, but it starts with the sentence "if two separate RCTs" -- do you see that?

MR. ROBERTS: Doctor, it's still the first column --

MR. WISNER: Yeah, still the first --

MR. ROBERTS: -- towards the bottom.

THE WITNESS: Okay. "If two separate," yeah.

BY MR. WISNER:

Q Yeah. Okay.

So it reads: "If two separate RCTs with P less than 0.05 were to mean approval of a drug, it would take only 40 RCTs to approve a drug absolutely equivalent to placebo. And if each trial were run at the 80 percent power level, whatever the true effect size, it would only -- it would take only about three. This means that those with deep enough pockets can eventually get their desired results. Essentially anything can be approved with the right number of studies of large enough size."

Do you see that?

A I do see that.

Q So this person's discussing a concern that by just random probability, you will eventually

get a sufficient number of studies that have a P-value of less than 0.05.

MR. ROBERTS: Objection.

THE WITNESS: And -- and as I was saying before, we have done calculations to try and get an idea of where you would cross that threshold of -- you know, of getting two trials at 0.05 based on chance, which is what this is saying, and -- and the number is well above 12 trials, it's probably closer to 20.

So, I don't -- I don't agree that you can -- you can achieve that by doing -- and I told you that the probability, if you do four trials of getting -- of getting two that are significant and two that are not, is only four in a thousand. So it's -- it's a very low chance probability.

Now, you know -- and even as you get up to like ten, it's still -- it's still well below 0.05. So it isn't -- it isn't that easy, and it's going to be a rare company that has deep enough pockets to do, you know, 15 trials to get -- they would run out of money long before that given how much clinical trials cost these days.

BY MR. WISNER:

Q Fair enough.

Do you have any idea how much money companies like Allergan have, Doctor?

MR. ROBERTS: Objection.

BY MR. WISNER:

Q All right.

A Well, I mean -- I know -- I know you say that, but the truth is that companies are -- these days are backing out of psychiatric drug research and moving into other areas because it is so difficult. So I -- I think --

BY MR. WISNER:

Q Could it also be, Doctor, that the market is fluttered -- flooded with generic versions of psychiatric medicines and there's no more money to be made?

MR. ROBERTS: Objection.

THE WITNESS: I mean, I don't -- we don't want to take up all this time debating it.

BY MR. WISNER:

Q Okay.

A But I can -- I can push back against that.

Q Okay. That's fine.

(Exhibit No. 22 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what has been marked as Exhibit 22 to your deposition.

This is a document titled "A Randomized Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents."

Do you see that, Doctor?

A I do.

Q And this appears to have been published -- at least the lead author is Dr. Wagner. Do you see that?

A I do.

Q Do you also see that William Heydorn is on this?

A Yes.

Q Okay. And this was published in the American Journal of Psychiatry in 2004. Do you see that?

A I do see that.

Q You understand that this is the published version of the results of Study MD-18?

A Yeah, I've seen this paper.
Q Okay. During your time in your capacity at the FDA and even afterwards, have you had any conversations with anybody about this publication?
A No.
Q Okay. Have you spoken to Dr. Wagner about this publication?
A I -- I've never spoken to Dr. Wagner.
Q So fair enough, you don't recall ever speaking to anybody about this publication?
A I -- I think in my earlier work with Forest, I -- I believe that this publication was discussed, but I don't specifically recall the conversations.
Q Would you have reviewed something like this, by any chance, while you were at the FDA?
A A publication?
Q Mm-hmm.
A We ordinarily would not review published papers because we -- we have the data.
Q You have the final study report.
A Right.
Q And the final study report generally contains a heck of a lot more information than the

published paper, right?

MR. ROBERTS: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q All right. Now, if you turn to page -- in the journal, it's 1081.

A Okay.

Q And in the right-hand column, do you see the paragraph that starts "Citalopram treatment"?

A Yes.

MR. ROBERTS: They both do. There's two that start "Citalopram" --

BY MR. WISNER:

Q Fair enough. The one in the middle.

A Ah. Okay, got you.

Q Thanks.

It reads: "Citalotram treat- -- citalopram treatment shows statistically significant improvement compared with placebo on the children's depression rating scale revised as early as week 1, which persisted through the study, Figure 1. At week 8, the effect size on the primary outcome measure, Children's Depression Rating Scale R -- scale revised, last observation carried forward was

2.9."

Do you see that?

A Yes.

Q Now, there's no mention there from what I can tell of -- that results are being based on data from patients that were potentially unblinded, right?

MR. ROBERTS: Objection.

THE WITNESS: Again, I'd -- I would have to read the whole paper, but I take your word that it's not -- that it's not mentioned.

BY MR. WISNER:

Q Okay. It says an effect size of 2.9. If that's a Cohen effect size, that is exceptionally high, isn't it?

A I --

MR. ROBERTS: Objection.

THE WITNESS: I'm sorry. I don't mean to interrupt you.

BY MR. WISNER:

Q Sure.

A I'm quite sure that's not the Cohen effect size. It -- it's more likely the difference between drug and placebo and change from baseline

as -- as a measure of effect size.

Q Okay.

(Exhibit No. 23 was marked for identification.)

BY MR. WISNER:

Q All right. I want to hand you what has been marked as Exhibit 23 to this deposition.

This is a copy of the letters to the editor that were submitted --

MR. ROBERTS: Wait, just give me one second just to get it, if you don't mind.

BY MR. WISNER:

Q -- letters to the editor --

MR. ROBERTS: Thank you.

BY MR. WISNER:

Q -- that were published following the publication of the study.

A Okay.

MR. WISNER: Are you okay?

MR. ROBERTS: Yeah. I just wanted to have the exhibit in front of me.

MR. WISNER: Sure. Just trying to keep it going.

BY MR. WISNER:

Q All right. Have you ever looked at these before, by any chance?

A I don't recall looking at these.

Q Okay. All right. If you look here, if you look on page 817, which is the first page, there is -- it says: "Child psychopharmacology, effect sizes, and the big bang."

Do you see that?

A Yes.

Q And if you look to the right, it says the authors are Andres Martin, Walter Gilliam, Jeffrey Bostic and Joseph Rey. You see that?

A I do.

Q Do you know Dr. Bostic?

A The -- the name is familiar, but I -- I don't -- I don't think I have met him. I --

Q I know you're doing work at Massachusetts General; is that right, nowadays?

A I -- I am, but I'm not up there very often. I do most of it from home. So...

Q Okay. Fair enough.

All right. So I want to go through some of this -- and if you actually turn the page, on the bottom right-hand corner, it says: "Dr. Wagner and

colleague's reply."

Do you see that?

A I do.

Q So it appears that there were a few letters to the editors published, and then obviously Dr. Wagner and the colleagues responded to those letters.

Do you see that?

A I do.

Q Okay. All right. Let's look to the first one, "The Child Psychopharmacology, Effect Sizes, and the Big Bang."

It reads: "We read with interest the article by Karen D. Wagner, M.D., Ph.D., et al., in the June issue in their study comparing citalopram to placebo. We were surprised to find" --

A I'm sorry.

Q Oh.

A Can you tell me again exactly --

Q Well, the first page.

A Oh, okay.

Q The bottom left column.

A Oh, okay.

Q All right. It continues: "We were

surprised to find the authors reporting an overall effect size of 2.9. The commonly cited criteria set forth by Cohen effect sizes can be considered trivial, less than 0.2; small, 0.2 to 0.5; moderate, 0.5 to 0.8; or large, greater than 0.8."

Do you see that?

A I do.

Q That's sort of consistent with what we just discussed a few minutes ago, right?

A Yes.

Q All right. It continues: "By these metrics, the reported effect size can be characterized as gargantuan, big bang-worthy. The value does not appear to be a benign typographical error for the 0.29 given that 2.9 appears twice."

Would you agree generally that a Cohen effect size of 2.9 would be -- would be gargantuan?

MR. ROBERTS: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q Okay. If you turn to the next paragraph, the sentence begins: "A Trickster Decimal," question mark. Do you see that?

MR. ROBERTS: Where are you?

THE WITNESS: So you're into the second --

BY MR. WISNER:

Q Yeah, sorry. See the next paragraph?

A Yes.

Q It says "A trickster" --

A The third sentence.

Q Yeah, you see that?

A Yes.

Q Okay, great.

So it reads: "A trickster decimal point may be to blame, and a demoted effect size of 0.29 may gain in honesty what it loses in sex appeal of an inflated 2.9 status. A smaller effect size seems more plausible and not only because a meta-analysis of 33 trials of selective serotonin reuptake inhibitors, SSRIs, for the treatment of adult depression arrived at a pooled effect size of 0.4, but because the current study, although statistically significant, was not that clinically impressive. Only a 36 percent of patients treated with citalopram responded compared to 24 percent of those with placebo for a lukewarm number needed to treat of 8."

Do you see that?

A Yes.

Q I'm going to first ask you, you would agree that a response rate of 36 percent is pretty small.

MR. ROBERTS: Objection.

THE WITNESS: I -- I -- again, the problem is that the effect size, as we discussed -- I mean that the -- a response rate depends on how you define "response."

BY MR. WISNER:

Q Sure.

A So you can float it all over the place depending on how you define it.

Q Well, at least based on how this study was defined --

A Yes.

Q -- a priori, it had a 36 response rate, right?

A Yeah.

Q And you would agree that's pretty small?

MR. ROBERTS: Objection.

THE WITNESS: It's -- it's -- it's pretty modest, I agree with that.

BY MR. WISNER:

Q And I mean, to put it in layman's terms, that means about two-thirds of all the children put on citalopram didn't have a response as defined by the study.

MR. ROBERTS: Objection.

THE WITNESS: That -- that's correct. But, again, it doesn't -- it doesn't mean that the improvement that they had was -- was not meaningful in some way. I'm just cautioning that response rate depends on how you define a response.

BY MR. WISNER:

Q I hear you, and I'm just saying that based upon how the response rate was defined in MD-18 before the study was conducted, it ultimately resulted in about two-thirds of children not responding to the medication.

MR. ROBERTS: Objection. Is that a question?

THE WITNESS: Based on this definition of "response," that's absolutely correct.

BY MR. WISNER:

Q Okay. And it says here that the number needed to treat was 8. You see that?

A Yes.
Q That's a pretty high NNT, right?
MR. ROBERTS: Objection.
THE WITNESS: It -- it's -- it's fairly high. It's not too far out of line for what we're seeing these days in psychiatric trials, unfortunately.
BY MR. WISNER:
Q And you say "unfortunately" because you would agree with me that a number needed to treat represents a pretty small effect, doesn't it?
MR. ROBERTS: Objection.
THE WITNESS: It's -- it's not as big as we would like them to be for sure.
BY MR. WISNER:
Q I mean it means in layman's terms that for us to see one additional patient to get a benefit from citalopram over taking a placebo, we would need to treat eight different children, right?
MR. ROBERTS: Objection.
THE WITNESS: That -- that is what it means in common sense terms. Again, we could -- we could have a very extended discussion of this, and I don't want to take up the time here to do that. But

it is -- there is no question, these effects are modest.

BY MR. WISNER:

Q And you also would agree, Doctor, at least from what you can tell, that this response rate as well as the NNT number discussed here, that actually included the data that had the potentially unblinded patients in it, didn't it?

MR. ROBERTS: Objection.

THE WITNESS: That -- that's true.

BY MR. WISNER:

Q All right. Now, if you look at the last paragraph in that letter, it reads: "Alternatively, the authors may have used a different definition or formula to calculate the effect size. This would be unfortunate because the basic job description of an effect size is to facilitate communication among investigators and across measures."

Do you see that?

A I do.

Q And that's what you said a minute ago, that one of the reasons we use a Cohen effect size is because it helps standardize comparisons of different outcomes in different studies.

MR. ROBERTS: Objection.

THE WITNESS: Yes, but, again, in fairness, different groups, you know, are accustomed to using different measures of effect size. At FDA, the Cohen's measure metric is not used that often. They're more -- more likely to use what these authors used.

So I think it's a little bit unfair to attack them, you know, for making the assumption that what they're presenting is the Cohen effect size when they were using a more commonly used measure of effect size, say, within FDA or perhaps within some other communities.

BY MR. WISNER:

Q Okay. And I'm sorry, I don't mean to be attacking Dr. Wagner here and her colleagues. I was just reading what it said here.

I just want to know, do you agree that the Cohen effect size is typically used so you can compare the results from different studies across?

MR. ROBERTS: Objection.

THE WITNESS: I think it would have been better for the authors to -- to present several different measures of effect size, rather than just

relying on -- on the -- you know, the one that FDA tends to rely on.

BY MR. WISNER:

Q Okay. Now, if you turn to page -- where am I -- 818. Do you see that?

A I do.

Q All right. Sorry, 819. The last paragraph in the left column. Do you see that?

It starts with "Dr. Martin and colleagues."

A Yes.

Q Okay. It reads: "Dr. Martin and colleagues inquire about the value of 2.9, which was calculated as the quotient of the least square mean divided by the common standard -- standard error of the mean for each treatment group."

Do you see that?

A Yes.

Q That's not the -- that's not a Cohen effect size, right? 2.9?

A I'm not sure what they mean by "the quotient of the least square mean." It's the difference between the mean change from baseline of drug and placebo divided by the common standard

deviation.

MR. ROBERTS: And just to clarify for the record, this is the Dr. Wagner and colleagues' reply section.

MR. WISNER: Yeah.

MR. ROBERTS: Okay.

MR. WISNER: I don't think there is any confusion about that, Counsel.

MR. ROBERTS: Well, now there's not.

MR. WISNER: Okay. Again, if you could limit your commentary objections, I would appreciate that.

MR. ROBERTS: Okay.

MR. WISNER: Thanks.

MR. ROBERTS: And I will clarify for the record every once in a while.

MR. WISNER: Okay, great.

BY MR. WISNER:

Q The next sentence reads: "With Cohen's method, the effect size was 0.32."

Do you see that?

A I do.

Q Okay. So it looks like they ultimately did a -- calculated the Cohen effect size and it was

determined to be 0.32, right?

A Right.

Q And under the standard of the FDA and just generally amongst academics, that's a -- that's a small effect size, right?

MR. ROBERTS: Objection.

THE WITNESS: It -- it's typical of what you see for antidepressants. But it is modest. It's -- it's small.

BY MR. WISNER:

Q Okay. And, again, that -- it appears that that effect size was in fact calculated again with including data from those potentially unblinded patients, right?

MR. ROBERTS: Objection.

THE WITNESS: Most likely.

BY MR. WISNER:

Q All right. Now, if you could turn back to the page before, on page 818.

A Okay.

Q You see there's another letter to the editor, it starts at the bottom of the left column. Do you see that to the editor, at the very bottom?

A The one right under "Dr. Wagner and

colleagues' reply" or --

Q No, no, to the left of that.

A Yes.

Q Just "To the editor, we read with interest."

A Okay. Okay.

Q So I'm going to go through this letter to the editor and ask you some questions about it. And you can see that it was sent by Maju Mather -- Mathews. Do you see that?

A I do.

Q It has a bunch of different physicians listed there. Do you see that?

A I do.

Q Just quickly reading through that, do you recognize any of those individuals?

A Maju Mathews used to work for me when I was at FDA.

Q Oh, really. Well, what did Maju -- Dr. Mathews do for you?

A He was a clinical reviewer. He's a psychiatrist.

Q Do you know what years he worked with you?

A I -- I don't -- you know, it's -- I would -- I would have to guess. It was sometime maybe, I'm guessing here, but probably 2007, 2008 through maybe 2010, something like that.

Q Okay. Anyone else here that you recognize?

A Oh. No. No. No. No.

Q Okay. All right. Now, in the right column, do you see the sentence -- the paragraph that begins "Our great -- greatest concern"?

A Yes.

Q Okay. So it reads: "Our greatest concerns -- concern is with the results and conclusions drawn. There is no table showing the results in detail. The authors have only stated that 36 percent of citalopram-treated patients met the criteria for response compared to 24 percent of patients receiving placebo. This response rate, while itself marginal compared to other studies of antidepressants, does not in itself show that citalopram is better than placebo."

Do you see that, Doctor?

A Yes.

Q You would agree with me that the response

rate seen in depression trials is usually higher than 36 percent, right?

MR. ROBERTS: Objection.

THE WITNESS: It is usually higher, but, again, it -- it depends on how "response" is defined.

BY MR. WISNER:

Q You are aware that Prozac received a pediatric indication for treatment of depression?

A Yes.

Q Do you -- do you recall, by any chance, what the fluoxitine response rate was?

A I don't.

Q Okay. It continues: "We calculated the absolute benefit increase of using citalopram as 0.12. 95 percent confidence interval equals 0.015 to 0.255."

MR. ROBERTS: That's negative 0.015.

MR. WISNER: Sorry. Thank you.

"Negative 0.015 to 0.255."

BY MR. WISNER:

Q What is absolute benefit increase?

A I -- I don't know offhand.

Q Okay. It continues: "The relative benefit increase that could be attributed to

citalopram was 50 percent, 95 percent confidence interval, a negative 135 percent to 6 percent."

Do you see that?

A I do.

Q Do you know what relative benefit increase is?

A I'm not familiar with these metrics that they're talking about.

Q Okay. It continues: "The odds ratio, i.e., the odds of improving while taking citalopram compared to placebo, was 1.75, a confidence -- 95 percent CI, 0.92 to 3.43."

Do you see that?

A Mm-hmm. Yes.

Q Do you know what an odds ratio of improvement is?

A No, I'd have -- I would have to think about this. I'm not -- these are -- these are not commonly used metrics.

Q Okay.

A In my view, but...

Q All right. Well, then the next sentence reads: "The number needed to treat, i.e., the number of children who need to be treated with citalopram,

for one additional positive outcome was 8. 95 percent confidential interval equals 4 to infinity. None of these shows that citalopram is any better than placebo."

Do you see that?

A I see that.

Q Do you understand why the authors are concerned that the observed difference between citalopram and placebo was not clinically meaningful?

MR. ROBERTS: Objection.

THE WITNESS: I -- I understand the concern that the effect size is -- is relatively small. It is in general for antidepressants. I mean, the results in adult depression trials for antidepressants is not so different. It's very challenging to do acute studies in depression.

If you -- if you look at, and we did a -- sort of an aggregate analysis of maintenance trials in depression that shows a much bigger effect size. So, in other words, for patients who have responded to an antidepressant, the -- you know, there is a much bigger effect size. Basically, the risk of relapse is reduced by about 50 percent, which is

quite impressive compared to these kinds of results.

But there's no question, it -- it's a real challenge to do studies in acute depression whether you're talking about adults or children.

BY MR. WISNER:

Q And you would agree based upon the relatively small effect size observed here in this study that this study by itself doesn't provide conclusive evidence that Celexa is in fact effective in treating pediatric patients?

MR. ROBERTS: Objection.

THE WITNESS: I agree with that, and of course, we didn't approve that supplement.

BY MR. WISNER:

Q Now, Doctor, we know that all the protocol specified secondary endpoints for Study MD-18 were negative, right?

MR. ROBERTS: Objection.

THE WITNESS: At the week 8 endpoint, yes.

BY MR. WISNER:

Q We know that the observed cases endpoint on the primary efficacy variable was negative at week 8, right?

MR. ROBERTS: Objection.
THE WITNESS: That's correct, although that wasn't the -- that wasn't the protocol specified primary analysis.
BY MR. WISNER:
Q Sure. But we know that the OC results for the people who actually completed the clinical trial, that actually was negative for efficacy, right?
A That's true.
Q We know that with Study MD-18 that there were nine patients that Dr. Flicker characterized as being unmistakenly unblinded, right?
MR. ROBERTS: Objection. Mischaracterizes the evidence.
THE WITNESS: That's correct.
BY MR. WISNER:
Q And we know that when those nine patients are excluded from the primary efficacy analysis pursuant to the LOCF analysis, that the P-value goes higher than 0.050, right?
MR. ROBERTS: Objection.
THE WITNESS: That's -- that's true. However, I would push back a little bit on that to

make the point that that analysis was a sensitivity analysis to get -- to gauge -- you know, to get some sense of sort of the impact of -- of the patients who were -- who were potentially unblinded, or I guess in this case, may be more than potentially unblinded. And you expect when you do a sensitivity analysis and you throw patients away that the power of that study is going to diminish.

And so a P-value of 0.052 is not bad for a sensitivity analysis that you know going in is losing power. And that -- that's the purpose frankly of it. It's -- I would argue that it's still not the correct P-value if you're characterizing, you know, that study. It's just -- it's something to do to try and get a sense of -- of the impact of those -- of those patients on the -- on the trial.

And to me, it suggests that the impact was not great. In other words, yes, there was potential unblinding or perhaps they were unblinded, I don't know the answer to that, but it didn't have a huge impact on the -- on the significance.

Yes, it was 0.052, and I know you want to argue that that's not statistically significant, and, of course, by usual standards, it doesn't meet that

threshold, it misses by 2/1000ths. But to me, it argues that those patients were not inordinately impactful on the -- on the outcome of that study.

BY MR. WISNER:

Q Well, you do know that the inclusion of those unblinded patients in the study results changed the numerical difference between placebo and citalopram at week 8, right?

MR. ROBERTS: Objection.

THE WITNESS: In terms of the P-value?

BY MR. WISNER:

Q No, in terms of the actual different -- differential between placebo and citalopram.

MR. ROBERTS: Objection.

THE WITNESS: The effect size is measured by difference between drug and placebo and change from baseline.

BY MR. WISNER:

Q That's right. You understand the difference at week 8 with the patients included was 4.6 points on the CDRS-R score, and that when they're removed, it drops to 4.3.

Did you know that?

MR. ROBERTS: Objection.

THE WITNESS: I -- I think I remember reading it someplace. But, again, I'm not sure how to -- how to evaluate the importance of that.

BY MR. WISNER:

Q Well, let's -- let's just talk numbers for a second. I mean, you remove nine patients' data from the analysis out of a cohort of over 170, and just the removal of those nine patients creates a numerical point difference of 0.3 in the difference between placebo and citalopram, right?

MR. ROBERTS: Objection.

THE WITNESS: But the -- the 0.3 is a relatively small number, and I don't -- again, you know, we're getting back to this issue of -- of how do you measure clinical significance. I don't know what the clinical significance of a four-point difference is. I have no idea what the clinical significance of a -- a difference of 0.3 is.

BY MR. WISNER:

Q I get you there, Doctor.

And I guess what I'm trying to say is it wasn't just a powering issue. It actually changed the values of the difference between placebo and the drug group, correct?

MR. ROBERTS: Objection.

THE WITNESS: I -- I -- I don't really agree with you on that point.

BY MR. WISNER:

Q Okay. Well, it was a significant enough -- of enough difference to at least have changed the P-value to a number that was above 0.05, correct?

MR. ROBERTS: Objection.

THE WITNESS: It -- it did do that.

BY MR. WISNER:

Q Okay. So then, you know, in light of the -- the effect size of Study MD-18, the fact that all the secondary endpoints were negative at week 8, that the OC results on the primary endpoint were negative at week 8, and that Study 94404 was negative on both the primary and secondary endpoints, that data combined together wasn't sufficient in your opinion while you were at the FDA to determine that Celexa was effective for pediatric patients.

MR. ROBERTS: Objection.

THE WITNESS: That's correct. We didn't approve the supplement.

BY MR. WISNER:

Q Based on this data, can you definitively say to a degree of scientific certainty that Celexa is superior to placebo in treating pediatric patients?

A Well, our -- our ultimate decision on approving Lexapro depended on that positive Celexa study. And so, you know, as you I'm sure know, there were two studies done with Lexapro. The active component of Celexa, of racemic citalopram, is escitalopram. The R-citalopram has no effect on the serotonin transporter, so it's entirely driven by the escitalopram. And that -- that's why we made the judgment that we could -- we could combine the data from those two programs in making a judgment about Lexapro.

Q Doctor, we're going to get to Lexapro in a second. I might have said that in my question and that was an error. We will get -- we will get into all this shortly. I don't -- I don't want to get too off -- off track because I really want to get through this --

A Okay.

Q -- and get you home.

But I guess my question is, is based on

all the data we know about Celexa specifically, can you as a scientific definitively state that Celexa is superior to placebo in treating pediatric depression?

MR. ROBERTS: Objection.

THE WITNESS: So, this -- and this is -- because the company, of course, never came back with a supplement for Celexa. There was no reason to do that. But the same logic -- and that's why I brought in the Lexapro.

BY MR. WISNER:

Q Oh, I see.

A The same logic applies in the reverse.

If you believe that the active ingredient is the escitalopram in terms of an effect on the serotonin transporter, then the Lexapro study can contribute to making a judgment that Celexa is a -- because in terms of the active ingredient, they're the same drug. And of course, it's not approved for pediatric depression. Only Lexapro is.

But I -- I think one could easily extrapolate back, and as a clinician, say, make that judgment. I personally as a clinician would not use Celexa because it has some other problems that

Lexapro doesn't have. But I -- I have -- if I believe that Lexapro works as an antidepressant, I have every reason to believe that Celexa does.

Q Okay. Maybe it was an inartfully worded question. I guess I meant based on the data that existed as of 2002, there was no way to definitively determine that Celexa was effective in treating children; is that right?

MR. ROBERTS: Objection.

THE WITNESS: I -- I agree, and I think that's reflected in our decision not to approve the supplement.

BY MR. WISNER:

Q And you would agree then that it wasn't until Forest was able to obtain a positive result in adolescents for Lexapro in 2008, prior to that there was not sufficient evidence that either Celexa or Lexapro were effective in pediatric patients.

MR. ROBERTS: Objection.

THE WITNESS: I -- I think in general, I could say that's true, but I -- I want to qualify it -- again, I don't want to spend too much time qualifying these -- these questions. But as a clinician who only had access to Celexa at that

point, I don't think it would have been unreasonable -- not based on the data just from Celexa in pediatric patients, but based on -- on the -- the data in adult patients as well. Because I think extrapolating from adults to children, when we believe that it's essentially the same -- especially in adolescents, that it's essentially the same disease, is not -- is not unreasonable, and for that reason; not because of -- of the single Celexa trial in pediatric patients.

BY MR. WISNER:

Q Fair enough, Doctor. I guess -- I guess I appreciate your candor about what a doctor's decision to prescribe a drug for use in children, and I don't want to get there.

I guess my question to you is more from an academic FDA perspective. Until Study MD-32, which is the positive study in Lexapro, was completed in 2008, 2009, there was no definitive evidence that these drugs were effective in treating children. Is that fair to say?

MR. ROBERTS: Objection.

THE WITNESS: It -- it's fair to say, and for the umpteenth time, we didn't approve the

supplement.

MR. WISNER: Yes, exactly. Okay, great.

Let's take a short break.

THE VIDEOGRAPHER: The time is 4:11 -- excuse me, 4:12. This is the end of disc No. 4. We will go off the video record.

(Recess.)

THE VIDEOGRAPHER: This is the beginning of disc No. 5 in the deposition of Dr. Thomas Laughren. The time is 4:26 p.m. Back on the video record.

MR. WISNER: Let's go off the record.

THE VIDEOGRAPHER: 4:26, off the record.

(Pause in the proceedings.)

THE VIDEOGRAPHER: The time is 4:27. Back on the video record.

BY MR. WISNER:

Q All right, Doctor, we're going to skip for now Exhibit 24. So we will just put a placeholder sheet for 24, unless I end up using it later.

(Exhibit No. 25 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what has been marked as Exhibit 25 to your deposition.

This is a document entitled "Summary Report for Protocol No. SCT-MD-15, a double-blind, placebo-controlled evaluation of the safety and efficacy of escitalopram in pediatric depression."

Do you see that, Doctor?

A I do.

Q Do you recognize this document?

A I -- I don't offhand recognize it. I mean, I -- I do know which study MD-15 is, escitalopram study.

Q And this appears to be the study report for MD-15. Do you see that?

A Yes.

Q It's dated December 3rd, 2004?

A Yes.

Q So this would have been after the FDA denied a pediatric indication for Celexa; is that right?

A That's correct.

Q Okay. If you turn to page 45 in this document.

A Okay.

Q You see there is a section that says "Efficacy Analysis"?

A I do.

Q And then below that, you see it specifies within that section the primary efficacy analysis?

A Yes.

Q All right. And it reads: "The primary efficacy parameter was the change from baseline visit to week 8 in CDRS-R score."

Do you see that?

A Okay. Yes.

Q Okay. So the primary endpoint for MD-15 appears to be nearly identical to the primary endpoint for MD-18; is that right?

A That's correct.

Q And below that you see that there are three-secondary efficacy endpoints.

Do you see that?

A I do.

Q The first one is CGI score at week 8, the second one is change from baseline to week 8 in the CGIS score, and the third one is change from baseline to week 8 in the CGAS score.

A Yes.

Q All right. And then finally, if you turn the page to page 46, there's actually another section that says "Additional Efficacy Analysis."

Do you see that?

A Yes.

Q And it lists two additional efficacy parameters.

Do you see that?

A Yes.

Q The first one is the CDRS-R response rate. Do you see that?

A Right.

Q And it defines it appears -- I'm sorry, that's at week 8, right?

A Correct.

Q And it defines response rate at less than or equal to 28. Do you see that?

A Yes.

Q So my understanding of that is, if a patient's CDR score was less than or equal to 28, that would be considered a response.

A Correct.

Q Okay. And then the CGI-I response rate, it says: "CGI-I, less than or equal to 2 at week 8."

Do you see that?

A I do.

Q What is your general understanding of the difference between a secondary efficacy parameter and an additional efficacy parameter?

A I -- I would have to look back to the analysis plan to see if they -- if they defined any of these, if these were included in the hypothesis testing. I don't know how offhand.

Ordinarily, the only secondary measures that -- that, say, the psychiatry division would focus on would be those that are designated as key secondary endpoints and are included in the hypothesis testing. Any -- any other endpoints would be considered exploratory.

Q Okay. Turn to page 100 in this document. Do you see the Table 3.1?

A Yes.

Q It's very similar to MD-18. Table 3.1 lists the change in baseline and the CDRS-R at week 8.

Do you see that?

A I do.

Q And the P-value represented there is

0.310. Do you see that?

A I do.

Q That's negative?

A It's not statistically significant, correct.

Q Okay. It's not close enough, right?

A No.

Q Okay. Now, Table 3.2, which is on page 101, do you see that?

A Yes.

Q And that lists the secondary efficacy endpoint of CGI improvement at week 8.

Do you see that?

A Yes.

Q That has a P-value of 0.169?

A Yes.

Q Again, that's negative?

A Not statistically significant.

Q Okay. And generally, that's known as being negative, right?

A Yes.

Q Okay. And then the next table, 3.3, that's another secondary efficacy endpoint.

Do you see that?

A Yes.
Q Change from baseline in CGI severity at week 8?
A Yes.
Q And that has a P-value of 0.057. Do you see that?
A I do.
Q That's close to statistically significant, but it's not there, is it, right?
A No.
Q Okay. Look at the next table, Table 3.4, it has another secondary endpoint change from baseline in CGAS at week 8.
Do you see that?
A I do.
Q And that has a P-value of 0.065.
Do you see that?
A I do.
Q And, again, that's not statistically significant, is it?
A It doesn't meet that threshold, correct.
Q Okay. Let's move on to Table 3.5. This lists the results of an additional efficacy parameter.

Do you see that?

A I do.

Q It's the analysis of the CDRS-R response rate at week 8.

A Yes.

Q A P-value of 0.317. Do you see that?

A I do.

Q That's also negative?

A It's, again, not statistically significant.

Q All right. Table 3.6. This is the final additional efficacy parameter. It's the analysis of CGI-R response at week 8.

Do you see that?

A I do.

Q Again, it has a P-value of 0.144.

A Correct.

Q That was not statistically significant, correct?

A Correct.

Q Okay. So to be clear then, based on these tables, it appears that the primary efficacy endpoint, the secondary efficacy endpoints, as well as the additional efficacy parameters, they were all

negative, correct?

A I -- based -- based on what you've shown me here, yes.

Q Okay. And in fact, it is your understanding that MD-15 was considered a negative study, right?

A Yes.

Q These results with all the endpoints being negative at week 8 is consistent with that conclusion.

A That's correct.

Q Okay. Do you think that MD-15 provides scientifically valid evidentiary support for the use of Celexa in use in children?

A No.

Q Do you think that it provides scientifically based information -- sorry, do you think it provides similar support -- scientific support for the use of Lexapro in children?

A No.

MS. KIEHN: Objection.

BY MR. WISNER:

Q And to be clear, MD-15, that study population included both children and adolescents; is

that right?

A I believe that's correct.

Q Okay. And same thing with Study MD-18, that also had children and adolescents, right?

A Yes.

Q Now, you understand that Study 94404 was just in adolescents. You know that, right?

A Correct.

(Exhibit No. 26 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what has been marked as Exhibit 26.

All right. This is a letter from Russell Katz at the FDA to Andrew Friedman at Forest.

Do you see that?

A I do.

Q Have you ever seen this letter before?

A (Perusing document.)

I don't -- I don't offhand remember it, but -- it doesn't -- it doesn't surprise me that we would have been asked that question and responded to the company.

Q Okay. And if you look at the last page

of the document, it's electronically signed by Russell Katz on November 16, 2004.

Do you see that?

A Yes.

Q All right. And just for my own edification, what does it mean when there's an electronic signature like that on an FDA document?

A Virtually all documents now, all letters that go out are -- are signed electronically. FDA has an electronic document system, and so, you know, rather than signing a paper copy, which is what we did in the old days, you go into that document system, you know, find the -- you get a notification that there is a letter waiting for you or some other document or a review that you're expected to look at, and if you agree with, sign off on and so forth.

And so that's just an acknowledgment that -- that the decision to -- to sign the letter was made on that day at that time.

Q Okay. Because it's electronically signed, that doesn't make the document any less valid, right?

A No. No. No. There isn't -- there isn't going to be any -- any paper copy of -- of this

document. It's just -- it resides in that -- in that system.

Q Okay, great.

All right. If you look at -- do you recall independently if you had any role in preparing this letter?

A I -- I don't offhand recall the discussion. I'm sure that I was included in this decision to -- to draft this letter, and I may have written parts of it. I -- you know, I --

Q Okay.

A A letter like this has to be signed off by the division director.

Q Okay. And at this point, though, 2004, Dr. Katz was the division director?

A Yes.

Q Okay. Now, the letter -- if you look at the third paragraph, you said -- it's the third paragraph on the first page.

A On the first --

Q Yeah.

A On the first page.

Q It starts off with "we have reviewed." Do you see that?

A Yes.

Q Okay. It says: "We have reviewed the referenced material and have the following comments and recommendations. For clarity, we've repeated your questions with our response immediately following the question."

Do you see that?

A Yes.

Q So it appears that this is a response to a series of questions posed by Forest to the FDA; is that right?

A That's correct.

Q Now, we noted a second ago that this was dated November 16th, 2004, but the final study report for MD-15 was dated December 2004.

Do you see that?

A Yes.

Q So it appears that the final study report for MD-15 was not submitted to the FDA until after it had received this letter from the FDA.

A Correct.

Q Okay. Now, bullet -- or paragraph number 2, do you see it says, "Would a positive" -- do you see that?

A Yes.

Q All right. So it reads: "Would a positive study with escitalopram using a conventional acute treatment design, Study B, along with the previous positive study of citalopram, Study CIT-MD-18, be adequate to support an indication for acute treatment in pediatric patients aged 12 through 17."

Do you see that?

A Yes.

Q So based on what I read here earlier, this is the question that Forest posed to the FDA; is that right?

A Yes.

Q Okay. And here's the response. It says: "We believe that one additional positive acute treatment study of adolescents in addition to Study CIT-MD-18 would support a claim for the acute treatment of adolescents with MDD. In this case, the study designed to be similar enough to provide a sense of replication. Again, we do not concur with your position that the post hoc analysis of the failed trial is supportive of efficacy from a regulatory perspective."

Do you see that, Doctor?

A Yes.

Q What is your understanding of this idea of sense of replication?

A Of sense?

Q Yeah, it says here: "In this case, the study is designed to be similar enough to provide a sense of replication."

A Oh, a sense of replication.

Q What does that mean?

A I -- I'm not sure what Dr. Katz means by that in this context. But I think what he is saying is that two studies of similar design in the same population, and, you know, it's not -- it's not included in this language, but obviously he is making the judgment that -- that citalopram and escitalopram from the standpoint of the active ingredient are the same drug. So...

Q You mentioned that earlier, and I guess I will just explore that with you now.

Is it your belief that Lexapro and Celexa are essentially the same compound?

A They're not the same compound.

Q Okay.

A They're not the same compound. Celexa, racemic citalopram, is a mix of R-citalopram and S-citalopram. They have -- you know, S-citalopram has an effect on the serotonin transporter; R-citalopram does not. And there is a lot of evidence to suggest that it's the S-citalopram that is the active ingredient of racemic citalopram, animal data and other data.

So that's the basis for the belief that -- I agree that this is -- this is unusual in a regulatory context to -- you know, to base an approval on -- on two compounds that are not identical drugs. There is no question, you know, that this racemic mixture is not identical. In fact, there is other data to suggest that -- that the racemic mixture, probably because of the R-citalopram, has some risks that the S-citalopram, that that isomer by itself, does not have.

So, they're not the same compound except from the standpoint of an effect on the serotonin transporters.

Q All right. But you would agree, though, that the S-citalopram compound of Celexa is what drives its serotonin effect.

A Yes.

MS. KIEHN: Objection.

BY MR. WISNER:

Q And you believe obviously the same thing with escitalopram itself, right?

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q Okay. Considering what you just said, do you think it's appropriate that Forest should have been allowed to have exclusivity over S-citalopram, even though it essentially was just the effective part of Celexa?

MS. KIEHN: Objection.

THE WITNESS: Again, as I -- excuse me. As I -- as I said, there are important differences between S-citalopram and racemic citalopram. Mostly on the safety side. So they're not -- they're not the same compound.

BY MR. WISNER:

Q Okay. Are you familiar, just by any chance, with the phrase "evergreening"?

A No.

Q Okay. All right. So my understanding

based on the response from the FDA is that if Forest could produce a positive double-blind, placebo-controlled clinical trial with Lexapro in children aged 12 to 17, it would then agree to provide an indication for Lexapro for that age group.

A Yes, that's -- that is what it's saying. I mean, of course, it would -- you know, it would have to be reviewed. It's subject to review by FDA. But in principle, yes, that is what this letter says.

Q And -- and this agreement that the FDA made was done notwithstanding the fact that Study MD-18 was a study that was not relegated solely to adolescents, right?

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

Q And that -- I'm sorry.

A However, as -- and, again, it's -- you know, this was an exploratory post hoc analysis, but I did show at least in my memo that -- that the effect size was -- you know, the effects were probably more driven by the adolescents than by the children in that study.

Q Sure. And I -- I'm not saying that you didn't do that, Doctor.

I guess my question, though, is

Study MD-18 had both younger children and adolescents in there, right?

A But it was -- you know, it was considered a positive study for that entire age group.

Q Okay.

A And so if you make the argument that you have, you know, one drug that's -- that in that study is shown effective in children and adolescents, and you have another drug that's just studied in adolescents, that's enough to approve the -- you know, that drug, if you're willing to extrapolate from -- from the Celexa data to Lexapro. That's the argument.

Q I understand the argument. I guess my question actually was really simply Study MD-18 had both younger children and adolescents in it, right?

A Yes.

Q And Study 94404 was actually a study specifically aimed at looking at adolescent depression, right?

A Well, that's true.

Q And 94404 was negative, right?

A It -- it's true that it was negative. However, it had some other problems in it that --

that 18 didn't have.

Q Fair enough. I'm just saying Study 94404 was specifically limited to adolescents, that's all. Right?

A That's true.

Q And it was negative.

A It was negative.

Q Okay. Now, at this point when the FDA has made this promise to give -- or, sorry, I shouldn't say "promise."

When the FDA has entered into this agreement that it will give an adolescent indication for Lexapro after they've given a positive study for adolescents with Lexapro, they did not have the final study report for MD-15, did they?

MS. KIEHN: Objection.

THE WITNESS: It -- I mean, this -- this suggests that we had something on -- on 15.

BY MR. WISNER:

Q The final study report suggests you didn't have that document, correct?

A Right, but -- but obviously we -- and again, I don't have the package in which these -- these questions were embedded. But Question 1

assumes that there was quite a bit of information on MD-15 included in the -- in the package that was reviewed as the basis for this letter. That's all I'm saying.

Q Okay. If MD-18 was negative -- okay, just assume that for a second -- would the FDA have made this agreement?

MS. KIEHN: Objection.

THE WITNESS: No. I don't -- I don't believe so. That would be my impression that -- that we would not have -- have reached that agreement.

BY MR. WISNER:

Q All right. Now, you understand that at some point Forest did in fact complete Study MD-32, which studied Lexapro in adolescents, right?

A Correct.

Q And that study was positive, wasn't it?

A Yes.

Q And you understand that that study had a particularly large sample size, right?

MS. KIEHN: Objection.

THE WITNESS: I -- again, I haven't -- I haven't looked at 32 any time recently, so I -- I'm assuming you're going to give me something here.

BY MR. WISNER:

Q Sure. I'm trying to figure out what to give you.

All right. I'm actually going to hand -- I'm going to go out of order, but we're going to go back to Exhibit 27, but I'm going to hand you Exhibit 28 because that will help answer the question I just asked you.

(Exhibit No. 28 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what is Exhibit 28 to your deposition. It's actually not marked. Let me see that for a second.

Oh, it is. Okay, we're good.

This appears to be a memorandum prepared February 17th, 2009. Do you see that?

A Yes.

Q And this is a memorandum prepared by Dr. -- is it -- Kin?

A Yes.

Q And he was team leader --

A She.

Q Sorry. She was a team leader at the

Division of Psychiatric Products, right?

A Yes.

Q So she actually held the position that you once held.

A Correct.

Q And if you turn to page 3, Section 5.2, there is a "Summary of Study Pertinent to Efficacy Claim."

Do you see that?

A Yes.

Q And you see there is a discussion of Study MD-32?

A Correct.

Q If you go down to the third paragraph in that thing, it says: "This study was conducted at 40 study centers in the United States."

Do you see that?

A I do.

Q "A total of 584 patients were screened for eligibility. 316 patients were randomized."

Do you see that?

A I do.

Q So 316 patients randomized into the study, that is a considerably larger sample size than

in MD-18, right?

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q And we discussed earlier that when you increase the sample size in a clinical trial, what would otherwise be statistically insignificant differences between the placebo arm and the drug arm can suddenly reach a statistically significant P-value, correct?

MS. KIEHN: Objection.

THE WITNESS: There's no question that -- that the sample size will -- an increase in the sample size can in some settings -- it doesn't always, but it can reduce variance, and therefore, you know, increase the chance of getting a statistically significant P-value.

BY MR. WISNER:

Q Now, in Study MD-18, they actually did children and adolescents, so there was only approximately 80 adolescents in that study, right?

MS. KIEHN: Objection.

THE WITNESS: I'd have to go back and look, but I -- but let's assume that it was evenly

split. I -- I don't know. I guess it was probably about that.

BY MR. WISNER:

Q Okay. Well, let's not assume. Let's quickly just look -- look at your memo. That will have it on it.

A Do you know which exhibit number my memo is?

Q Exhibit 3.

A Great.

Q And you see on the page where you break down the -- the adolescents and the -- on page 3?

A Right. But I don't -- I don't --

Q Oh, you don't have the N on there.

A I don't have the N in there.

Q Okay. All right. Let's go to study -- let's go to Exhibit 8, which is the final study report. And turn to page 101. I think that should have it. Sorry, page 100.

A Okay.

Q So we have -- on Table 3.1, you have the N for -- in the placebo group, you have 47 in adolescents.

Do you see that?

A Yes. Yes.
Q And you have 44 for adolescents in the citalopram group.
A Right. Yeah.
Q So that's roughly 90?
A Yes.
Q Okay. So in MD-18, the adolescent population studied was roughly 90 patients, right?
A Right.
Q And here in Study MD-32, we're -- we've rocketed it up to 316 patients. Do you see that?
MS. KIEHN: Objection.
THE WITNESS: Yes.
BY MR. WISNER:
Q Okay. All right. So let's go back to my -- give me one second, Doctor.
(Exhibit No. 27 was marked for identification.)
BY MR. WISNER:
Q All right. I'm going to hand you now what's Exhibit 27. We will come back to Exhibit 28 in a minute.
MS. KIEHN: I think you handed out 27, no?

MR. GRIFFIN: That was 28.

MR. WISNER: That was 28. We skipped one for a second.

BY MR. WISNER:

Q This is Exhibit 27, Doctor.

All right. This is a document titled "Clinical Review." Do you see that?

A I do.

Q And are you familiar with this document?

A I -- I mean, I haven't looked at it any time recently, but --

Q Okay.

A -- I notice that it only has what appears to be a couple of pages from it.

Q Sure.

So this is excerpts of the clinical review conducted by Roberta Glass at the FDA in response to Forest's adolescent submission for an adolescent indication.

A Yes.

Q Okay. And it looks like -- there are some dates on there. I just don't know if you can tell me what they mean. It has a letter date of May 22nd, '08.

Do you see that?

A Yes.

Q Do you know what that refers to?

A Literally the -- the date on the -- on the cover letter for -- for the supplement.

Q Okay. So it's basically when it was submitted?

A And the date -- well, the date that the company listed on the cover letter. The stamped date is when it's actually stamped into FDA.

Q All right.

A And then the goal date is -- it's ten -- ten months later. It's the standard, you know, time frame for -- for doing a review of a supplement.

Q Okay. So it's fair to say then that they submitted this application in May of 2008?

A Yes.

Q Okay. All right. If you turn the page, we're on page 22. Do you see that?

A Yes.

Q Okay. And you see the section titled "Study 18"?

A Yes.

Q This is referring to -- it appears to be

referring to Dr. Glass's review of Study MD-18.

A Correct.

Q Okay. It reads -- in the second sentence in that first paragraph, it reads: "Dr. Earl Hearst, FDA clinical reviewer, reviewed this positive study in addition to the negative Study 94404, September 12th, 2002."

Do you see that?

A I do.

Q That's referring to Dr. Hearst's clinical review, right?

A Correct.

Q Okay. And then it goes on to say -- well, I will stop right there.

It appears that Dr. Glass is, at least in part, relying on Dr. Hearst's review of MD-18.

A Yes.

Q Okay. Now, it goes on to say: "Later it was determined that Study 18 could" -- could -- I think it should be "could be used," but it said "Study 18 could used as one of the two positive studies required to submit pediatric labeling for escitalopram, an isomer of citalopram, in the treatment of MDD. DPP letter of November 16, '04."

Do you see that?

A I do.

Q So that letter right there is actually the one we just looked at a second ago.

A Yes.

Q All right. So it appears that Dr. Glass is operating off of the fact that Study MD-18 was positive and that they just had to look at whether or not there was an additional positive study for adolescents with Lexapro; is that right?

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q All right. Look at the last paragraph on this page. It reads: "The study is positive for the effi- -- for the primary efficacy variable of change from baseline of the CDRS-R total score P equals 0.038."

Do you see that?

A I do.

Q Now, we know that that's referring to the results of the primary efficacy endpoint including those nine patients that were unblinded, correct?

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q All right. It goes on to say: "As it can be seen from Table 6.1.3.4, there is a greater improvement for the adolescent group than the children group when comparing the differences to placebo. As Dr. Laughren notes in his memo of September 16th, 2002, quote: It appears that the positive results for this trial are coming largely from the adolescent subgroup."

Do you see that?

A I do.

Q It appears that Dr. Glass is relying on your exploratory analysis of the different effects observed in the pediatric and adolescent subgroup in your memo of September 16th, 2002.

A That's correct.

Q And indeed, she has pasted the results on the next page. It says "Summary of Primary Efficacy Variable for Study 18 by Age Subgroups," and it says -- literally says: "Extracted from memorandum by Laughren, September 16, 2002."

Do you see that?

A I do.

Q You see that she has copied and pasted that portion of your memorandum into here, correct?

MS. KIEHN: Objection.

THE WITNESS: She has given acknowledgment as well.

BY MR. WISNER:

Q Abso- -- oh, sorry, I wasn't suggesting that that was nefarious. She's relied on your prior work here, right?

A Yes.

Q It does not appear that she did a comprehensive clinical review of MD-18 at this point; is that right?

MS. KIEHN: Objection.

THE WITNESS: That's likely the case, yes.

BY MR. WISNER:

Q Now, earlier when we were discussing your memorandum of September 16th, 2002, do you recall that there had been an agreement not to conduct a statistical analysis of the efficacy data?

A Yes.

Q Do you know if a statistical analysis of the efficacy data was done at this point?

A Since one is not in the -- in the file that you've been able to obtain, I'm assuming that it was not done.

Q Yeah. Is that typical for a pivotal trial that's going to be used to support indication to have just not been given any statistical review?

MS. KIEHN: Objection.

THE WITNESS: It's prob- -- it's probably not typical.

BY MR. WISNER:

Q And you said earlier one of the reasons that you do a statistical review, although it's redundant, is to sort of hash out the various effects you're seeing in the data, right?

MS. KIEHN: Objection.

THE WITNESS: Generally, a statistical review -- it does a couple of things. I mean it -- very often the statistical reviewer will have the original actual dataset electronically and can do some additional exploratory analyses looking at -- you know, breaking it down by gender and age and ethnicity and that sort of thing. It can also confirm the analyses that are done by the sponsor.

BY MR. WISNER:

Q Do you think that probably would have been helpful, particularly since you're using a particular subgroup of an exploratory analyses that you did in your review of the study?

MS. KIEHN: Objection.

THE WITNESS: In -- in retrospect, I think I -- I would have preferred that.

BY MR. WISNER:

Q Okay. All right. Let's turn back to Exhibit 28, which is the one I handed you a minute ago.

A Okay.

Q This is the -- the memorandum by Dr. Kin?

A Yes.

Q And she was Dr. Glass's supervisor, correct?

A That's correct.

Q Okay. So this is sort of her memorandum kind of overseeing the clinical reviews that were done by, for example, Dr. Glass.

A Correct.

Q Okay. The subject of the memorandum is "Recommendation of approval action for Lexapro (escitalopram) for the acute and maintenance

treatment of major depressive disorder, MDD, in adolescents."

Do you see that?

A Yes.

Q Okay. So this appears to be a memorandum from Dr. Kin where she is recommending the approval of Lexapro for use in adolescents. Is that right?

A That's correct.

Q Okay. Turn to page 2.

Do you see the section that says "Overview of Studies Pertinent to Efficacy"?

A Yes.

Q All right. It reads: "To fulfill the requirement of positive results from two placebo-controlled studies to support efficacy of pediatric MDD for escitalopram, the Division has agreed to accept one positive pivotal study in citalopram Study CIT-MD-18," or Study 18, "and one positive study in escitalopram study SCT-MD-32, Study 32."

Did I read that correctly?

A Yes.

Q And that's the agreement we again discussed previously?

A That's correct.
Q It's the same agreement that was mentioned in Dr. Glass's review, right?
A Correct.
Q Would it be fair to say that they had marching orders at this point in their review that Study MD-18 was positive, just look at 32 and tell us if that's also positive?
MS. KIEHN: Objection.
THE WITNESS: I -- I don't -- I don't know that I would call that marching orders.
BY MR. WISNER:
Q Fair enough.
A I think there was -- there was that understanding that, you know, we had already looked at -- at 18 and made a judgment that it was a positive study. I mean, certainly no one instructed them not to look at 18.
Q Sure.
A I --
Q I appreciate that, Doctor, and I didn't mean to suggest they didn't look at it. But I was just saying that they appeared at least to have been relying upon the agreement that the FDA reached with

Forest in 2004.

A I think that's fair.

Q Okay. And if you look at page 4, there's a section that says "Study CIT-MD-18."

Do you see that?

A Yes.

Q And this goes on for about three short paragraphs.

Do you see that?

A Yes.

Q All right. Bear with me, Doctor, one second.

I'm actually -- sorry, I'm mixed up because I'm on the wrong page. Look at page 3 of document -- do you see the paragraph below the summary that starts off with "Study 18 is an eight-week" -- do you see that?

Third paragraph from the top, "Study 18 is an eight-week" --

A Oh, correct.

Q Do you see that?

A Yes.

Q All right. It says: "Study 18 is an eight-week double-blind, placebo-controlled,

flexible-dose citalopram, 20 to 40 milligrams a day, study in children 7 to 11 years and adolescents 12 to 17 years. I would refer to the clinical review by Dr. Hearst dated December 12, 2002, and the memorandum by Dr. Thomas Laughren dated December 16, 2002, regarding their reviews of materials submitted under supplemental NDA for citalopram on April 18, 2002. I will briefly summarize their interpretation of results from Study 18 in Section 5123 below."

Do you see that?

A I do.

Q So it appears that Dr. Kin is relying heavily, if not exclusively, on Dr. Hearst and yourself's analysis of Study MD-18.

MS. KIEHN: Objection.

THE WITNESS: That's correct. Now, of course, this is the team leader review. It's not the primary review.

BY MR. WISNER:

Q Sure.

A I don't have Dr. Hearst's complete review, so I don't -- I don't know exactly what -- what she did with regard to Study 18.

Q Okay. I represent to you that what I've

shown you is pretty much it.

A Okay.

Q And so it appears that they largely relied upon yours and Dr. Hearst's review.

MS. KIEHN: Objection.

THE WITNESS: It -- it does appear that way.

BY MR. WISNER:

Q Okay. If you turn to page 5 now, sorry, do you see the paragraph that says "This study was positive" at the top -- third from the top in paragraph 5 -- on page 5?

A Yes.

Q Okay. It says -- it says: "The study was positive for the primary efficacy variable of change from baseline of the CDRS-R score. Citalopram, minus 21.7 plus 1.6; placebo, minus 16.5 plus 1.6; P equals 0.038."

Do you see that?

A I do.

Q Again, he is representing the results of the primary efficacy endpoint regarding -- I'm sorry. Sorry. Strike that. It's getting late.

He's referencing the efficacy endpoint

and the primary endpoint which included data from those nine unblinded patients, right?

A She is, correct.

Q Sorry. She is. I keep saying that, forgive me.

It goes on to say: "Please see Table 2 in Section 5.1.3 regarding summary of primary efficacy results by age group for CID -- CIT-MD-18 LOCF data extracted from Dr. Laughren's memo dated September 16, 2002."

Do you see that?

A I do.

Q So, once again, there he -- she is referencing -- in fact, referencing the reader to look at a table that was extracted from your memo; is that right?

A That's correct.

Q All right. And then if you look at Table 2, it's on the next page, page 6.

It says: "Summary of Primary Efficacy Results by Age Group for Study CIT-MD-18 LOCF."

Do you see that?

A I do.

Q It says again, "Data extracted from

Dr. Laughren's memo, September 16, 2002."

Do you see that?

A I do.

Q Okay, great. So in that table there, although it doesn't look identical to your table, it has the same information, right?

A Yes.

Q Okay. So, again, it looks like not only to Dr. Glass but Dr. Kin also inserted the table from your exploratory analysis on MD-18 in this analysis.

A That's correct.

Q When you prepared your memo for CD -- for MD-18, and you did this exploratory analysis dividing the adolescents from the children, did you anticipate that that being -- that was going to be used to support an indication for a different drug in adolescents?

MS. KIEHN: Objection.

THE WITNESS: I -- I doubt that I was thinking ahead that far.

BY MR. WISNER:

Q Fair enough.

In retrospect, it seems that that's exactly what happened.

A That's true. But -- but let me just -- just point out that we -- we made -- we reached a conclusion based on Study 18 that it was a positive study for both adolescents and children. And so it's -- it's that part of it, it's the adolescent part of that that is being incorporated into this judgment that these two studies, Study 18 for Celexa and Study 32 for Lexapro, were sufficient as a source of evidence for the -- the effectiveness of Lexapro in -- in adolescents.

(Exhibit No. 29 was marked for identification.)

BY MR. WISNER:

Q I'm handing you what has been marked as Exhibit 29 to your deposition.

Doctor, this is a letter actually from you related to the supplemental application for Lexapro for use in adolescents, correct?

A Yes.

Q And, unfortunately, I don't have the page that says the date of this letter, but do you recall that this was in early 2009?

A I -- I can't remember back to 2009 and -- but that sounds about right.

Q And so since you were the division director, at the end of the day, whether or not Lexapro would be approved for adolescents was your decision.

A I was the -- the final signatory authority on that.

Q So, to be clear, it's sort of an interesting turn of events, but it looks like your review of an exploratory variable for MD-18 for adolescents was then relied upon, separate clinical reviewers as well as another team leader, for an application that you later on approved; is that right?

MS. KIEHN: Objection.

THE WITNESS: Although that is true, let me -- let me again just qualify this by pointing out that we made a judgment back when we reviewed the Celexa supplement that Study 18 was a source of evidence for both adolescents and children. And I did this exploratory analysis simply to point out that, if anything, more of the effect appeared to be coming from the adolescents than it did from the children. But -- but overall, it was a source of evidence for adolescents.

BY MR. WISNER:

Q Sure.

A Apart from my exploratory analysis. So...

Q Okay. Now, you understand that Lexapro was then approved in -- was approved for adolescent use, correct?

A Correct.

Q Are you aware that prior to that -- and if you're not aware, it's fine -- but are you aware prior to that, Forest was promoting the use of Lexapro for use in adolescents?

MS. KIEHN: Objection. That's false.

THE WITNESS: I don't -- I don't have any -- any specific knowledge of that. I mean, I -- again, this -- this fact may have come up in my work with Forest and I just don't remember it, but I -- I in general did not consult with them on issues of promotions. It was never my thing at FDA. It wasn't within my authority to make judgments about promotion when I was at FDA.

BY MR. WISNER:

Q Fair enough, Doctor. I appreciate that answer. Let me ask you a slightly different

question.

If Forest was promoting the use of Lexapro for use in adolescents prior to this approval, based on your understanding, that was against the law, correct?

MS. KIEHN: Objection. Calls for a legal conclusion.

THE WITNESS: Again, it's not -- not my area of expertise, but -- but my impression is that -- that you can't promote for an indication that's -- that's not approved. So...

BY MR. WISNER:

Q Now, I've shown you a lot of documents today that suggest that some of the patients were unblinded in Study MD-18, right?

MS. KIEHN: Objection.

THE WITNESS: That's -- that's certainly a possibility.

BY MR. WISNER:

Q And I've also shown you some documents which suggest that Forest didn't properly disclose that fact to the FDA in its submissions, correct?

MS. KIEHN: Objection.

THE WITNESS: It -- it certainly would

have been my preference that -- that Forest be more transparent with FDA about the issue of unblinding. I don't believe in the end that would have made any difference in our judgment, as I've explained, but -- but I do -- I do feel that drug companies should be fully transparent with FDA in what they provide to them about the -- you know, the conduct of a study.

BY MR. WISNER:

Q Now, considering that they weren't transparent about that issue, do you think -- and also in consideration of the fact that Study MD-18 never had a statistical analysis of the efficacy data, do you think that it would be appropriate for the FDA to take another look at this data just to make sure that in fact Study 18 was -- was positive as Forest has represented?

MS. KIEHN: Objection.

THE WITNESS: It -- it isn't my judgment at this point.

BY MR. WISNER:

Q Sure.

A So, I mean I -- that -- that's for FDA to decide at this point. I mean, I -- I feel fairly confident about our decision to approve Lexapro. I

was obviously involved in that. I -- I feel that was probably the -- the right decision. Whether or not FDA -- and I also told you that, in retrospect, I would have had a statistical review done on -- on 18.

But my overall view is that it probably would not have made a difference. We probably still would have -- would have reached that same judgment. And it's -- it's up to FDA to decide whether or not, you know, based on this -- on this, you know, new information, which I think is probably new information from FDA because I wasn't aware of it at the time. But it's not my call.

Q Okay, great.

MR. WISNER: Let's take a break.

THE VIDEOGRAPHER: The time is 5:14. We will go off the video record.

(Recess.)

THE VIDEOGRAPHER: The time is 5:23. Back on the video record.

BY MR. WISNER:

Q I want to talk briefly again about Study MD-18. And, you know, we know that all the secondary prespecified endpoints were negative, right?

A That's my recollection, yes.
Q And we know that the OC analysis on the primary endpoint was negative, right?
A That's correct.
Q We know that the treatment by age group interaction term was also negative, right?
A Yes.
Q And we know that when these patients that were unblinded are excluded from the efficacy analysis, the P-value on the only positive endpoint peaks just above 0.05, right?
MS. KIEHN: Objection.
THE WITNESS: That's correct.
BY MR. WISNER:
Q You'd agree with me that in light of all those secondary and additional analysis of the data that -- and considering the fact that these nine unblended -- unblinded patients had an effect on the P-value as such, would you agree with me that Study MD-18 was not a clear and convincing positive study?
MS. KIEHN: Objection.
THE WITNESS: I -- I don't agree with that. I -- I do consider Study 18 a source of

evidence for the efficacy of, you know, of Celexa. You know, the -- the effect size is not huge. You know, it's -- it's a low effect size by -- by usual standards.

I'm not that concerned about the change in the P-value in the sensitivity analysis, an analysis which reduces the power of the study and still comes very close to being statistically significant, and in my view is not the primary P-value to focus on for the study.

So I don't -- I don't think that -- I don't think that the argument that the potential unblinding or actual unblinding, if that's what actually happened -- I don't think we'll ever know what actually happened there -- I don't -- I don't think that undercuts the overall finding for the study. That's just -- that's my view.

BY MR. WISNER:

Q I mean if you were to make that determination, you'd have to ultimately conclude that you were wrong, right?

MS. KIEHN: Objection.

THE WITNESS: I -- I'm not -- I'm not opposed to changing my mind. I have -- there have

been many occasions when I changed my mind when -- when I was at FDA. There was an NDA that we -- we turned it down, and this is for iloperidone. You know, the company challenged it and came back in with some additional analyses, and -- and they were able to persuade me that -- that I was wrong, and -- and I recommended approval, and Bob Temple agreed with me, and we ultimately approved it.

So there have been situations where I -- I agreed with an argument that I was wrong and reversed myself. That certainly isn't the only circumstance. I -- I just don't see this as one of those circumstances.

BY MR. WISNER:

Q If MD-18 was in fact negative, would you ever have approved Lexapro for use in adolescents?

MS. KIEHN: Objection.

THE WITNESS: I mean, if -- if -- if you couldn't rely on 18 as a source of evidence, then you would've only had one source of evidence for Lexapro. So the answer is this is speculation, but I -- I would not have recommended approving it.

BY MR. WISNER:

Q You're the one who ultimately did approve

it, right?

A Because I -- I considered Study 18 a reasonable source of evidence.

Q No, I know. And I'm just saying it's not speculation because you're actually the one who ultimately signed off finally on Lexapro's approval for adolescents, right?

A Yes.

MS. KIEHN: Objection.

THE WITNESS: Yes.

BY MR. WISNER:

Q And you're saying you wouldn't have approved it if there was only one study, positive Study 32, right?

MS. KIEHN: Objection.

THE WITNESS: That's correct.

BY MR. WISNER:

Q Do you agree, though, Doctor, that a reasonable regulatory person at the FDA could come to a different conclusion about the positive results of MD-18?

MS. KIEHN: Objection.

THE WITNESS: It -- this is always a matter of judgment. So the answer would be, yes,

different people looking at the same dataset can reach a different conclusion.

BY MR. WISNER:

Q Are you aware that there has been a peer-reviewed publication last year discussing the results of MD-18?

MS. KIEHN: Objection.

THE WITNESS: I -- I have -- I have not been following the literature in that particular area, so...

BY MR. WISNER:

Q So you have not seen any peer-reviewed journal article coming to the conclusion, having looked at the data without the unblinded patients, that it was negative; is that correct?

MS. KIEHN: Objection.

THE WITNESS: I -- I don't recall seeing that. If there is such a paper, I haven't seen it.

BY MR. WISNER:

Q Okay, great. But we do agree, and I think this has been established and I just want to make sure we're on the same page, that until Study MD-32 was completed and reviewed by the FDA, prior to that, with Study 94404 being negative for

primary and secondary endpoints, Study MD-15 being negative for primary and secondary endpoints, and Study MD-18 being negative on the secondary endpoints as well as the OC analysis of the primary endpoint, at that point there was not sufficient evidence to conclude that either Celexa or Lexapro were definitely effective in pediatric populations.

MS. KIEHN: Objection.

THE WITNESS: And that's reflected in the fact that we did not approve the -- the supplement for Celexa, and we didn't even consider the supplement for Lexapro until they had a positive study.

BY MR. WISNER:

Q So the answer is "yes"?

MS. KIEHN: Objection.

THE WITNESS: The answer is yes.

MR. WISNER: Okay. I pass the witness.

EXAMINATION BY COUNSEL FOR DEFENDANTS

BY MS. KIEHN:

Q Good afternoon, Dr. Laughren. I have a few questions.

You referred a few minutes ago to the information that Mr. Wisner had presented to you as

new information.

Do you recall that?

A Yes.

Q What specifically were you referring to when you said "new information"?

A I -- I wasn't aware, you know, based on the -- on the pediatric supplement for Celexa that -- that patients were actually given tablets that had the brand name Celexa on them. That's my understanding of -- of what actually happened.

Rather than my -- my understanding, and I believe the understanding of our review team, was that there might have been a different color for the tablets that -- for patients who got active drug and for those who got placebo. And that was -- that would have been of less concern to us in terms of unblinding.

And so -- so the -- you know, the information that patients were actually, as I understand it, provided tablets that had the brand name Celexa on them is -- is further evidence of potential unblinding that comes much closer to being actual unblinding.

And so I think it would have been better

for Forest to -- to provide that information in the supplement. Again, I -- I don't think that would have made a difference because, as I've said, blinding is something that you -- that you strive for but you often don't achieve, and is not as critical an element in the validity of a study as randomization.

And often I think in trials, we -- we don't achieve it, whether or not there is this kind of problem. And in fact, as I pointed out, there are trials in psychiatry that were explicitly open label, and FDA relied on as a source of evidence for a new claim. So...

Q Do you know for a fact that the tablets had the name Celexa imprinted on them?

A Unfortunately, I don't think we were ever provided with enough information to even make that judgment. I mean, that -- that's the problem. The only -- the only thing that, based on my memo and the supplement, that we were informed of is that there was a different color of the tablets for patients who got active drug than those who got placebo.

Q But your testimony that the new information you received today was that the tablets

bore the brand name Celexa, that was based exclusively on things that Mr. Wisner showed you or implied to you, correct?

A That's correct. That is absolutely correct.

Q Okay. I'm going to hand you --

MS. KIEHN: What's the next -- what's the next exhibit number?

MR. WISNER: 30.

(Exhibit No. 30 was marked for identification.)

BY MS. KIEHN:

Q I've handed you what's been marked as Exhibit 30. I will represent to you that this is an exhibit that was introduced by Mr. Wisner at another deposition in this matter.

Have you ever seen a branded antidepressant tablet?

A I can't say that I have.

Q Do you know whether branded antidepressant tablets typically have the brand name imprinted on them?

A Typically not, no.

Q Does this image of Celexa tablet contain

the name Celexa anywhere?

A It -- it doesn't. However, it does -- it does include the strength of -- of the tablet. And that's -- that's different than simply a tablet that has a slightly different color than the inactive tablet.

Q And why is it different?

A It -- it refers -- it refers to a strength, and -- again, I don't know, I don't know if this actually unblinded patients.

All I'm saying is that, from my standpoint, it would have been preferable if this information had been included in the supplement.

Q And what information are you referring to?

A The -- the actual nature of the error.

Q So what was imprinted on the tablets?

A What was imprinted on the tablet.

Q Okay. I'm going to hand you what is being marked as Exhibit 31.

(Exhibit No. 31 was marked for identification.)

BY MS. KIEHN:

Q Earlier today Mr. Wisner showed you some

deposition testimony of Dr. William Heydorn. Do you recall that?

A Yes.

Q This is an additional excerpt.

I think I gave you my marked copy.

A Oh.

Q Does it have a mark on it?

A Yes.

Q Well, it's just directing you to the -- to the relevant section.

MR. ROBERTS: Here is another copy.

MS. KIEHN: Wait, we got to put this thing on it.

MR. WISNER: Why don't you just do a new one.

MS. KIEHN: All right.

(Exhibit No. 31 was remarked for identification.)

THE WITNESS: Just put this in the -- over here, okay.

BY MS. KIEHN:

Q If you can turn to page 314.

A Okay.

Q At the top, I'm going to read some

testimony into the record.

"Q. Dr. Heydorn, you've answered a number of questions regarding some patients who participated in MD-18 who were potentially unblinded today. Correct?

"A. Yes.

"Q. You don't actually know whether those patients were in fact unblinded, do you?

"A. No, I do not.

"Q. To the extent in your testimony you referred to, quote, unblinded patients, you don't actually know that those patients were unblinded, correct?

"A. No, I do not.

"Q. To the extent you adopted Mr. Baum's use of the term 'unblinded patients,' you also don't know that those patients were in fact unblinded. Correct?

"A. No, I do not."

Do you see that?

A I do.

Q I'm going to hand you what we are marking as Exhibit 32.

(Exhibit No. 32 was marked for identification.)

BY MS. KIEHN:

Q Exhibit 32 are excerpts from the deposition of Charles Flicker.

Do you recall Mr. Wisner showing you some excerpts from Mr. Flicker's deposition earlier today?

A I do.

Q Please turn to page 203. Starting at line 12, I'm going to read some testimony in:

"Q. You don't think that the blind was unmistakably violated for these nine patients?

"A. No.

"MR. ROBERTS: Objection.

"BY MR. BAUM: You don't think that the blind was compromised for these nine patients?

"MR. ROBERTS: Objection. He testified he doesn't recall the

dispensing error.

"THE WITNESS: I think it was potentially compromised. It seems to me perfectly possible that none of those nine patients had any hint whatsoever of what their treatment group was.

"Q. But the investigators knew, right?

"MR. ROBERTS: Objection. Mischaracterizes testimony, no foundation.

"THE WITNESS: I don't know."

Do you see that?

A I do.

Q So these two Forest witnesses have testified under oath they do not in fact know whether the patients were unblinded, correct?

A Correct.

Q And you testified earlier that on page 63 of the study report, all nine patients -- strike that.

You testified earlier that on page 63 of the study report, the report suggested all nine

patients received pink tablets.

Do you remember that?

A I -- I stated that?

Q Yeah, we can go -- do you want to go back and look?

A Yes.

Q Okay. Exhibit 8.

A I don't -- I tried to keep track of these things.

MR. WISNER: It's one of the thicker ones. If that helps. I don't know.

THE WITNESS: It must have gotten misplaced somehow.

MR. WISNER: It's right there (indicating).

THE WITNESS: Oh. Okay. Sorry.

Okay, I've got it.

BY MS. KIEHN:

Q Okay. Page 63. So this is the MD-18 study report.

A Okay.

Q So Mr. Wisner had directed you to the language that stated: "Nine patients -- I won't read the numbers in -- "were mistakenly dispensed one week

of medication with potentially unblinding information," open paren, "tablets had an incorrect color coating," close paren.

Do you see that?

A Yes.

Q And under questioning, you had testified that that language suggested to you that all nine patients received pink tablets; is that correct?

A I -- I may have. I guess I -- I misunderstood from this statement that -- I had thought from what I was told that the -- the incorrect color coating applied to the active medication and not to the -- and not to the placebo medication.

Is that incorrect.

MS. KIEHN: Do you mind my answering or -- I think the documents you've been shown --

MR. WISNER: Honestly, I don't think you can answer that because I don't know if there is an answer to the question, so --

MS. KIEHN: I think there is an answer.

MR. WISNER: But I don't think it's correct.

BY MS. KIEHN:

Q Do you recall that Dr. Tiseo's facts described the tablets as the active drug had been mistakenly packaged?

A Yes.

Q Do you recall that?

A Yes.

Q Okay.

A But this says that -- that all tab- -- the tablets had an incorrect color coating. It sort of implies that -- that all nine patients had tablets with an incorrect color coating.

Q It's possible because that's correct -- incorrect; is that right?

A I mean, if -- if some of the patients had -- had the correctly packaged placebo, then it -- then it wouldn't have been all nine patients. But that's --

Q Okay. I'm going to hand you what we are marking as Exhibit 33.

(Exhibit No. 33 was marked for identification.)

BY MS. KIEHN:

Q So Exhibit 33 is an e-mail from Andrew Friedman to Gregory Dubitsky.

Do you see that?

A Yes.

Q And you are in the cc line; is that correct? You see it?

A Yes. Yes.

Q And the date is July 26, 2004, correct?

A Correct.

Q And Andrew Friedman writes: "Dear Dr. Dubitsky: Attached please find the requested information. I will submit the official response along with a cover letter tomorrow; however, I wanted to get it to you as soon as possible. If you have any further questions or comments, please do not hesitate to contact me."

If you look down below, the e-mail he was responding to was from Dr. Dubitsky sent on July 17, 2004.

Do you see that.

A Yes.

Q And you are cc'd again, correct?

A Yes, I am.

Q And Dr. Dubitsky writes: "Hello, Dr. Friedman. I am the FDA medical officer reviewing your May 4, 2004 submission which included the

protocols and study reports for studies CIT-MD-18 and 94404. There are a few additional pieces of information I need to request from you."

Do you see that?

A I do.

Q If you turn to number 3 on the next page, Dr. Dubitsky writes: "The study report for CIT-MD-18 discusses nine patients who possibly became unblinded during treatment. Please provide a breakdown of these patients by treatment group as well as the breakdown of protocol violators in this trial by group and type of violation as for 94404."

Do you see that?

A I do.

Q Do you recall this e-mail chain?

A Unfortunately, no.

Q If you can turn to page 9, please.

A Okay.

Q So at the top under FDA Request No. 3, this repeats what Dr. Dubitsky had included in his e-mail.

And then below, Forest's Response No. 3 indicates: "The breakdown of patients who possibly became unblinded during treatment is provided in

panel 7."

And if you look at that table there, do you see that there were five patients in the active citalopram group and four in the placebo group?

A Yes.

Q And do you see a note there for Patient 505, that that patient did not receive study medication?

A Correct.

Q So would this suggest that in fact only four patients received pink tablets.

A And so the -- the placebo patients in this -- in this panel received the -- the placebo preparation which was given to all patients in the trial with no markings on it whatsoever?

Q Correct. As far as we know.

MR. WISNER: Objection. Move to strike that as testimony by the attorney. It's not established, Doctor.

You can ask your question.

THE WITNESS: I mean this is why I said earlier that -- that I don't -- I don't think we know here whether or not there was -- and to what extent there was unblinding.

All I -- all I was saying is that my -- my preference as -- as an FDA reviewer would have been that -- that some more of this information would have been provided in the supplement, rather than just saying that -- implying that there was a -- that the placebo and the active tablets could be distinguished on the basis of color. It appears that it was more than just color. That it was the actual commercial formulation of -- of Celexa that was provided to patients.

I mean, it's possible -- it's possible -- well, I don't -- I'd have to look at the exclusion criteria for the study. It's unlikely actually that the patients, that these patients would have -- would have had prior exposure to -- to Celexa.

I'm just saying that -- that in general, I think FDA would provide to have -- to have all the information that a sponsor has about the conduct of a trial in making its judgment. I don't think it would have made any difference in this case, but -- that's all I'm saying.

BY MS. KIEHN:

Q Okay. And you said you don't think it would have made any difference in this case, correct?

A Well, again, that -- that has to do with -- with the -- with the fact that we did the sensitivity analysis, and with the reduced power, the P-value moved up, but it -- it didn't -- I don't think it had a material effect on the overall judgment about that being a positive study. That's just my view.

Q One moment.

I'm going to hand you what is -- we are marking as Exhibit 34.

(Exhibit No. 34 was marked for identification.)

BY MS. KIEHN:

Q Now, earlier Mr. Wisner showed you Exhibit 15, which was an e-mail with an attachment. This is the same e-mail but with the e-mails that came after it in the chain.

So if you look at page 2, the e-mail from Joan Barton sent December 6, 2000, that was the e-mail that Mr. Wisner showed you earlier.

Does that look familiar?

A Yes.

Q So I would like you to take a look at the e-mail just above, which if you look at the bottom of

page 1 is an e-mail from Jane Wu to John Barton, cc Joan Howard, James Jin, Paul Tiseo, Charles Flicker, Carlos Cobles and Edward Lakatos dated December 8, 2000.

Do you see that?

A I do.

Q And Mr. Wisner represented to you earlier that Jane Wu was one of the senior statisticians on the MD-18 study.

Do you recall that?

A I vaguely recall that.

Q So if you flip the page, Jane writes: "Joan" -- and let me just step back a minute and refresh you that Joan's original e-mail was asking whether the issue with the packaging would alter the total number of child or adolescent patients to be randomized.

So Jane responds: "I don't think this should alter the total number of patients to be randomized in either group, but if we could enroll a few more patients without jeopardizing the timeline, it is not going to hurt us. By the intent to treat principle, we have to include them in the analyses anyway."

Do you see that?

A I do.

Q So the senior statistician on MD-18 is indicating here that the primary efficacy analysis will be conducted consistent with the study protocol, correct?

MR. WISNER: Objection. Misstates the document.

THE WITNESS: Well, that -- that's why I -- I asked earlier if -- if there was any actual change in the analysis plan, and it doesn't sound like there was. Because the analysis that was in the study report included the original -- included all patients. That was my impression.

BY MS. KIEHN:

Q And Jane sent this e-mail before Forest had the results of MD-18, correct? December 2000?

A Yes.

Q Dr. Laughren, when you were at the FDA, were you involved in the review and approval of package inserts?

A Yes.

Q What's the purpose of an FDA review of a package insert?

A To make sure that the information is -- is, number one, accurate and complete enough to inform prescribers about the appropriate use of a -- of a product.

Q Is one purpose also to make a determination that the label is not false or misleading in any particular --

A Well, that is the under- -- I'm sorry, that is the underlying principle behind our review of labeling, to make sure that it's not false and misleading, but as part of that, we look at things like whether or not it's complete enough, whether or not it -- it's accurate, it provides accurate information, and, you know, allows prescribers to appropriately use a product. But false and misleading is the underlying principle coming from the law.

Q And we talked about earlier Lexapro was FDA approved for adolescent depression in March 2009, correct?

A That sounds right.

Q And you were involved in the decision to approve Lexapro for adolescent depression, correct?

A That's correct.

Q Were you also involved in the review and approval of the Lexapro package insert?

A Yes.

Q All right. I'm going to hand you what we are marking as defendant's -- or just Exhibit 35.

(Exhibit No. 35 was marked for identification.)

BY MS. KIEHN:

Q So I'm handing you the Lexapro package insert, which I will represent to you was printed off of the FDA's website and has a date of 2012.

Do you recognize this?

A It -- it looks like the Lexapro package insert.

Q If you can please turn to --

MR. WISNER: Hey, Kristin.

MS. KIEHN: Yes, sir.

MR. WISNER: This has a bunch of missing dates on it and stuff. Is this a draft package insert?

MS. KIEHN: This is printed off the FDA website, correct?

MR. ROBERTS: Yeah.

MR. WISNER: You understand that the --

the final package insert is actually created by the sponsor, not FDA.

MS. KIEHN: But do you understand that the approved package inserts are all on the FDA website?

MR. WISNER: I understand, but this isn't the actual package insert. This is the FDA's approval of the package insert.

MS. KIEHN: Are you suggesting that the actual one differs from this?

MR. WISNER: I hope it's not different. You guys will be in trouble if it is. But I just want to point out that this isn't the actual package insert. I'm not saying that the substance is in any way different. There are dates here, for example, that need to be filled in.

If you look at the back, it has --

THE WITNESS: Yeah.

MR. WISNER: -- a copyright of 20XX --

THE WITNESS: Right.

MR. WISNER: -- Forest Laboratories. The final page. And on the front it has recent major changes and it has month/month, year/year/year/year. I don't think substantively it makes a difference,

but to keep the record clear.

MS. KIEHN: Oh, you only have one -- well, I happen to have a copy of the package insert dated 2009 printed off of the FDA website. However, I only have one copy.

MR. WISNER: Okay.

MS. KIEHN: So we will mark that as --

MR. WISNER: 36.

MS. KIEHN: -- Exhibit 36 in response to Mr. Wisner's objection. Let me locate the relevant --

MR. WISNER: Don't -- don't write on it.

MS. KIEHN: Can I come over?

MR. WISNER: Sorry, can I just look at it two seconds before you hand it to the witness?

MS. KIEHN: Yeah, I think we just have to both come over. You want -- can we go off the record?

MR. WISNER: Let's go off the record.

THE VIDEOGRAPHER: The time is 5:55. We will go off of the video record.

(Recess.)

(Exhibit No. 36 to be subsequently marked for identification.)

THE VIDEOGRAPHER: The time is 5:59. Back on the video record.

BY MS. KIEHN:

Q Dr. Laughren, if you can look at page 21 of Exhibit 35. I think you're there already, correct?

A Yes, I'm there.

Q You see the section titled "14, Clinical Studies; 14.1, Major Depressive Disorder"?

A I do.

Q And then the heading "Adolescents"?

A I do.

Q I direct your attention to the second paragraph, which I'm going to read into the record.

"The efficacy of Lexapro in the acute treatment of major depressive disorder in adolescents was established in part on the basis of extrapolation from the eight-week flexible-dose, placebo-controlled study with racemic citalopram, 20 to 40 milligrams per day. In this outpatient study in children and adolescents, 7 to 17 years of age, who met DSM-IV criteria for major depressive disorder, citalopram treatment showed statistically significant greater mean improvement from baseline compared to placebo on

the CDRS-R. The positive results from this trial largely came from the adolescent subgroup."

Do you see that?

A I do.

Q You were involved in the approval of that language, correct?

A That's correct.

Q So you determined that that language is neither false nor misleading; is that correct?

A That's true.

Q Is that still your view today?

A Yes.

Q You concluded that Study MD-18 was a positive study, correct?

A That's correct.

Q Does that remain your view?

A It does.

Q In your opinion, the decision as to whether an efficacy study is a positive or negative study a decision that is appropriately made by the FDA?

A I do.

Q That's the role of the FDA, right?

A That is our job, to look at the data in

support of a -- of a new claim and then make a judgment about that.

Q Because if it's a close call, the decision should be made by the scientific experts at the FDA and not by plaintiff's attorneys and juries; is that correct?

MR. WISNER: Objection. Move to strike as argumentative and misstates the facts.

THE WITNESS: It -- it's true that -- that basically the law, I believe, gives FDA authority to make those judgments.

BY MS. KIEHN:

Q And that's proper because the FDA has the scientific expertise to do so; is that correct?

A Right. Correct.

Q Would it be fair to say that protocol violations are relatively common in a clinical study?

A They are.

Q In your experience, does a protocol violation automatically invalidate the results of a study?

A No.

Q That would depend on the nature of the protocol violation, correct?

A It -- it would depend on -- on the nature of the protocol -- the protocol violation, but as you point out, it would be very difficult to find a clinical trial that did not have some protocol violations.

Q In the opinion -- sorry, in the opinion of the FDA, was CIT-MD-18 a double-blind, randomized, placebo-controlled study?

MR. WISNER: Objection. This witness does not speak for the FDA.

THE WITNESS: When I was at FDA, it was my judgment that it met those criteria.

BY MS. KIEHN:

Q Was it also your judgment that CIT-MD-18 was an adequate and well controlled study?

A That was my judgment at the time, yes.

Q Do you continue to believe that MD-18 was a double-blind, randomized, placebo-controlled study, notwithstanding anything plaintiff's counsel has shown you today?

A I continue to believe that -- that overall it still met those criteria.

Q One moment.

When you reviewed the study report with

Mr. Wisner, you saw that Forest provided the primary efficacy analysis that included the allegedly unblinded patients and the post hoc secondary analysis that excluded those patients, correct?

A That's correct.

Q So FDA had both of those analyses in front of it when the agency was reviewing the application.

A That's true.

Q So the FDA was fully aware that excluding the allegedly unblinded patients, that the P-value on the primary efficacy analysis changed from 0.038 to 0.052, correct?

A That's correct.

Q I'm going to hand you what we're marking as Exhibit 37.

MS. KIEHN: 36?

(A discussion was held off the record.)

(Exhibit No. 37 was marked for identification.)

MR. WISNER: This is Exhibit 37?

MS. KIEHN: Correct.

BY MS. KIEHN:

Q Dr. Laughren, I'm handing you what's been

marked as Exhibit 37.

A Okay.

Q That's the new document we just handed you.

A Right. I don't have a 36, so that's --

Q Is that -- that's not 37 that she just handed you?

A This is 37.

Q Okay. So you have that before you?

A I do have 37 before me, correct.

MR. WISNER: And just for the record, Exhibit, I think, 36 --

MS. KIEHN: -- was the 2009 Lexapro package insert.

MR. WISNER: Okay. And I believe you're going to -- we agreed off camera, but we agreed that you are going to submit a clean copy of that for the court reporter, correct?

MS. KIEHN: Correct.

MR. WISNER: Okay.

THE WITNESS: Okay. Got you.

BY MS. KIEHN:

Q Exhibit 37 is excerpts from a deposition of James Jin, Ph.D. Do you see that at the very

bottom?

A Yes.

Q The date is October 21st, 2016. Do you see that?

A I do.

Q I will represent to you that Mr. -- or Dr. Jin was one of the statisticians on Study MD-18. If you turn to page 464.

A Okay.

Q I'm going to read into the record at the very top:

"Q. Mr. Jin, do you personally know whether all of the nine patients received pink pills?

"A. Not personally."

Skip down to line 15:

"Q. In your opinion, did any protocol violations in MD-18 impact the validity of your statistical analyses?

"A. I think the study result's still valid.

"Q. In your opinion, did any protocol violations in MD-18 impact

the validity of the study's positive results in the primary efficacy analysis?

"A. No."

Turning the page to page 465:

"Q. Do you personally know whether the nine patients were actually unblinded?

"A. No.

"Q. Assuming they were unblinded, would that change how you conducted the primary efficacy analysis?

"A. No. The ITT is still ITT.

"Q. Assuming that they were unblinded, would that change the result of the primary efficacy analysis?

"A. ITT analysis result would not be changed.

"Q. The study would still be positive from a statistical standpoint?

"A. The primary analysis, yes. Mm-hmm.

"Q. Do you have any concerns that MD-18 was analyzed incorrectly from a statistical standpoint?

"A. No.

"Q. Do you have any doubt that MD-18 was a positive study?

"A. No."

You would agree with Dr. Jin's testimony, wouldn't you?

A I -- I largely agree with it. The one difference that I just want to point out that -- just to emphasize that the way you explored the question of whether or not the primary analysis would have been impacted by the potentially unblinded patients was to do the exploratory analysis and see what effect that had on the P-value. And in my view, that basically confirmed the impression that it did not have a major impact on the -- on the primary analysis. So...

Q I believe you testified earlier that Study 94404 had some problems. Do you remember that?

A If -- if I recall correctly, the responder analysis in 94404 showed that the responder rate in the two groups, in placebo and drug, was

approximately 60 percent, which is extraordinarily high for a response rate in a -- in a depression trial.

And there's a lot of data now looking at -- at the ability of a depression trial to distinguish drug from placebo being essentially inverse related to the response rate. And when you get up around 60 percent, you're -- you're getting close to the ceiling, and a study like that has very little chance of distinguishing drug from placebo.

So I think from that standpoint, it raises questions about the assay sensitivity of 94404. That was really my major concern about that study.

Q Are you aware of any other issues with the study, with either the design or the conduct of the study?

A I -- off the top of my head, no. The design was -- was appropriate reasonably. The dose was what it should have been. And it's been a long time since I looked at that in detail, but that is the one feature of that study that -- that always stood out in my mind. In fact, I think the remission rate was close to 50 percent in both groups. You

know, again, very unusual for a depression study.

Q In your opinion, are SSRIs effective in treating pediatric depression?

A The -- the answer is yes. Of course, only two SSRIs are approved for the treatment of pediatric depression. But I -- I -- I think that the data that we have in -- in principle supports that conclusion. Again, we only have -- we only have positive data for -- for two of them. Well, for three if you include Celexa and Lexapro as different drugs.

Q You testified a few minutes ago -- strike that.

A few minutes ago, you agreed with Mr. Wisner that there was not sufficient evidence to definitively conclude that either Celexa or Lexapro were definitively effective in pediatric populations prior to 2009.

Do you recall that?

MR. WISNER: Objection.

THE WITNESS: I'm sorry. Repeat the question.

BY MS. KIEHN:

Q So Mr. Wisner asked you if you agreed

with this statement, and you did: That there was not sufficient evidence to definitely conclude that either Celexa or Lexapro were definitively effective in pediatric populations.

MR. WISNER: Objection.

BY MS. KIEHN:

Q Do you recall that?

A I -- I do.

Q Does that mean that neither drug was effective in pediatric patients prior to 2009?

A No, it doesn't mean that. It means that there is not sufficient evidence to reach a conclusion that they are effective. It doesn't -- you know, the absence of evidence is not evidence of absence.

And as I -- as I said -- I believe I said this in my testimony, that it would not be unreasonable for a thoughtful clinician to use either one in treating pediatric depression based on clinical judgment. But there was not enough evidence -- there was not sufficient evidence for FDA to reach a conclusion, a positive conclusion that either drug was effective in pediatric depression.

Q And to your knowledge, were psychiatrists

prescribing Celexa and Lexapro for pediatric patients --

MR. WISNER: Objection --

BY MS. KIEHN:

Q -- before 2009?

MR. WISNER: Objection. Lacks foundation.

THE WITNESS: It -- it's -- you know, I don't -- I don't have prescribing data to rely on in making the statement, but it certainly was my impression that they were both being prescribed.

BY MS. KIEHN:

Q So in your opinion, there is evidence supporting the efficacy of both Celexa and Lexapro in the treatment of pediatric depression; is that correct?

MR. WISNER: Objection.

THE WITNESS: Let -- let me -- let me rephrase that in a way that's acceptable to me.

There -- you know, based on FDA's review, there is evidence that Lexapro is effective in treating pediatric depression. I think, you know, based on back extrapolation, one could likely reach the same conclusion for Celexa, but in fairness, FDA

has not been asked to, nor have they looked at that question.

BY MS. KIEHN:

Q But I believe you testified earlier that MD-18 was evidence of efficacy for citalopram in pediatric depression; is that correct?

A As -- as a standalone study, it provided -- it didn't provide -- on its own, it didn't provide evidence of the effectiveness of Celexa in treating pediatric depression. What I -- what I -- based on what we had back in 2002, and obviously that's reflected in FDA's decision not to approve the supplement.

Q It didn't provide evidence of effectiveness sufficient for FDA approval, correct?

A Correct.

Q But the MD-18 study itself does provide some evidence of efficacy for Celexa in the treatment of pediatric depression, correct?

MR. WISNER: I renew my objection.

THE WITNESS: It -- it's -- it's a positive study in that population. And again, I -- in my -- and again, I'm not -- I'm not at FDA anymore. In my judgment, it's not unreasonable for a

clinician to take some reassurance from that study in making a decision to -- to use it in pediatric depression. But that's a different question than, you know, whether or not there is sufficient evidence for a regulatory body like FDA to reach that conclusion.

BY MS. KIEHN:

Q Is there anything that plaintiff's counsel has shown you or said to you today that has caused you to doubt any prior decision you made about Celexa or Lexapro while you were at the FDA?

A No.

MS. KIEHN: Nothing further.

FURTHER EXAMINATION BY COUNSEL FOR PLAINTIFFS

BY MR. WISNER:

Q Doctor, a few follow-up questions. Let's start off where you ended off on cross-examination/redirect.

There has actually never been a positive study for Lexapro in children under 12, correct?

A That's correct.

Q In fact, it was studied in MD-15 and it was negative, right?

MS. KIEHN: Objection.

THE WITNESS: MD-15 was -- was a negative study.

BY MR. WISNER:

Q So you would agree that even at where we stand here today, there is insufficient evidence to conclude that Lexapro is effective in pediatric patients below 12 years old.

A That's correct.

Q And you would agree with me that when a patient is going -- is getting older, between 12 and as they're reaching their adolescence, their body changes, right?

A That's correct.

Q They go through puberty.

A Yes.

Q And one of the explanations as to why there might be a difference between children under 12 and adolescents over 12 in the results of depression or the treatment of depression is that depression manifests itself differently in children the way it does in adolescents?

A It does have --

MS. KIEHN: Objection.

THE WITNESS: It does have a different

phenomenology in children compared to adolescents and adults.

BY MR. WISNER:

Q Now, let's go back to Exhibit 8 briefly. It's the final study report.

Hopefully, it's not too far buried in there. It's probably in that pile (indicating).

A No, I got it right here.

Q Oh, you got it? Okay, great.

On page 63, you recall that defense counsel, Ms. Kiehn, asked you some questions regarding the first sentence in the second paragraph there?

A Yes.

Q And it reads that: "Nine patients," and it lists the patient numbers, "were mistakenly dispensed one week of medication with potentially unblinding information."

Do you see that?

A I do.

Q Now, there was some back and forth about whether or not patients in the placebo arm got the wrongly colored pills.

Do you recall that?

A I do.
Q You would agree that, at least the way it's written here, it suggests that that in fact happened.
MS. KIEHN: Objection.
THE WITNESS: I -- which -- which happened?
BY MR. WISNER:
Q I'm sorry. The way it's written here, it does sure look like that all nine patients received the wrongly colored pill.
MS. KIEHN: Objection.
THE WITNESS: Um, that -- that's the way I interpreted it when I -- when you showed it to me previously.
BY MR. WISNER:
Q And if in fact that wasn't the case, this would just be another example of the final study report being inaccurate.
A Well, it --
MS. KIEHN: Objection.
THE WITNESS: I don't -- I wouldn't -- I would characterize it more the way that the characterization that you've used throughout the day

is inartfully written. How is that?
BY MR. WISNER:
Q Okay. That works.
Turn your attention to page 30 -- I'm sorry, Exhibit 33. It's probably over there in that pile. It's one of the defendant's exhibits.
A Yes.
Q Okay. This is an e-mail exchange from Gregory Dubitsky at the FDA with people at Forest. Do you see that?
A I -- I do.
Q And in this e-mail exchange in July of 2004, it appears that Gregory Dubitsky is asking for clarification about the nature of the unblinding; isn't that true?
A Yes.
Q Now, to be clear, this is dated July 17, 2004, right?
A Correct.
Q So this is -- this is long after your memorandum and review of MD-18, correct?
A Correct.
Q And if you actually look at the answer, it's on page 9 of 11 in the attachment --

A Yes, I have that.

Q -- Forest provides a response to the inquiry, right?

A Correct.

Q Nowhere in that response does Forest state that the blind was unmistakenly violated. Correct?

A There's simply -- to my understanding, in that panel, simply providing the distribution of treatment assignment, you know, for those -- for those nine patients.

Q This sure would have been a great point at which Forest could have disclosed what happened with those unblinded patients since the FDA is specifically asking about it.

MS. KIEHN: Objection. Misstates the document.

THE WITNESS: I -- I -- again, my view that I've expressed throughout the day is -- is in general, I think -- I think it's -- it's appropriate for drug companies to provide as complete information as they can about what actually happened in the conduct of a study.

BY MR. WISNER:

Q I agree, Doctor, and I'm just saying this is yet another example where Forest had an opportunity to do that with regards to these unblinded patients.

A Let me -- let me read the question that the FDA asked.

Q Sure.

A (Perusing document.)

I mean technically it's -- it's answering the question that was asked. But, again, my -- my view was -- was that more complete information on the potential unblinding could have been provided in the -- in the original supplement.

Q Now, Doctor, you agree that scientific debate about science is an important part of the scientific process.

MS. KIEHN: Objection.

THE WITNESS: In general, I -- I have to support debate in science, yes.

BY MR. WISNER:

Q And you would agree that the FDA is not the final authority when it comes to whether or not a drug is effective or not, correct?

MS. KIEHN: Objection.

THE WITNESS: Congress has given FDA legal authority to make that judgment.

BY MR. WISNER:

Q But it's not the final authority, right?

MS. KIEHN: Objection.

THE WITNESS: Well, it's -- FDA is the final authority from the standpoint of whether or not a product can be marketed and promoted for a particular indication.

BY MR. WISNER:

Q Now, you have -- are you familiar with the -- the sort of landmark Supreme Court decision Wyeth v. Levine?

A You -- I mean I -- I've heard that. You'll have -- you will have to fill me in.

Q Do you understand that the U.S. Supreme Court has held that the content of the labeling, the final responsibility rests with the drug manufacturer at all times? Do you understand that?

MS. KIEHN: Objection. Mischaracterizes the decision.

THE WITNESS: I -- I think, you know, companies have an obligation to write a proposed labeling that -- you know, that is consistent with

the available data about a drug. But FDA has the final authority over -- over whether or not that proposed labeling is acceptable.

BY MR. WISNER:

Q Absolutely. However, a drug manufacturer, they write the label, right?

MS. KIEHN: Objection.

THE WITNESS: Well, it -- it -- it depends. FDA, when a drug is first approved, has a lot to do, probably more than most people understand, about the actual language that goes into a label. There's extensive editing typically of a -- of a proposed labeling that comes with part of the NDA.

BY MR. WISNER:

Q Now, isn't it true, Doctor, that if there is a falsehood or misrepresentation in the labeling, it's the drug manufacturer's responsibility, not the FDA's?

MS. KIEHN: Objection.

THE WITNESS: I -- I think -- again, and this comes right out of the law, the expectation is that companies will propose labeling that's not false and misleading.

BY MR. WISNER:

Q But when it is, the responsibility lies with the manufacturer, not the FDA, right?

MS. KIEHN: Objection.

THE WITNESS: I -- I think both share responsibility for -- for, you know, making judgments about -- because it's not a -- it's not a black and white issue whether or not it's false or misleading. You know, it's the kind of thing that is -- is subject to debate.

BY MR. WISNER:

Q It's sort of like a disputed issue of fact, right?

MS. KIEHN: Objection.

THE WITNESS: It -- it's -- it's a dispute about how you interpret particular findings.

BY MR. WISNER:

Q Are you aware that the U.S. Supreme Court has held that lawsuits which challenge labeling or dig deeper into internal documents, kind of like we've done today, actually help the FDA with its mission of ensuring that drugs are safe and effective?

A I -- I --

MS. KIEHN: Objection. Mischaracterizes

the decision.

THE WITNESS: I don't -- I don't question that.

BY MR. WISNER:

Q I'm going to give you what I've marked as Exhibit --

MR. WISNER: What are we at here?

MS. KIEHN: 38.

MR. ROBERTS: 38.

BY MR. WISNER:

Q I'm going to mark this as Exhibit 37-A. Okay? This is additional testimony by Mr. Jin.

Do you recall that defense counsel read to you portions of Dr. Jin's testimony?

A Should this be marked as 37-A?

(Exhibit No. 37-A was marked for identification.)

BY MR. WISNER:

Q Thank you, Doctor.

So I've given you what has now actually been marked as Exhibit 37-A. These are additional excerpts of the deposition of James Jin.

Do you see that, Doctor?

A Yes.

Q All right. If you turn to page 181 -- well, before that, do you have Exhibit 37, the exhibit that -- that counsel showed you?

A Here it is. Yeah. Yeah.

Q And you recall that she read portions of this transcript starting on page 463. Do you see that?

A Yes.

Q And you see that actually the questions that Mr. Jin was answering were in response to Ms. Kiehn's questions.

Do you see that?

A I -- I see that, yes.

Q I will represent to you that this interchange occurred after a break, do you understand that, in the deposition.

A Okay.

Q Okay. Let's look at what Dr. Jin said before that break. Okay?

A Okay.

Q So if you look at page 181 in the deposition transcript that I've handed you. It's Exhibit 37-A. Page 181, starting on line 8:

"Q. Now, if you look at the P-value

over on the right midway, you see it's 0.52?

"A. Yeah, I see that."

MS. KIEHN: 0.052.

MR. WISNER: Sorry. Did I say 0.52? Good grief, sir.

THE WITNESS: You and I make the same mistake.

MR. WISNER: I guess it's a common typographical error. Let me try this again. It's getting late.

BY MR. WISNER:

Q All right.

"Q. Now if you look at the P-value over on the right midway, you see it's 0.052.

"A. Yeah, I see that.

"Q. Was that a statistically significant outcome?

"A. Not.

"Q. So it was negative, not in favor of Celexa's efficacy, correct?

"MS. KIEHN: Objection.

"THE WITNESS: Yeah, I think

it's -- the P-value is not meet the criteria for a 0.05."

Do you see that?

A I do.

Q All right. And I will just represent to you that Mr. Jin does not speak English particularly well, so that's why some of these -- the grammar might seem a bit off. Okay?

A Okay.

Q All right. Now, if we turn to the next page, page 219, it -- starting on line 6, it says:

"Q. So you don't care whether they were unblinded or not?

"MS. KIEHN: Objection.

"THE WITNESS: I cannot say I don't care, but we just -- we have to exactly follow the definition.

"MR. BAUM:

"Q. With the patients in, with the unblinded patients in, it corrupted the data for the ITT population, didn't it?

"MS. KIEHN: Objection.

"THE WITNESS: Has some impact,

yeah."

Do you see that?

A I do.

Q So it appears that Mr. Jin is conceding that inclusion of these unblinded patients potentially corrupted the data, didn't he?

MS. KIEHN: Objection.

THE WITNESS: That -- that is what he's saying here, and -- and I've already expressed my slightly alternative view of that.

BY MR. WISNER:

Q I understand.

A That the appropriate way to see whether or not those potentially unblinded patients had an impact on the -- the correct P-value for the study, and I agree with him there that the ITT is -- is the dataset to use to generate the P-value for the trial, but the sensitivity analysis is the way to determine whether or not there was a significant impact on -- on the P-value. And -- and that was done, and in my judgment, it didn't have a -- an important impact. So...

Q I appreciate your answer, Doctor. I'm just saying, according to Mr. Jin --

A Yes.
Q -- it corrupted the data?
A I'm sorry. Yes.
MS. KIEHN: Objection. Mischaracterizes the testimony.
BY MR. WISNER:
Q That's a "yes," Doctor?
A I'm sorry?
Q That's a "yes," Doctor? I'm sorry, I didn't hear it. She objected.
A I mean in reading and interpreting his answers here, he seems to be implying that.
Q Okay. He also testified earlier on page 181, right, that he believed, as the statistician conducting the analysis, the sensitivity analysis that we were discussing, he believed that it was negative, correct?
MS. KIEHN: Objection.
THE WITNESS: I'm sorry.
BY MR. WISNER:
Q Sorry. On page 181, it's the first portion that we read.
A Oh, okay.
Q Sorry.

A Yes. That's correct, he does say that.

Q So you agree then that it appears that Forest's lead statistician -- I'm sorry, Forest's statistician on MD-18 appears to have agreed that the sensitivity analysis showed that the study was negative; is that right?

MS. KIEHN: Objection.

THE WITNESS: I -- I don't -- I don't interpret what he is saying that way. Again, I can't know what was in his mind when he was making the statement, but the way I -- the way I read this is that he's saying that technically a P-value of 0.052 does not meet the -- the standard, you know, threshold of -- of 0.05.

Again, in my -- in my judgment, that's an incorrect use of P-value. A sensitivity analysis that has reduced power should not be held to that same standard. That -- that's where we disagree.

BY MR. WISNER:

Q I got you, and I -- I understand you don't agree and we've covered that several times.

I guess my question to you, Doctor, is it says here:

"Q. So it was negative, not in

favor of Celexa's efficacy, correct?"

And he responds:

"Yeah. I think it's -- the P-value is not meet the criteria for 0.05."

Do you see that?

A That -- that's what he says.

Q So he is saying it's negative.

MS. KIEHN: Objection.

THE WITNESS: Yes.

MR. WISNER: Okay. No further questions.

FURTHER EXAMINATION BY COUNSEL FOR DEFENDANTS

BY MS. KIEHN:

Q Dr. Laughren, does Mr. Jin actually say that the data were correct?

MR. WISNER: It's on the next page, Doctor.

THE WITNESS: Well, I mean, at the top of this page, the question is: "That's corrupted data, though, isn't it?"

And the witness says: "There is some data question, yeah, agreed. Mm-hmm."

So I don't -- I don't -- I don't know quite how to interpret that -- that answer in

response to that question.
BY MS. KIEHN:
Q But Mr. Jin never says the data was corrupted, correct?
A He says there is some data question.
Q He doesn't say it was corrupted.
A He does not -- he does not directly state that the data are corrupt.
Q Do you believe that the data in MD-18 were corrupt?
A No. I -- I -- again, I believe the correct P-value for that study is the 0.038, and I believe it was proper to do the sensitivity analysis to look to see whether or not there was any impact of the data that were potentially unblinded. And -- and the answer from that analysis is that it did not have a -- in my view, a substantial impact, negative impact on -- on the analysis. And so that's just my judgment.
MS. KIEHN: One minute. I'm thinking.
MR. WISNER: People have families they need to get home to, Ms. Kiehn.
MR. ROBERTS: You're here till Sunday.
MR. WISNER: I'm not talking about me. I

don't have a family. I'm too young of a lawyer for that.

MS. KIEHN: No further questions.

MR. WISNER: Thank you, Doctor, for your time.

THE WITNESS: Thank you.

MR. WISNER: That concludes the deposition.

MS. KIEHN: Thanks, everybody.

MR. GRIFFIN: Thanks, all.

THE VIDEOGRAPHER: The time is 6:36 p.m. This is the end of disc No. 5 and the end of the video deposition. We will go off the video record.

(Signature having not been waived, the deposition of THOMAS LAUGHREN, M.D. was concluded at 6:36 p.m.)

CERTIFICATE OF NOTARY PUBLIC

I, LESLIE A. TODD, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was taken by me in stenotypy and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

Dated this 3rd day of February 2017.

_____

LESLIE A. TODD
Notary Public in and for the
State of Maryland

My commission expires:
December 23, 2018

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E R R A T A

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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