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.

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.

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

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.

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 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?

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,

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?

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

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

"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.

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.

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

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

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

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

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

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

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.

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?

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