1	IN THE UNITED STATES DISTRICT OF MAS	
3	DISIRICI OF MAS	DACUDDIID
4	x	
	IN RE: CELEXA AND LEXAPRO	
5	MARKETING AND SALES PRACTICES	
6	LITIGATION) 09-MD-2067-(NMG)
	PAINTERS AND ALLIED TRADES) Case No. 13-CV-13113
7) (NMG)
	CARE FUND, A THIRD-PARTY)
8	HEALTHCARE PAYOR FUND, on) Hon. Nathaniel Gorton
0	behalf of itself and all	
9	others similarly situated, Plaintiffs,) Hon. Marianne Bowler
10	v.)
)
11	FOREST PHARMACEUTICALS, INC.,)
	and FOREST LABORATORIES, INC.,	
12	Defendants.)
13	IN RE: CELEXA AND LEXAPRO) MDI NO. 2067
	MARKETING AND SALES PRACTICES	
14	LITIGATION) 09-MD-2067-(NMG)
	DELANA S. KIOSSOVSKI and) Hon. Nathaniel Gorton
15	RENEE RAMIREZ, on behalf of)
1.0	themselves and all others	
16	_) 14-CV-13848 (NMG)
17	Plaintiffs, v.) Hon. Nathaniel Gorton
- /	••)
18	FOREST PHARMACEUTICALS, INC.) Hon. Marianne Bowler
	and FOREST LABORATORIES, INC.,)
19	Defendants.)
20	X	
20 21	VIDEOTAPED DEPOSITION OF TH	
22	ROCKVILLE, MAR	
23	FRIDAY, JANUARY	
24	9:08 A.M.	

Thomas Laughren, M.D. Oh, at the time I left the VA? Q Yes. Α No, that was -- that was pre-SSRI. So the first SSRI that I'm aware of was 0 Prozac; is that right? Α That's correct. And that was approved after you arrived 0 at the FDA. А That was -- that was late '80s. That was probably '87, something like that. Were you at all involved with the Q approval or review of Prozac?

13 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?

-

17 A That's correct.

18 Q Some of those include Paxil, Zoloft,

19 Celexa, Lexapro.

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20 Are you aware of those?

21 A Luvox.

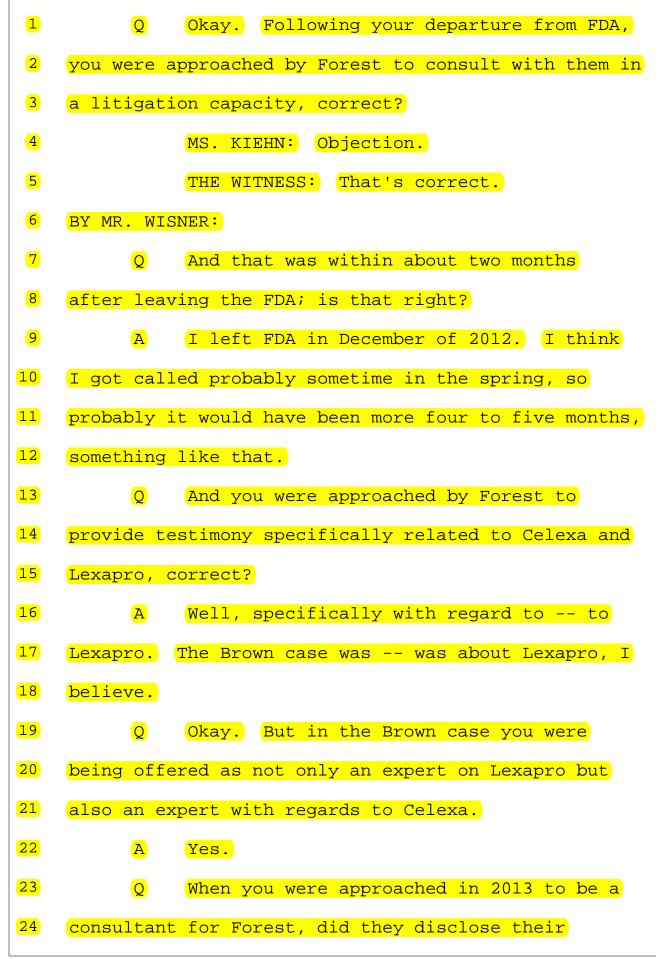
22 Q Luvox.

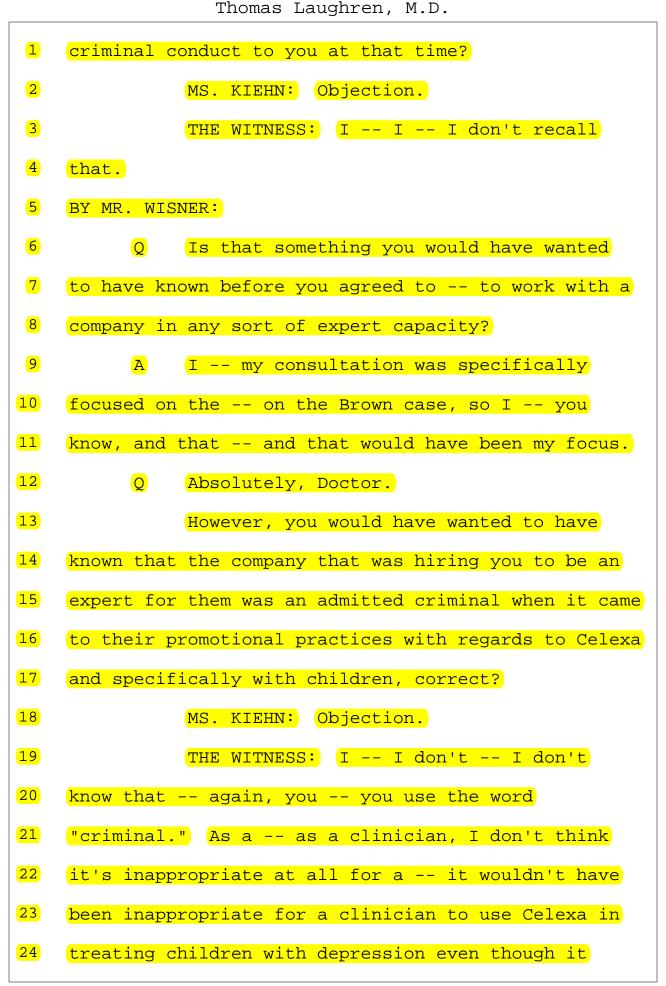
Would it be fair to say that during your time at the FDA, you were involved in some capacity

1	with the approval or review of all of those SSRIs?
2	A Every one of them, because I was about
3	three years after I started at FDA, I became team
4	leader for psychopharmacology in the division of
5	neuropharmacological drug products, and so I was
6	involved with with every every psychiatric drug
7	development program.
8	Q And that also includes, I assume,
9	antipsychotics as well?
10	A Absolutely.
11	Q Now, the most recent SSRI that I'm
12	familiar with that's been approved is you can
13	correct me if I'm wrong, you probably know better
14	than me but is it Viibryd?
15	A Vilazodone. It's a
16	Q Vilazodone.
17	A it's not a is not an SSRI. It's a
18	much more complicated product. It has other it
19	has some some serotonin reuptake activities, but
20	it also has some other activities, 5-HT1A and so
21	forth. It's not it's not considered an SSRI,
22	although it has it has effects on the serotonin
23	transporter which is characteristic of the SSRIs, but
24	it's a more complex drug.

1	was based solely upon statistical significance and
2	that clinical meaning whether or not something was
3	clinically meaningful was something for the academics
4	and the doctors to figure out?
5	MS. KIEHN: Objection.
6	THE WITNESS: I don't I don't entirely
7	agree with that. I I know Paul Lieber very well.
8	BY MR. WISNER:
9	Q Sure.
10	A I've known him for many, many decades,
11	and and he was the division director at the time
12	that Zoloft was under consideration, so he would have
13	approved Zoloft. I don't think he would have
14	approved Zoloft if he didn't think that it was a
15	clinically meaningful effect, despite what he might
16	have said at an advisory committee, because Paul
17	Paul liked to talk a lot.
18	Q Does the FDA in reviewing a compound for
<mark>19</mark>	approval review internal correspondence from the drug
20	company?
21	A That's typically not part I mean, FDA
22	tends to focus more on the data. And so actually
23	often when a clinical reviewer gets an application,
24	they often go right to the data rather than even
a 11	

1	reading the summary, because they don't want to be
2	influenced by by, you know, the company's spin on
3	the data. So they just go right to the datasets and
4	the tables and look at the data.
5	Q Now, during your time at the FDA, do you
6	ever recall looking at a dataset and going, I think
7	this is all made up?
8	MS. KIEHN: Objection.
9	THE WITNESS: I I don't recall ever
10	reaching that judgment on a based on a dataset.
11	BY MR. WISNER:
12	Q Would it be fair to say that when a drug
13	sponsor submits the data from a clinical trial, you
14	take it at face value as being true and accurate?
15	MS. KIEHN: Objection.
16	THE WITNESS: I I wouldn't say that we
17	took it at face value. You know, we we
18	certainly you know, part the process of
19	reviewing a new drug application is very complex. It
20	includes doing you know, there's an Office of
21	Scientific Investigations that goes out and actually
22	looks at trial sites to try and and get at that
23	very issue, you know, whether a question like
24	whether or not the data are real, whether or not



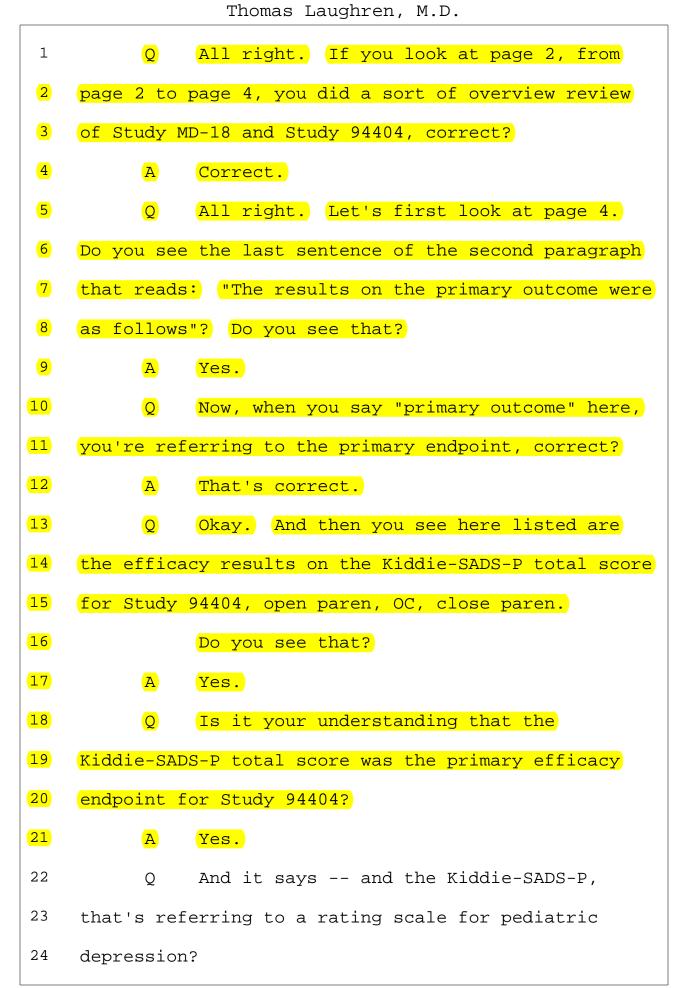


1	wasn't specifically labeled for that. Because, you
2	know, I if there is ever a reason to believe that
3	these drugs, even though they were initially studied
4	in adults, would work in children, and and
5	childhood depression is a very serious problem that
6	needs to be addressed. So, again, I wouldn't have
7	been focused on that aspect of things. That's all I
8	can say.
9	BY MR. WISNER:
10	Q Okay, Doctor, but you understand that
11	Forest didn't plead guilty because doctors used
12	Celexa off label. They pled guilty because they
13	promoted the off-label use of Celexa in children.
14	You understand that?
15	MS. KIEHN: Objection.
<mark>16</mark>	THE WITNESS: I understand that.
17	BY MR. WISNER:
18	Q And I guess my question is now, at this
19	moment, the fact that a company that was hiring you
20	had pled guilty to committing the crime of off-label
21	promotion with regards to children, is that something
22	that you would have liked to have known?
23	A I don't
24	MS. KIEHN: Objection.

1	Q All right. If you look at the next
2	sentence, it says: "Since there was agreement
3	between the sponsor and FDA that these trials were
4	negative, there was no need for a statistics review
5	of the efficacy data."
6	Do you see that?
7	A Yeah, I I see I see that now, and
8	that's a of course, a misstatement because one of
9	the studies was positive. And I noticed that I I
10	state that in the first paragraph here. I state it
11	again on page 3 in my comment on Study MD-18. I say:
12	"I agree with Dr. Hearst that this is a positive
13	study."
14	And I say it several times later in the
15	document. So I don't I don't recall why why I
<mark>16</mark>	said that. But the statement you know, the the
17	conclusion is still the same. Since our requirement
18	for approving a pediatric supplement would have been
<mark>19</mark>	two studies, two positive studies, and since it
20	didn't meet that threshold so since we knew that
21	we weren't going to approve it, we often wouldn't get
22	a full statistical review at that time.
23	Q Would it be fair to say then that when
24	you stated here that the agreement between the

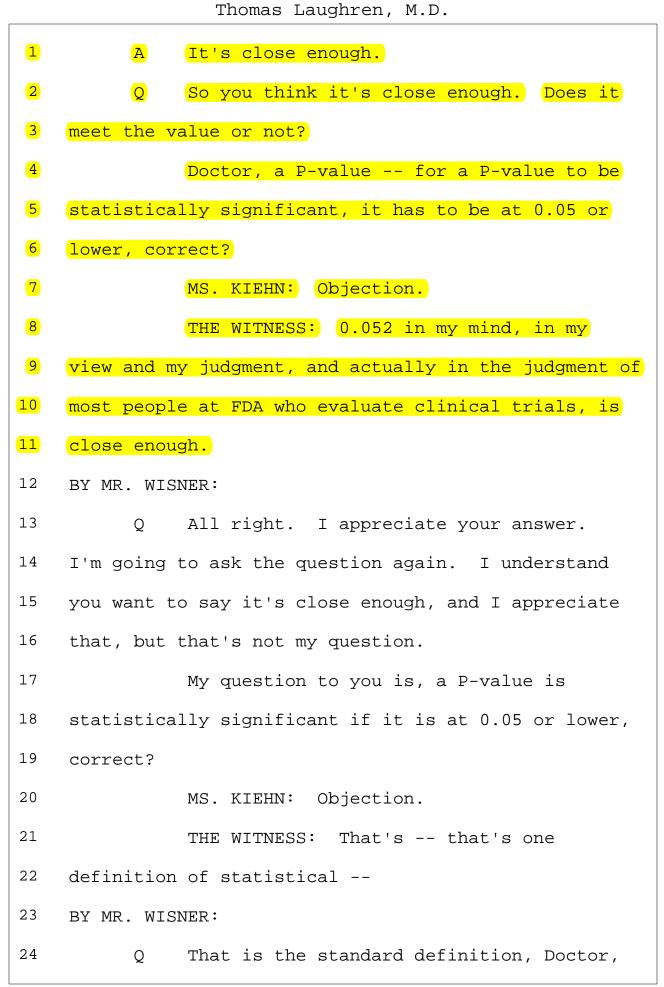
1	sponsor and FDA that these trials were negative
2	was referring to negative in the sense that it
3	wouldn't be sufficient to secure a pediatric
4	indication?
5	A That's that's the way I interpret
6	that, yes.
7	Q Now, it says "sponsor" here. I just want
8	to be clear that's referring to Forest, correct?
9	A Correct.
10	Q Okay. It says: "There was no need for a
11	statistics review of the efficacy data."
12	What is a statistics review?
13	A It it's an overlapping review that
14	specifically focuses on the on the efficacy data.
15	Somewhat redundant with the clinical review.
<mark>16</mark>	Q And what what is the difference, if
17	there is any, between a statistics review and a
18	clinical review?
<mark>19</mark>	A The the statistical review would
20	likely go into more detail on the on the analysis
21	plan and whether or not it was followed in in
22	conducting the analysis.
23	Q And by analysis plan, you are referring
24	to the prespecified efficacy parameters and the

	Thomas Laughren, M.D.
1	protocol?
2	A And and the plan for analyzing the
3	data.
4	Q So that also would apply to adverse
5	events, safety data as well?
6	A Typically a statistics reviewer would not
7	look at at adverse events because there's there
8	wouldn't have been any hypothesis testing, and their
9	focus is primarily on hypothesis testing.
10	Q Do you have any independent recollection
11	of having any discussions with Forest about there not
12	being a need for a statistics review of the efficacy
13	data?
14	A No. No.
15	Q Okay. Is that a discussion, based on the
16	sentence you read here, that you probably did have at
17	some point?
18	A I I doubt that I doubt that we
19	actually had a discussion about that. It was it
20	would have been just obvious since everyone knew what
21	the standard was that you had to have two studies to
22	get a claim, and they they clearly acknowledged
23	that one of their studies was negative. So there
24	wouldn't have been any basis for a claim.

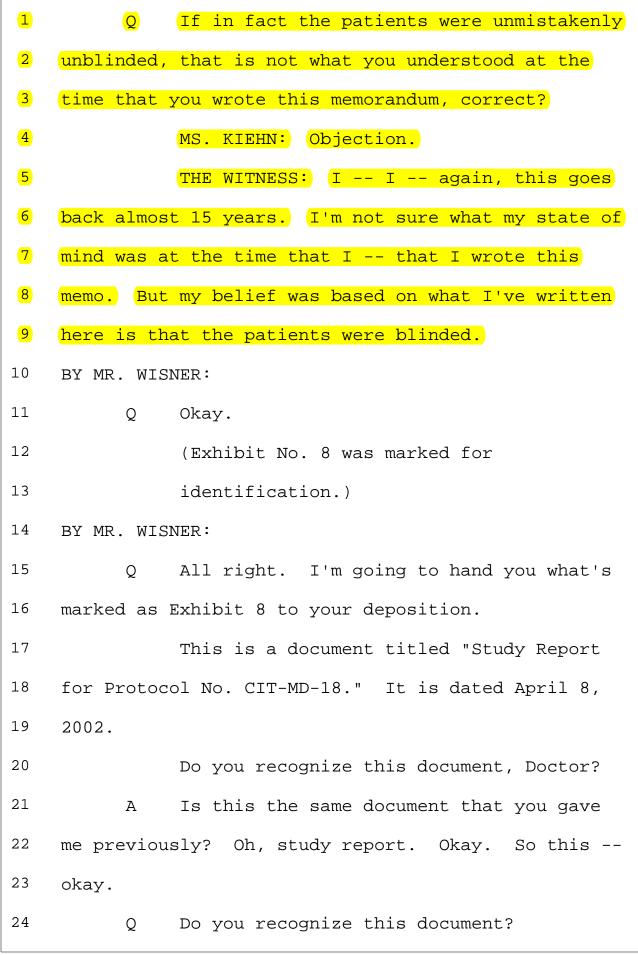


1	A General generally, you know, at that
2	time we tended to rely more on LOCF analyses than
3	observed cases. They both have their pros and cons.
4	Q I don't want to get into a longwinded
5	answer, and if it takes too long to explain, that's
6	fine, but what are sort of the pros and cons of the
7	two analyses?
8	A Well, the problem with the observed cases
9	is that it's a it's a truncated analysis in the
10	sense that you're not using data from patients who
11	didn't complete.
12	The problem with an LOCF analysis is that
13	you're you're assuming that the score at eight
14	weeks is that if that patient continued, it would
15	have been that same score at 12 weeks, and that's
16	that's an assumption that's you don't have any way
17	of verifying that. So
18	Q So you agree then that the OC approach as
<mark>19</mark>	well as the LOCF approach are really two different
20	ways of looking at the same data?
21	A Yes.
22	Q And typically the protocol will specify
23	whether or not the primary endpoint will use an LOCF
24	or an OC analysis, right?

1	My question was to you, is there anything
2	that was truthful or accurate about this, and you
3	specified that there was a typo, 0.52; is that right?
4	A That that's correct.
5	Q Okay.
6	A It's it's 0.052.
7	Q Now, you also just testified that a
8	P-value of 0.052 is statistically significant; is
9	that right?
10	A It's close enough.
11	Q I'm sorry, that wasn't my question.
12	Does a P-value of 0.052 meet the
13	threshold of statistical significance, yes or no?
14	A Whether whether or not a a P-value
15	meets that standard is a judgment. It is a judgment.
<mark>16</mark>	Most people in looking at a P-value of 0.052 would
17	round it to 0.05. And so in my in my view, that's
18	close enough.
19	Q I'm sorry, Doctor. My question to you
20	was not whether it's close enough.
21	My question to you and to this jury and
22	under oath, and as someone who worked at the FDA for
23	29 years, a P-value of 0.052, does that meet the
24	definition of "statistically significant" or not?



	Thomas Laughren, M.D.
1	MS. KIEHN: Objection.
2	THE WITNESS: I would need, you know, the
3	full documents because I obviously made a made a
4	typo.
5	BY MR. WISNER:
6	Q Okay. Now, in that sentence, before
7	that, you said: "There was a packaging error in
8	tablets being distinguishable for drug and placebo
9	for nine patients, although still blinded."
10	It was your understanding that the
11	patients, despite getting a different color tablet,
12	were still blinded, correct?
13	MS. KIEHN: Objection.
14	THE WITNESS: I I'm assuming that I
15	made that statement based on something that I had
16	seen in in the supplement.
17	BY MR. WISNER:
18	Q Okay. So it was your understanding that
19	the patients, despite receiving different color
20	tablets, were still blinded, correct?
21	MS. KIEHN: Objection.
22	THE WITNESS: Well, that that was
23	that was my assumption, correct.
24	BY MR. WISNER:



1 changed	d the results, doesn't he?
2	MS. KIEHN: Objection.
3	THE WITNESS: Well, he he states
4 that	- yes, he does state that, you know, that
5 exclud	ing those patients led to a decrease in the
6 least s	squares' mean difference and increased the
7 P-value	e.
8 BY MR.	WISNER:
9 (Q And the exclusion of those nine patients,
10 accord	ing to him, changed the P-value from being
11 0.038	to 0.052. Do you see that?
12	A I do.
13	Q Now, you agree that 0.038 is is
14 statis	tically significant?
15	A I do.
16 0	Q That is clearly statistically
17 signif:	icant, right?
18 2	A Yes.
19 (Q That is below 0.05, right?
20	A That's correct.
21	Q Now, 0.052, you testified already that
22 that is	s statistically significant I believe you
23 said i	t was close enough; is that right?
24	A <mark>I did.</mark>

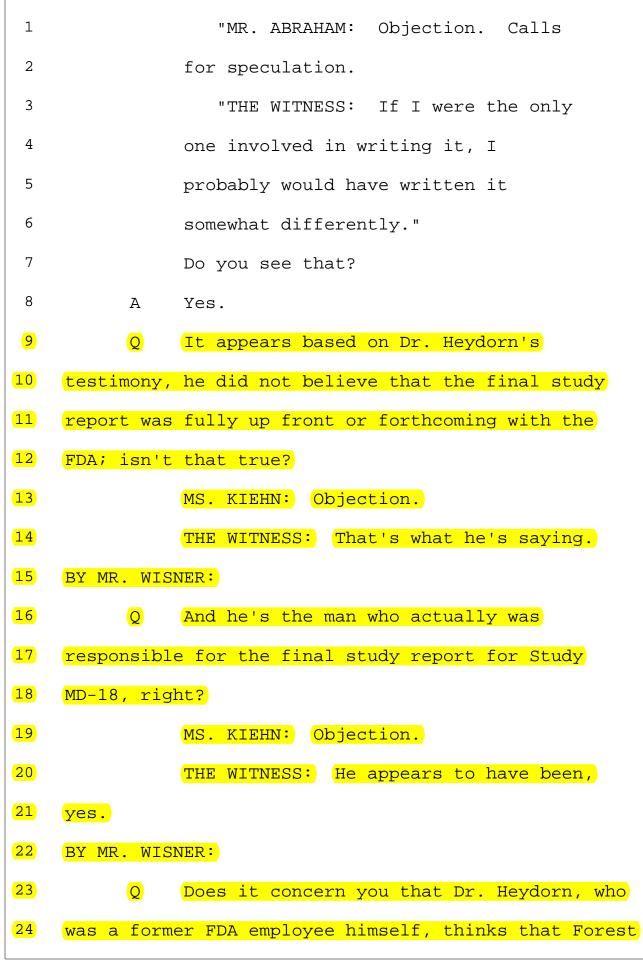
Q Okay. But you agree that 0.052 is more 1 2 than 0.050, right? 3 MS. KIEHN: Objection. Asked and answered. 4 5 THE WITNESS: I -- I do. 6 BY MR. WISNER: 7 Okay. It appears, based on the fact that 0 8 Dr. Hearst copied and pasted a portion of the final 9 study report into his own clinical review, that 10 Dr. Hearst relied upon the statements made in the final study report. 11 12 MS. KIEHN: Objection. 13 THE WITNESS: It certainly appears that 14 he read it. 15 BY MR. WISNER: 16 And do you recall whether or not you had 0 any conversations with Dr. Hearst about this 17 unblinding issue? 18 19 MS. KIEHN: Objection. 20 MS. WEINMAN: Objection. 21 THE WITNESS: I -- I don't recall. 22 BY MR. WISNER: 23 0 Okay. And I don't want to know any of 24 the substance of any of those conversations, but if

	-
1	state that the integrity of the blind was
2	unmistakenly violated, did it?
3	A No.
4	Q In fact, the final study report stated
5	that they were otherwise blinded, didn't it?
6	A It it suggests that there was a
7	potential for unblinding, but didn't acknowledge
8	that that the investigators at least, if
9	they received if they noticed that the tablets had
10	the you know, the name "Celexa" on them and were
11	commercial tablets, that the investigators at least
12	would have would have been unblinded with regard
13	to those patients.
14	Q Before we get to the next e-mail, does it
<mark>15</mark>	concern you that the clinical medical director at the
<mark>16</mark>	time, Dr. Flicker, believes that a letter that is
17	being proposed to the FDA contains "a masterful
18	stroke of euphemism"?
19	MS. KIEHN: Objection.
20	THE WITNESS: Yeah, no, that's that's
21	concerning, I would say.
22	BY MR. WISNER:
23	Q Okay. Let's take a look at Mrs. Rubin's

that that's dated March 15, 2000? 1 2 А I do. 3 0 This is the day after Dr. Flicker's e-mail. Do you see that? 4 5 А I do. 6 0 She states: "Thanks for the compliment. 7 Part of my job is to create, " quote, "masterful," 8 unquote, "euphemisms to protect medical and 9 marketing." 10 Do you see that? 11 А I do. 12 Now, I will represent to you Amy Rubin 0 was in regulatory affairs for Forest. 13 14 Does it concern you that an employee for 15 Forest whose job it is to interact with the FDA 16 states that it's part of her job to "create masterful 17 euphemisms to protect medical and marketing"? 18 MS. KIEHN: Objection. 19 THE WITNESS: It -- it is objectionable. 20 I mean, my -- my expectation of -- of companies is 21 that they will be, you know, completely transparent with -- with the FDA about what happened in the 22 23 conduct of a trial. 24 BY MR. WISNER:

1	Q Now, earlier in 2013 you were actually
2	asked to be an expert for Forest, weren't you?
3	A An expert in in litigation, yes.
4	Q For the Brown case, correct?
5	A Yes.
6	Q And, actually, one of the
7	THE VIDEOGRAPHER: Doctor, if you would,
8	I think your phone is in your shirt pocket.
9	(A discussion was held off the record.)
10	THE VIDEOGRAPHER: Excuse me.
11	MR. WISNER: No problem.
12	BY MR. WISNER:
13	Q I'm sorry, Doctor, you were saying you
14	believed that it's important for pharmaceutical
15	companies to be straightforward and honest with the
16	FDA, right?
17	A Yes.
18	Q And does it concern you and I'm sorry
19	if I asked this question already, but I got
20	distracted, so I just want to keep the record clear.
21	Does it concern you that Ms. Rubin, whose
22	job it was to interact with the FDA, believes that
23	it's her job to "create masterful euphemisms to
24	protect medical and marketing"?

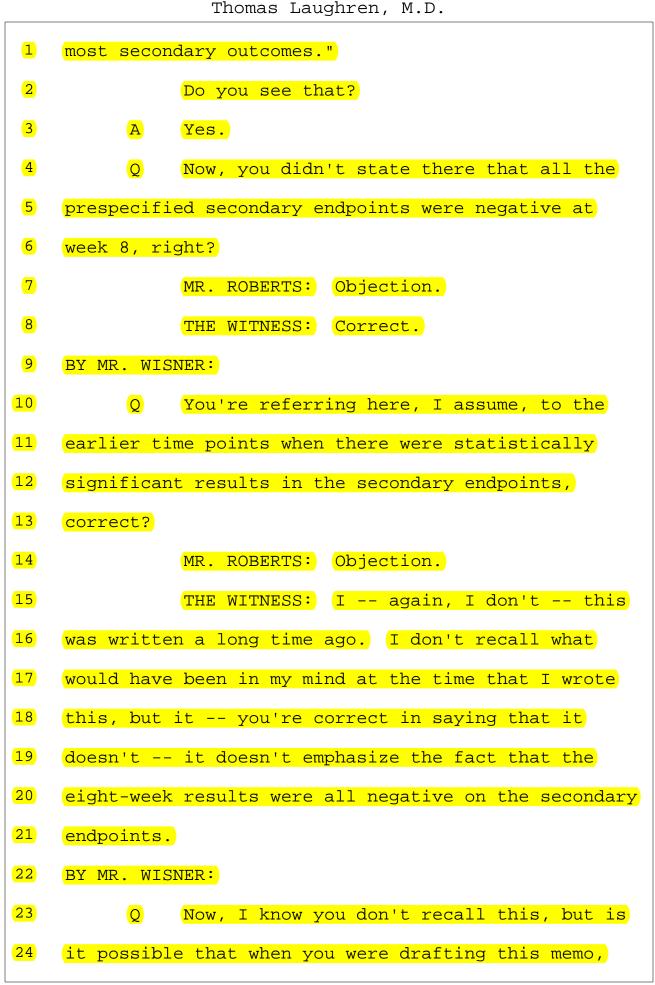
[Thomas Laughren, M.D.
1	MS. KIEHN: Objection.
2	THE WITNESS: What what concerns me
3	is is that you know, what was represented to
4	FDA was not precisely what happened.
5	BY MR. WISNER:
6	Q Doctor, it kind of looks like Ms. Rubin
7	here is bragging about misleading the FDA, doesn't
8	it?
9	MS. KIEHN: Objection.
10	THE WITNESS: I it I must say I
11	I find that kind of language objectionable. But,
12	again, what I mostly object to is, is the fact that
13	Forest apparently knew that that it wasn't just a
14	difference in coloring. The tablets that were sent
15	actually had the brand name on them. That appears to
16	be what happened. It would have been more
17	transparent to say that.
18	I'm not sure that it would have made a
19	difference in this case, you know, based on the data
20	that I've seen, but I think it would have been more
21	up front to to be, you know, transparent with FDA.
22	BY MR. WISNER:
23	Q Now, I this is where I was going
24	earlier and now I remember. In 2013, you were asked

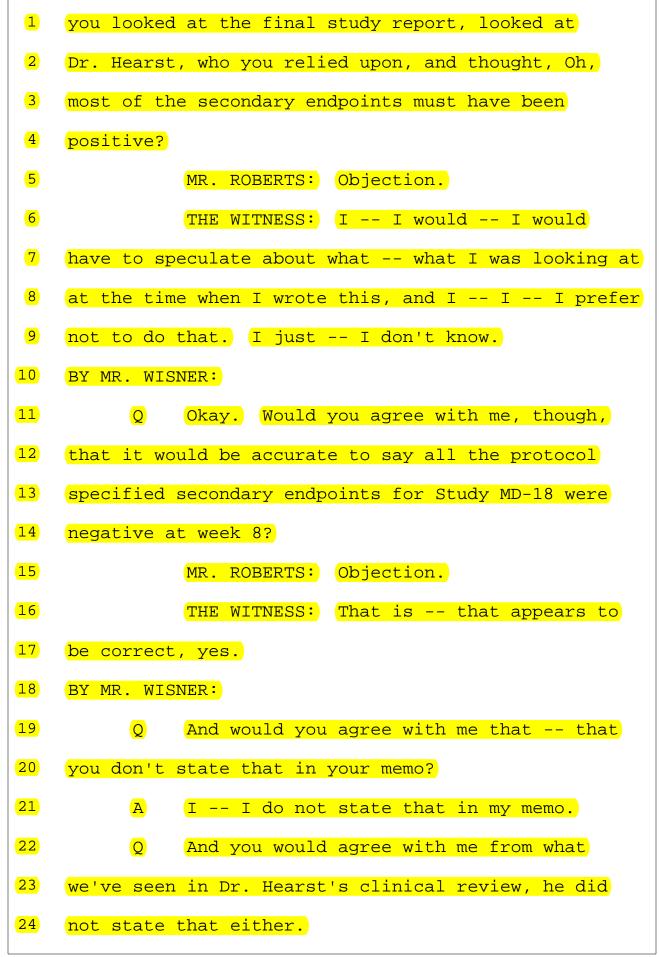


(Thomas Laughren, M.D.
1	was not as forthcoming as it should have been with
2	the FDA about its representation of the results from
3	(MD-18?)
4	MS. KIEHN: Objection.
5	THE WITNESS: Yes.
6	BY MR. WISNER:
7	Q You would agree, Dr. Laughren, that I've
8	shown you several documents today that suggest that
9	at least people within Forest believed that these
10	nine patients who were subject to the dispensing
11	error were unblinded.
12	MS. KIEHN: Objection.
13	THE WITNESS: It appears that that is the
14	conclusion that that some people reached.
15	BY MR. WISNER:
16	Q And you would agree with me that the
17	final study report did not disclose unequivocally
18	that these patients were unblinded, correct?
19	MS. KIEHN: Objection.
20	THE WITNESS: It it referred it
21	referred to them as potentially unblinded. And
22	and that is still a possibility, but probably less a
23	probability than if they had just been different
24	colored tablets without the brand name on them.

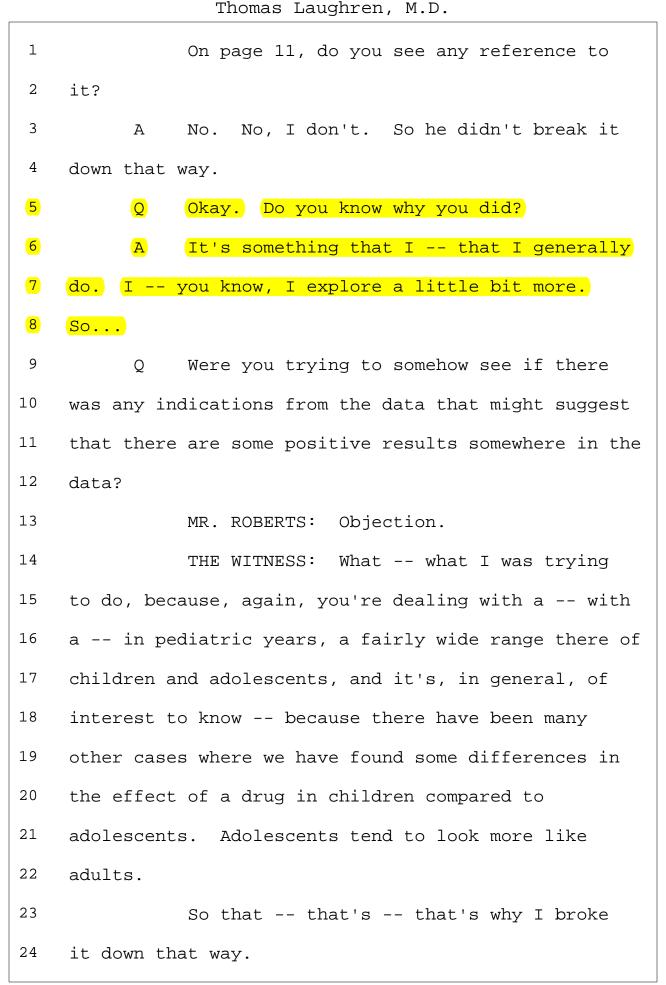
1	you know, what what he what he looked at before
2	he used this language.
3	So, again, I you know, we're making a
4	lot of assumptions that he never actually looked at
5	any of these data tables. I don't I don't know
6	that.
7	BY MR. WISNER:
8	Q Fair enough.
9	Now, Doctor, in the course of your work
10	at the FDA, do you recall copying and pasting
11	language from a final study report into your medical
12	review?
13	A No, I I I did not do that.
14	Q Why not?
<mark>15</mark>	A Because I preferred to reach my own
<mark>16</mark>	conclusions.
17	Q Now, the way this is written in the final
18	study report and transcribed into Dr. Hearst's
19	review, that does appear to have been trying to
20	emphasize the positive results to earlier time points
21	and avoid discussion of the fact that all the
22	secondary endpoints that we gave were negative,
23	right?
24	MR. ROBERTS: Objection.

1 THE WITNESS: Well, I	- I don't want to
2 assume motive. I I don't know w	what he had in mind
³ when he did this.	
4 BY MR. WISNER:	
5 Q Fair enough.	
6 Putting Dr. Hearst aside	e, I'm talking
7 about Forest, we saw that they had	a conference where
8 they said they were going to emphase	size this.
9 A Yes. Yes. No, it's	it is consistent
10 with with that view of focusing	on the positive
11 and not giving a complete picture.	
12 Q And it appears that that	t spin that Forest
13 put into the final study report mad	de it into
14 Dr. Hearst's report, correct?	
15MR. ROBERTS:Objection	
16THE WITNESS:It it a	appears to have,
17 yes.	
18 BY MR. WISNER:	
19 Q Okay. Let's go back to	Exhibit 3, which
20 is your memorandum.	
21 All right. If you turn	to page 3. Now,
22 on page 3, just above the paragraph	n that says
23 "comment," there is a sentence that	t reads: ("Results
24 also significantly favored citalop	ram over placebo on

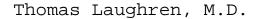


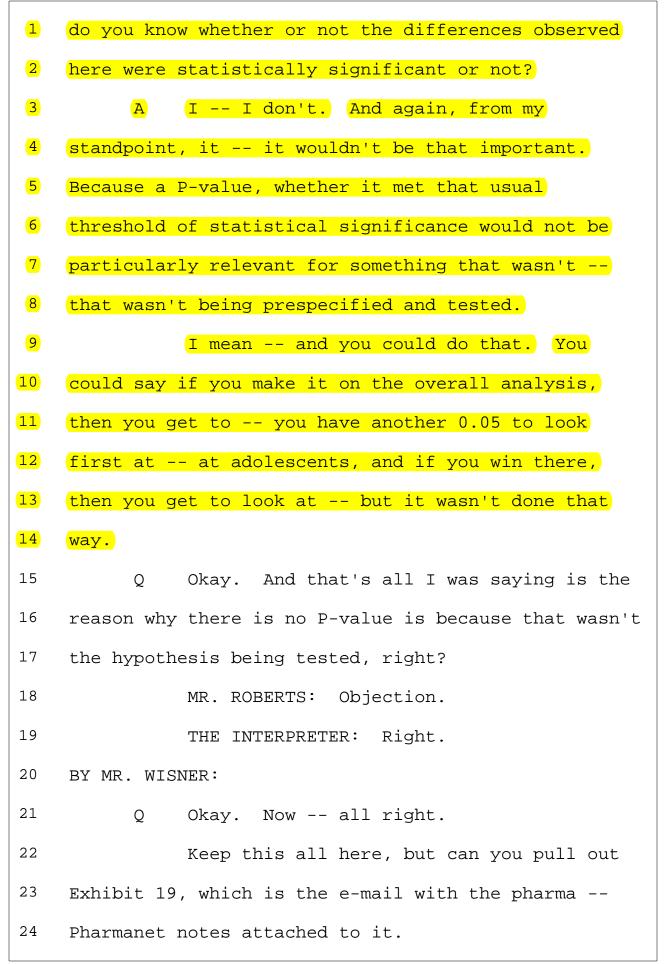


1	A He did not appear appear to do that
2	either.
3	Q Okay. So on the same page you have
4	your memo in front of you, right?
5	A Yes.
6	Q Okay. You have broken down the efficacy
7	results between children and adolescents. Do you see
8	that?
9	A I do.
10	Q Now, you understand that Dr. Hearst
11	didn't present data this way, right?
12	MR. ROBERTS: Objection.
13	THE WITNESS: I would have to look at
14	BY MR. WISNER:
15	Q Please take a look and tell me if he did.
16	A (Perusing document.)
17	Can you direct me again to where on
18	his
19	Q Sure.
20	A his review the efficacy findings
21	Q It's just on page 11, that's that's
22	about it. That's the only reference to secondary
23	endpoints or even primary endpoints for MD-18 that
24	I've seen.

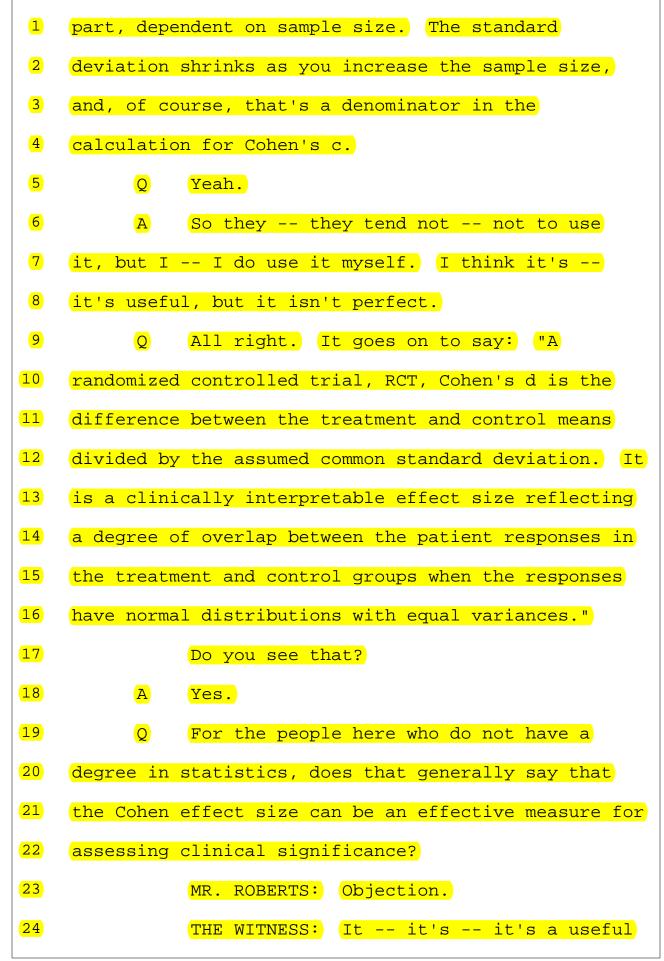


1	BY MR. WISNER:
2	Q Okay.
3	A I mean if you look at the findings, it's
4	not as if the findings are entirely coming from
5	adolescents, but the effect size is is somewhat
6	bigger in the adolescents. So in children, it's
7	about, you know, about four units difference on this
8	measure. In adolescents, it's closer to seven.
9	So
10	Q Now, in the in your memo you said:
11	"The sponsor did not calculate P-values for these
12	groups separately."
<mark>13</mark>	Do you see that?
14	
	MR. ROBERTS: Where is that?
15	MR. ROBERTS: Where is that? THE WITNESS: Where do I say that?
<mark>15</mark> 16	
	THE WITNESS: Where do I say that?
16	THE WITNESS: Where do I say that? Oh, right, right, right. Yeah, you
16 17	THE WITNESS: Where do I say that? Oh, right, right, right. Yeah, you ordinarily wouldn't do that in a in an
16 17 18	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.
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 16 17 18 19 20 21 	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.





1	significance, clinical significance remains elusive."
2	See that?
3	A IIdo.
4	Q And you agree with that, right?
5	A I do agree with that.
6	Q Okay.
7	A But we were talking about that earlier.
8	Q Exactly.
9	It continues: "Many statistical
10	methodologies have been put forth to measure the
11	magnitude of a clinical effect," open paren, "an
12	effect size," close paren. "One of the most
13	frequently used effect size measures is Cohen's d."
14	Do you see that?
15	A I do.
<mark>16</mark>	Q Are you familiar with the Cohen's d or
17	Cohen effect size?
18	A Yes.
<mark>19</mark>	Q Okay. Is that something that you would
20	consider in assessing whether or not the results of a
21	clinical trial are clinically meaningful?
22	A <mark>I I think I think it has value.</mark> I
23	don't think it's perfect, and and FDA
24	statisticians tend not to like it because it's, in

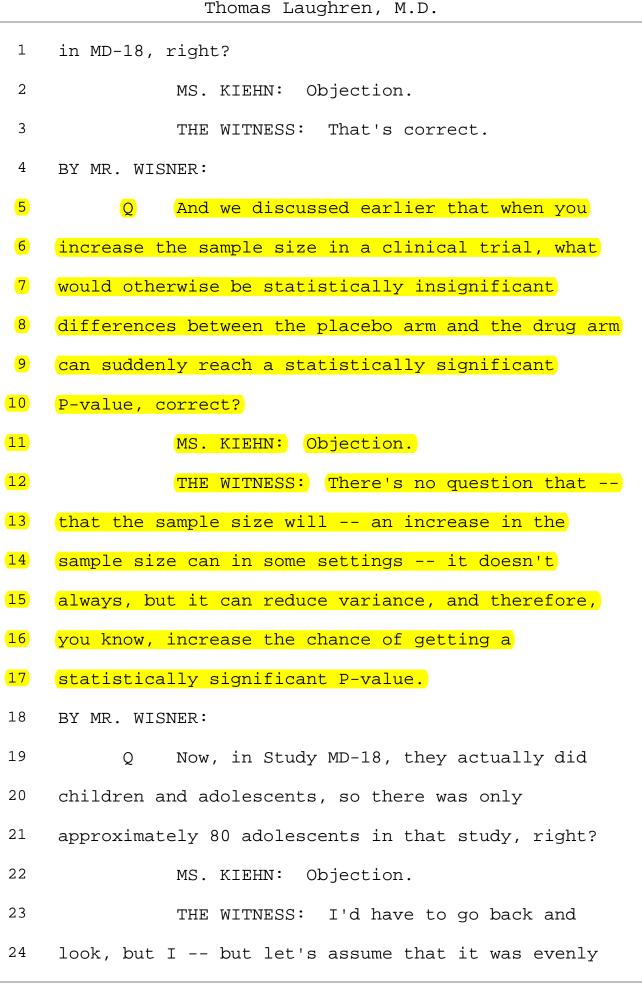


1	way of roughly assessing putting putting a
2	numeric putting a metric on effect size by sort of
3	standardizing it with the standard deviation. And so
4	it's a way of making comparisons across different
5	trials, across different diseases, across different,
6	you know, outcome measures. It's it's sort of a
7	standard and that's why, you know, we say, you
8	know, an effect size of like 0.3, which is typical of
9	what you get in a depression study, is pretty is
10	pretty small. In other disorders like ADHD, you get
11	much bigger effect sizes that are based based on
12	Cohen's d. So
13	BY MR. WISNER:
14	Q Sure. Are you familiar with something
15	called the number needed to treat?
16	A Yes.
17	Q And what is that?
18	A So the number needed to treat is is a
19	number that you can calculate if you're if you're,
20	you know, basically using percentage of responders,
21	proportion of responders as an outcome.
22	And so, say, if you have a trial where,
23	you know, 75 percent of patients in a in a trial
24	were assigned a drug have a, quote, response, however

1	MR. ROBERTS: Objection.
2	THE WITNESS: That's correct, although
3	that wasn't the that wasn't the protocol specified
4	primary analysis.
5	BY MR. WISNER:
6	Q Sure. But we know that the OC results
7	for the people who actually completed the clinical
8	trial, that actually was negative for efficacy,
9	right?
10	A That's true.
11	Q We know that with Study MD-18 that there
12	were nine patients that Dr. Flicker characterized as
13	being unmistakenly unblinded, right?
14	MR. ROBERTS: Objection.
15	Mischaracterizes the evidence.
16	THE WITNESS: That's correct.
17	BY MR. WISNER:
18	Q And we know that when those nine patients
19	are excluded from the primary efficacy analysis
20	pursuant to the LOCF analysis, that the P-value goes
21	higher than 0.050, right?
22	MR. ROBERTS: Objection.
23	THE WITNESS: That's that's true.
24	However, I would push back a little bit on that to
Colle	Dage 343

1 А Yes. 2 MS. KIEHN: Objection. BY MR. WISNER: 3 4 And you believe obviously the same thing 0 5 with escitalopram itself, right? 6 MS. KIEHN: Objection. 7 THE WITNESS: Yes. 8 BY MR. WISNER: 9 Okay. Considering what you just said, do 0 10 you think it's appropriate that Forest should have been allowed to have exclusivity over S-citalopram, 11 12 even though it essentially was just the effective part of Celexa? 13 14 MS. KIEHN: Objection. 15 THE WITNESS: Again, as I -- excuse me. 16 As I -- as I said, there are important differences between S-citalopram and racemic citalopram. Mostly 17 on the safety side. So they're not -- they're not 18 19 the same compound. 20 BY MR. WISNER: 21 Okay. Are you familiar, just by any 0 22 chance, with the phrase "evergreening"? 23 А No. 24 Q Okay. All right. So my understanding

1	based on the response from the FDA is that if Forest
2	could produce a positive double-blind,
3	placebo-controlled clinical trial with Lexapro in
4	children aged 12 to 17, it would then agree to
5	provide an indication for Lexapro for that age group.
6	A Yes, that's that is what it's saying.
7	I mean, of course, it would you know, it would
8	have to be reviewed. It's subject to review by FDA.
9	But in principle, yes, that is what this letter says.
10	Q And and this agreement that the FDA
11	made was done notwithstanding the fact that
12	Study MD-18 was a study that was not relegated solely
13	to adolescents, right?
14	A That that that's correct.
15	Q And that I'm sorry.
16	A However, as and, again, it's you
17	know, this was an exploratory post hoc analysis, but
18	I did show at least in my memo that that the
19	effect size was you know, the effects were
20	probably more driven by the adolescents than by the
21	children in that study.
22	Q Sure. And I I'm not saying that you
23	didn't do that, Doctor.
24	I guess my question, though, is

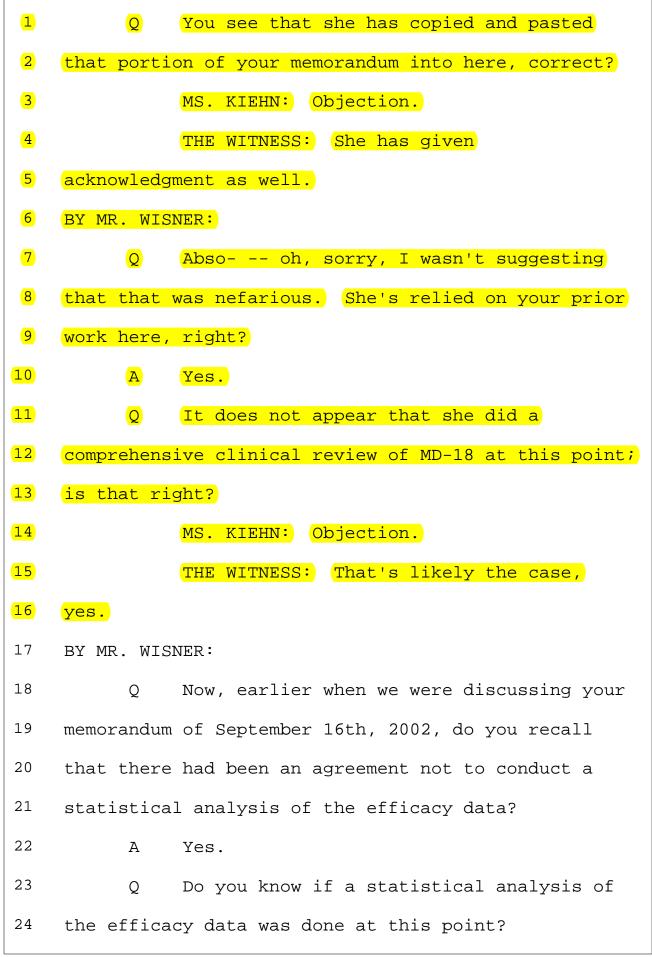


	Thomas Laughren, M.D.
1	Do you see that?
2	A I do.
3	Q So that letter right there is actually
4	the one we just looked at a second ago.
5	A Yes.
6	Q All right. So it appears that Dr. Glass
7	is operating off of the fact that Study MD-18 was
8	positive and that they just had to look at whether or
9	not there was an additional positive study for
10	adolescents with Lexapro; is that right?
11	MS. KIEHN: Objection.
12	THE WITNESS: That's correct.
13	BY MR. WISNER:
14	Q All right. Look at the last paragraph on
15	this page. It reads: "The study is positive for the
16	effi for the primary efficacy variable of change
17	from baseline of the CDRS-R total score P equals
18	0.038."
19	Do you see that?
20	A I do.
21	Q Now, we know that that's referring to the
22	results of the primary efficacy endpoint including
23	those nine patients that were unblinded, correct?
24	MS. KIEHN: Objection.

1	THE WITNESS: That's correct.
2	BY MR. WISNER:
3	Q All right. It goes on to say: "As it
4	can be seen from Table 6.1.3.4, there is a greater
5	improvement for the adolescent group than the
6	children group when comparing the differences to
7	placebo. As Dr. Laughren notes in his memo of
8	September 16th, 2002, quote: It appears that the
9	positive results for this trial are coming largely
10	from the adolescent subgroup."
11	Do you see that?
12	A I do.
13	Q It appears that Dr. Glass is relying on
13 14	Q It appears that Dr. Glass is relying on your exploratory analysis of the different effects
14	your exploratory analysis of the different effects
<mark>14</mark> 15	your exploratory analysis of the different effects observed in the pediatric and adolescent subgroup in
14 15 16	your exploratory analysis of the different effects observed in the pediatric and adolescent subgroup in your memo of September 16th, 2002.
14 15 16 17	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.
14 15 16 17 18	<pre>your exploratory analysis of the different effects observed in the pediatric and adolescent subgroup in your memo of September 16th, 2002.</pre>
14 15 16 17 18 19	<pre>your exploratory analysis of the different effects observed in the pediatric and adolescent subgroup in your memo of September 16th, 2002.</pre>
14 15 16 17 18 19 20	<pre>your exploratory analysis of the different effects observed in the pediatric and adolescent subgroup in your memo of September 16th, 2002.</pre>
 14 15 16 17 18 19 20 21 	<pre>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</pre>

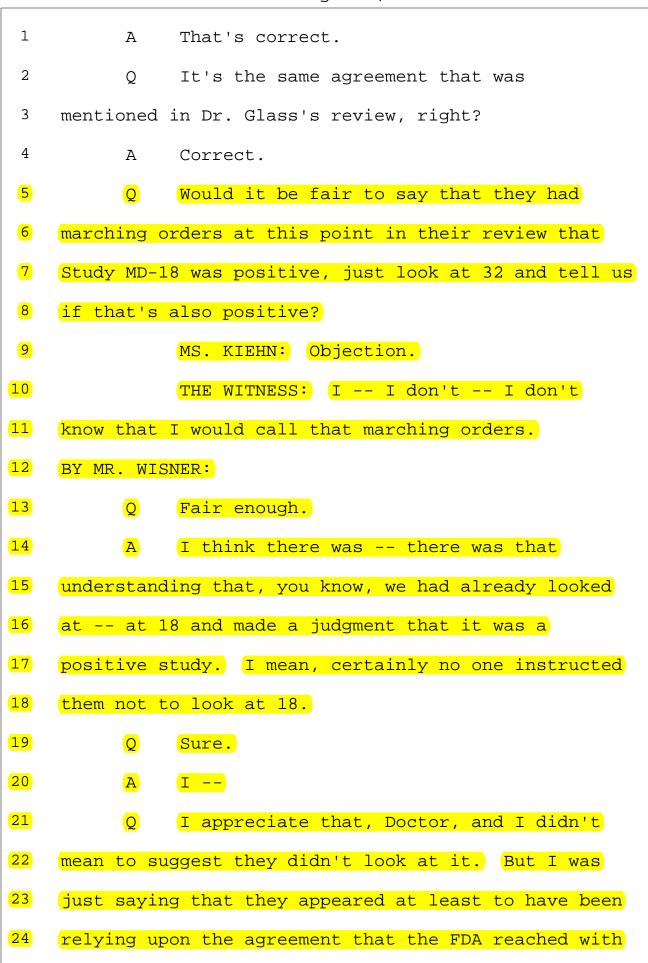
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1	A Since one is not in the in the file
2	that you've been able to obtain, I'm assuming that it
3	was not done.
4	Q Yeah. Is that typical for a pivotal
5	trial that's going to be used to support indication
6	to have just not been given any statistical review?
7	MS. KIEHN: Objection.
8	THE WITNESS: It's prob it's probably
9	not typical.
10	BY MR. WISNER:
11	Q And you said earlier one of the reasons
12	that you do a statistical review, although it's
13	redundant, is to sort of hash out the various effects
14	you're seeing in the data, right?
15	MS. KIEHN: Objection.
<mark>16</mark>	THE WITNESS: Generally, a statistical
17	review it does a couple of things. I mean it
18	very often the statistical reviewer will have the
<mark>19</mark>	original actual dataset electronically and can do
20	some additional exploratory analyses looking at
21	you know, breaking it down by gender and age and
22	ethnicity and that sort of thing. It can also
23	confirm the analyses that are done by the sponsor.
24	BY MR. WISNER:

1	Q Do you think that probably would have
2	been helpful, particularly since you're using a
3	particular subgroup of an exploratory analyses that
4	you did in your review of the study?
5	MS. KIEHN: Objection.
6	THE WITNESS: In in retrospect, I
7	think I I would have preferred that.
8	BY MR. WISNER:
9	Q Okay. All right. Let's turn back to
10	Exhibit 28, which is the one I handed you a minute
11	ago.
12	A Okay.
13	Q This is the the memorandum by Dr. Kin?
14	A Yes.
15	Q And she was Dr. Glass's supervisor,
16	correct?
17	A That's correct.
18	Q Okay. So this is sort of her memorandum
19	kind of overseeing the clinical reviews that were
20	done by, for example, Dr. Glass.
21	A Correct.
22	Q Okay. The subject of the memorandum is
23	"Recommendation of approval action for Lexapro
24	(escitalopram) for the acute and maintenance



Thomas Laughren, M.D. 1 Forest in 2004. 2 A I think that's fair. Okay. And if you look at page 4, there's 3 Q a section that says "Study CIT-MD-18." 4 5 Do you see that? 6 А Yes. 7 And this goes on for about three short Q 8 paragraphs. 9 Do you see that? 10 Α Yes. 11 All right. Bear with me, Doctor, one Q 12 second. 13 I'm actually -- sorry, I'm mixed up 14 because I'm on the wrong page. Look at page 3 of document -- do you see the paragraph below the 15 16 summary that starts off with "Study 18 is an 17 eight-week" -- do you see that? 18 Third paragraph from the top, "Study 18 19 is an eight-week" --20 Oh, correct. А 21 Do you see that? 0 22 А Yes. All right. It says: "Study 18 is an 23 Q 24 eight-week double-blind, placebo-controlled,

1	flexible-dose citalopram, 20 to 40 milligrams a day,
2	study in children 7 to 11 years and adolescents 12 to
3	17 years. I would refer to the clinical review by
4	Dr. Hearst dated December 12, 2002, and the
5	memorandum by Dr. Thomas Laughren dated December 16,
6	2002, regarding their reviews of materials submitted
7	under supplemental NDA for citalopram on April 18,
8	2002. I will briefly summarize their interpretation
9	of results from Study 18 in Section 5123 below."
10	Do you see that?
11	A I do.
12	Q So it appears that Dr. Kin is relying
13	heavily, if not exclusively, on Dr. Hearst and
14	yourself's analysis of Study MD-18.
15	MS. KIEHN: Objection.
<mark>16</mark>	THE WITNESS: That's correct. Now, of
<mark>17</mark>	course, this is the team leader review. It's not the
<mark>18</mark>	primary review.
19	BY MR. WISNER:
20	Q Sure.
21	A I don't have Dr. Hearst's complete
22	review, so I don't I don't know exactly what
23	what she did with regard to Study 18.
24	Q Okay. I represent to you that what I've
	Dage 200

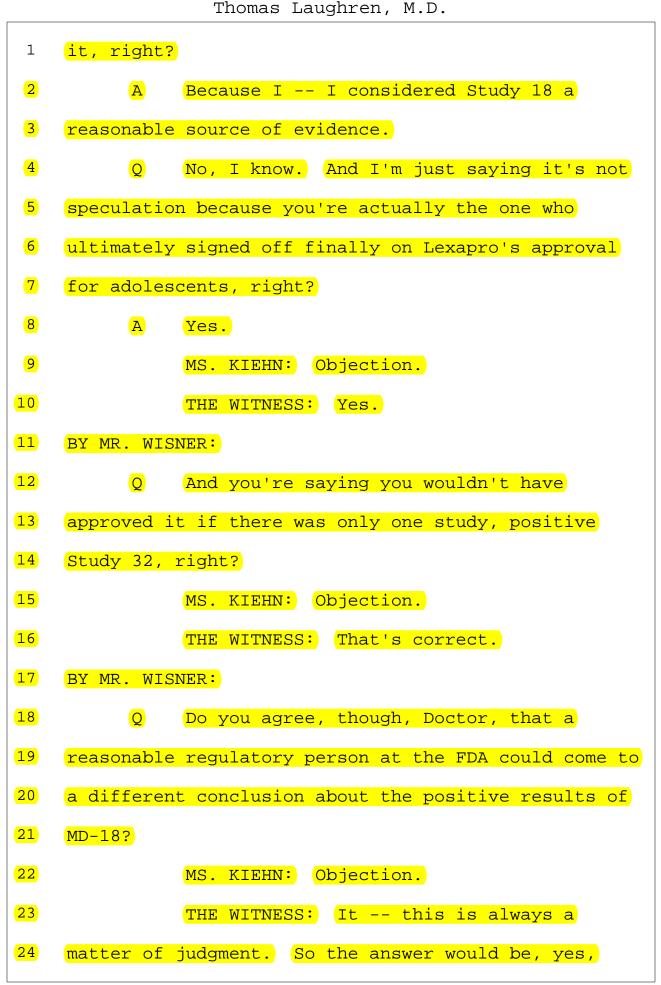
Dr. Laughren's memo, September 16, 2002." 1 2 Do you see that? 3 А I do. 4 0 Okay, great. So in that table there, 5 although it doesn't look identical to your table, it has the same information, right? 6 7 А Yes. 8 Okay. So, again, it looks like not only 0 to Dr. Glass but Dr. Kin also inserted the table from 9 your exploratory analysis on MD-18 in this analysis. 10 11 Α That's correct. 12 0 When you prepared your memo for CD -- for 13 MD-18, and you did this exploratory analysis dividing 14 the adolescents from the children, did you anticipate 15 that that being -- that was going to be used to 16 support an indication for a different drug in 17 adolescents? 18 MS. KIEHN: Objection. 19 THE WITNESS: I -- I doubt that I was 20 thinking ahead that far. 21 BY MR. WISNER: 22 0 Fair enough. 23 In retrospect, it seems that that's 24 exactly what happened.

1	<mark>A That's true.</mark> But but let me just
2	just point out that we we made we reached a
3	conclusion based on Study 18 that it was a positive
4	study for both adolescents and children. And so
5	it's it's that part of it, it's the adolescent
6	part of that that is being incorporated into this
7	judgment that these two studies, Study 18 for Celexa
8	and Study 32 for Lexapro, were sufficient as a source
9	of evidence for the the effectiveness of Lexapro
10	in in adolescents.
11	(Exhibit No. 29 was marked for
12	identification.)
13	BY MR. WISNER:
14	Q I'm handing you what has been marked as
15	Exhibit 29 to your deposition.
16	Doctor, this is a letter actually from
17	you related to the supplemental application for
18	Lexapro for use in adolescents, correct?
19	A Yes.
20	Q And, unfortunately, I don't have the page
21	that says the date of this letter, but do you recall
22	that this was in early 2009?
23	A I I can't remember back to 2009 and
24	but that sounds about right.

1	have been my preference that that Forest be more
2	transparent with FDA about the issue of unblinding.
3	I don't believe in the end that would have made any
4	difference in our judgment, as I've explained, but
5	but I do I do feel that drug companies should be
6	fully transparent with FDA in what they provide to
7	them about the you know, the conduct of a study.
8	BY MR. WISNER:
9	Q Now, considering that they weren't
10	transparent about that issue, do you think and
11	also in consideration of the fact that Study MD-18
12	never had a statistical analysis of the efficacy
13	data, do you think that it would be appropriate for
14	the FDA to take another look at this data just to
15	make sure that in fact Study 18 was was positive
<mark>16</mark>	as Forest has represented?
17	MS. KIEHN: Objection.
18	THE WITNESS: It it isn't my judgment
19	at this point.
20	BY MR. WISNER:
21	Q Sure.
22	A So, I mean I that that's for FDA to
23	decide at this point. I mean, I I feel fairly
24	confident about our decision to approve Lexapro. I

1	was obviously involved in that. I I feel that was
2	probably the the right decision. Whether or not
3	FDA and I also told you that, in retrospect, I
4	would have had a statistical review done on on 18.
5	But my overall view is that it probably
6	would not have made a difference. We probably still
7	would have would have reached that same judgment.
8	And it's it's up to FDA to decide whether or not,
9	you know, based on this on this, you know, new
10	information, which I think is probably new
11	information from FDA because I wasn't aware of it at
12	the time. But it's not my call.
13	Q Okay, great.
14	MR. WISNER: Let's take a break.
15	THE VIDEOGRAPHER: The time is 5:14. We
16	will go off the video record.
17	(Recess.)
18	THE VIDEOGRAPHER: The time is 5:23.
19	Back on the video record.
20	BY MR. WISNER:
21	Q I want to talk briefly again about
22	Study MD-18. And, you know, we know that all the
23	secondary prespecified endpoints were negative,
24	right?

1	been many occasions when I changed my mind when
2	when I was at FDA. There was an NDA that we we
3	turned it down, and this is for iloperidone. You
4	know, the company challenged it and came back in with
5	some additional analyses, and and they were able
6	to persuade me that that I was wrong, and and I
7	recommended approval, and Bob Temple agreed with me,
8	and we ultimately approved it.
9	So there have been situations where I
10	I agreed with an argument that I was wrong and
11	reversed myself. That certainly isn't the only
12	circumstance. I I just don't see this as one of
13	those circumstances.
14	BY MR. WISNER:
15	Q If MD-18 was in fact negative, would you
<mark>16</mark>	ever have approved Lexapro for use in adolescents?
17	MS. KIEHN: Objection.
18	THE WITNESS: I mean, if if if you
<mark>19</mark>	couldn't rely on 18 as a source of evidence, then you
20	would've only had one source of evidence for Lexapro.
21	So the answer is this is speculation, but I I
22	would not have recommended approving it.
23	BY MR. WISNER:
24	Q You're the one who ultimately did approve



1 different people looking at the same dataset can 2 reach a different conclusion. BY MR. WISNER: 3 4 0 Are you aware that there has been a 5 peer-reviewed publication last year discussing the results of MD-18? 6 7 MS. KIEHN: Objection. 8 THE WITNESS: I -- I have -- I have not 9 been following the literature in that particular 10 area, so... 11 BY MR. WISNER: 12 So you have not seen any peer-reviewed 0 journal article coming to the conclusion, having 13 14 looked at the data without the unblinded patients, 15 that it was negative; is that correct? 16 MS. KIEHN: Objection. 17 THE WITNESS: I -- I don't recall seeing If there is such a paper, I haven't seen it. 18 that. 19 BY MR. WISNER: 20 Q Okay, great. But we do agree, and I 21 think this has been established and I just want to 22 make sure we're on the same page, that until 23 Study MD-32 was completed and reviewed by the FDA, 24 prior to that, with Study 94404 being negative for