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January 24, 2018

Gregg Shapiro, Esq.
Chief of the Affirmative Civil Enforcement Unit
United States Attorney's Office
District of Massachusetts
1 Courthouse Way, Suite 9200
Boston, MA 02210

Re. How Forest Misled the FDA, DOJ, USAO, and the Public about the Results of Celexa Study MD-18

Dear Mr. Shapiro:

On September 15, 2010, Forest Laboratories, Inc. and Forest Pharmaceuticals, Inc. ("Forest") entered into a series of agreements with the United States Attorney's Office for the District of Massachusetts ("USAO").

First, Forest agreed to plead guilty to one count of obstruction and two counts of distributing a misbranded drug under the Food, Drug, and Cosmetic Act. The third count specifically related to Forest promoting the use of the antidepressant Celexa (citalopram) for use in children and adolescents between 1998 and 2002. The plea agreement imposed criminal fines of $39,500,000 for Celexa's off-label promotion. Second, Forest entered into a civil settlement agreement to resolve various *qui tam* False Claims Act lawsuits. The settlement resolved, in part, allegations of fraudulent off-label promotion for both Celexa and Lexapro (escitalopram) for children and adolescents between 1998 and 2005. Forest agreed to pay $149,158,057.66 to settle these claims. Third, Forest entered into a corporate integrity agreement to address Forest's promotional conduct for a period lasting five years. Each agreement was contingent on the others and each agreement required complete honesty from Forest.

We have been litigating various cases against Forest related to the off-label promotion of Celexa and Lexapro for pediatric use for some years now—inspired by the USAO's original investigation—in a multidistrict litigation proceeding in the District of Massachusetts. Over the past several years, our litigation has revealed that the scope and extent of Forest's fraud was not honestly disclosed to the USAO (or, to the Food and Drug Administration) and that Forest misrepresented material facts underlying the USAO's prosecution. Documents and testimony obtained in our litigation have been unsealed, over Forest's objection, and we have prepared a

detailed memorandum outlining Forest's misconduct and fraud with the hope the USAO will consider reopening its investigation. Obviously, we are not an unbiased source of information, however, we believe the documents and testimony speak for themselves.

For example, a central feature of Forest's wrongful conduct, which formed the basis of the government's investigation, involved the promotion and dissemination of a "positive" Celexa double-blind, placebo-controlled clinical trial in children and adolescents, MD-18, and the suppression of a negative Celexa double-blind, placebo-controlled clinical trial in adolescents, Study 94404. However, unsealed documents and testimony show that the "positive" MD-18 study was not actually positive, and that Forest misled the FDA, the USAO, and the public about this fact. Specifically, MD-18 was only able to achieve a positive result by including nine patients in the study that were, as Forest's medical director put it, "automatically unblinded" due to a dispensing error. In fact, when the mishap occurred, Forest told the FDA that it would exclude these patients from the primary results. However, when Forest learned it needed the unblinded patients to achieve a positive result, i.e., to show that Celexa outperformed a sugar pill, Forest snuck the patients back into the results, and falsely told the FDA the patients were not actually unblinded.

One internal document, in particular, reveals that this was deliberate fraud. Amy Rubin, a Forest Regulatory Affairs Manager, characterized the dispensing error as having "the potential to cause patient bias" in a draft letter to be sent to the FDA to disclose the unblinding problem. Dr. Charles Flicker, the Senior Medical Director overseeing MD-18, did not approve of this language, stating: "Altho 'potential to cause bias' 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 [sic] violated." Ms. Rubin responded: "Thanks for the compliement [sic]. Part of my job is to create 'masterful' euphemisms to protect Medical and Marketing." Thus, not only was the disclosure to the FDA dishonest, it was, according to a Forest Regulatory Affairs manager, *her job* to mislead the FDA and protect medical and marketing.

This "masterful euphemism" language was ultimately sent to the FDA. When we deposed Dr. Thomas Laughren, the former official at the FDA who reviewed this study and who, within six months after leaving the FDA, was working as a testifying expert for Forest, he testified that he believed at the time he reviewed the study that there had been no unblinding and, when shown our documents and testimony, that Forest did not honesty disclose the situation to him.

The gravity of this misconduct becomes even more acute when one considers that Lexapro was ultimately approved by the FDA for adolescent depression in 2009 based on the supposedly "positive" results of MD-18. Dr. Laughren personally approved the new indication for Lexapro and testified that, if MD-18 was negative, he would not have approved it. It is our understanding that this approval weighed heavily into the USAO's decision to settle their case against Forest.

We urge you to review the enclosed memorandum and accompanying evidence and consider reopening your investigation of Forest related to its promotion of Celexa and Lexapro for pediatric use. We would be happy to answer any questions you may have or to meet you in person to walk you through the evidence.

Sincerely,

BAUM HEDLUND ARISTEI & GOLDMAN, P.C.

By:_____

R. Brent Wisner

MEMORANDUM

How Forest Misled the FDA, USAO, and the Public about the Results of Celexa Study MD-18

January 24, 2018

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PART I. EXECUTIVE SUMMARY

In 2010, the USAO in the District of Massachusetts entered into a series of agreements with Forest Laboratories, Inc. and Forest Pharmaceuticals, Inc., ("Forest") relating, in part, to the off-label (unapproved) promotion of Celexa (citalopram) and Lexapro (escitalopram) for use in children and adolescents.[1] Forest agreed to plead guilty to engaging in a misdemeanor count of off-label promotion for Celexa between 1998 and 2002 and pay $39 million in fines.[2] Additionally, Forest entered into a civil settlement agreement to resolve, in part, allegations that Forest fraudulently induced false claims for the pediatric use of Celexa and Lexapro to be submitted to government healthcare payers between 1998 and 2005.[3] Forest agreed to pay $149 million to settle these claims.[4] Forest also entered into a Corporate Integrity Agreement ("CIA") designed to monitor the promotional practices of Forest for a period of five years.[5] The Plea Agreement, Civil Settlement, and CIA were conditioned on each other[6] and required that Forest be honest with the USAO about its conduct.[7]

A central feature of Forest's wrongful conduct involved the promotion and dissemination of a "positive" Celexa double-blind, placebo-controlled clinical trial in children and adolescents, MD-18, and the suppression of a negative Celexa double-blind, placebo-controlled clinical trial in adolescents, Study 94404. Forest's one-sided presentation of the efficacy data raised concerns about how companies such as Forest disclose and use data collected during clinical trials, particularly when used as part of an off-label promotion campaign. Indeed, the factual claim of one "positive" trial and one "negative" trial played an important role in the USAO's prosecution of the original case against Forest.

Recently unsealed documents and testimony, however, show that Celexa Study MD-18 was not a "positive study" and that Forest misled the FDA, the USAO, and the public about this fact. In other words, a material fact that formed the basis of the USAO's and Forest's negotiations was, at that time, false, and Forest knew it. Moreover, this misconduct does not stop there. Shortly before the USAO and Forest finalized their agreements, the FDA approved Lexapro for

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[1] *See* Exh. 1, DOJ Press Release.

[2] Exh. 2, Plea Agreement at 5; *see* Exh. 3, Criminal Information ¶¶ 55-71 (outlining allegations); Exh. 5, Side Letter Agreement with Forest Laboratories.

[3] Exh. 4, Civil Settlement Agreement at pp.3-4, ¶¶ G(1)-G(3). While the settlement encompassed the years 1998-2005, there is evidence that Forest's sales representatives were illegally off-label promoting Celexa and Lexapro through 2009. One of Forest's marketing executives testified: "I have knowledge that representatives may have presented Celexa or Lexapro inappropriately" and, when asked, "Between 2002 and 2009?" the marketing executive replied: "Yes." Exh. 7 Azari Depo at 236:1-237:22.

[4] *Id.* at pp. 6, ¶ 1.

[5] Exh. 6, Corporate Integrity Agreement.

[6] Exh. 2, Plea Agreement at pp. 11; Exh. 4, Civil Settlement Agreement at pp.3 ¶ E, pp. 10 ¶ 5; Exh. 6, Corporate Integrity Agreement at 1.

[7] Exh. 2, Plea Agreement at pp. 6; Exh. 4, Civil Settlement Agreement at pp.17 ¶ 15.

use in adolescents, based in part on the misrepresented MD-18 (Celexa) study. The fact that Forest obtained FDA approval for Lexapro for use in adolescents militated against the government's prosecution. The 2009 Lexapro approval, however, was based on the false claim that MD-18 was positive—a false assertion made to the FDA in 2002 (and reasserted to the FDA in 2008 as part of Forest's supplemental New Drug Application ("sNDA") for Lexapro). If MD-18 had properly been disclosed as negative, the FDA would not have approved Lexapro for use in adolescents[8] and the government's prosecution of Forest would have included Forest's misrepresentations regarding Celexa's efficacy in two studies—not just the suppression of Study 94404.

The issue centers on how Forest manipulated the MD-18 data to obtain a "positive" result. All of the secondary endpoints for MD-18 were negative, meaning Celexa did not outperform placebo in treating depression on all four of the pre-specified secondary endpoints.[9] Moreover, of those patients who completed the study, i.e., the observed cases, there was also no statistical difference between Celexa and placebo.[10] However, Forest represented to the FDA, USAO, and others that the primary endpoint for MD-18 was positive because, although the difference was very small, Celexa appeared to outperform placebo to a statistically significant degree. It turns out, however, that this "positive" result was based on data from nine patients who were unblinded during the study. When the data from these unblinded patients is removed, however, the primary result is negative—indeed, the results are negative across the board on every primary and secondary endpoint.[11]

How did this happen? At the beginning of the clinical trial, two clinical investigators informed Forest that some of their patients were receiving pink pills and others were receiving white pills.[12] This prompted an investigation by Forest, which discovered that a packaging error had caused the medication for the patients randomized to the Celexa group to be pink, Forest-stamped, dose-stamped, oval-shaped, commercial Celexa tablets.[13] Forest immediately notified

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[8] *See* Exh. 8, 2017 Depo. of T. Laughren at 401:15-402:10 (Dr. Thomas Laughren, the senior FDA official who approved Lexapro for use in adolescents admitting that he would not have approved Lexapro for adolescents if MD-18 was negative).

[9] Exh. 9, Excerpts of Study MD-18 Rpt. at pgs. 101-104, 244.

[10] *Id.* at 111 (listing p-value of observed cases analysis at week at as 0.1670); Exh. 8, 2017 Depo. of T. Laughren at 97:1-21, 99:18-21, 343:6-10 ("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."); Exh. 11, 2016 Depo. of W. Heydorn at 138:24-139:6, 144:6-9.

[11] Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 294:10-295:20 ("If they were removed from the study, I understand that the result would have been negative.").

[12] *See* Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1 (describing how Forest learned of the dispensing error).

[13] *Id.*; see Exh. 14, Memo re. Investigation of CIT-MD-18 Clinical Study Use of Trade-Dress Citalopram 20 mgs Tabs at 1-2; Exh. 15, Memo re. CIT-MD-18 (Deviation Report) at 1-2 ("It was brought to our attention . . . some patients enrolled in this study had pink tablets in their

the clinical investigators that the pink pills were commercial Celexa and instructed them to replace the medication with properly blinded white pills.[14] However, for the nine patients already randomized to the trial, Forest directed the clinical investigators to continue the patients with the wrong-colored pills.[15] This meant the first nine patients were unblinded—the investigators knew the patients taking the pink pills were taking Celexa and the patients taking white pills were on placebo.

In March 2000, after Forest learned of the dispensing error but before the results of the study were known, Forest drafted a letter to send to the FDA explaining the situation. In the original draft, Forest stated that the dispensing error could have "unblinded the study."[16] However, Forest's regulatory affairs manager, Amy Rubin, changed the letter to state that the dispensing error had the "potential to cause patient bias."[17] This prompted Forest's medical director, Dr. Charles Flicker, to respond: "***Altho 'potential to cause bias' 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.***"[18] Un-phased by Dr. Flicker's concern that Forest was not being "up front" with the FDA, Ms. Rubin responded: "***Thanks for the compliement [sic]. Part of my job is to create 'masterful' euphemisms to protect Medical and Marketing.***"[19] For Ms. Rubin, misleading the FDA was not only acceptable, it was part of her job. And, she did her job well. The letter sent to the FDA in March 2000 used the masterful euphemism language.[20]

The letter did, however, state that "[f]or reporting purposes, the primary efficacy analysis will exclude the . . . potentially unblinded patients[.]"[21] Thus, before Forest had the results of MD-18, Forest recognized the data was corrupted and promised that "[a] full complement of 160 patients" would still be "enrolled under standard double-blind conditions."[22]

The results for MD-18 were revealed to Forest in August 2001 and Forest learned, for the first time, that if the nine unblinded patients were excluded from the analysis, as it had promised

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bottles. We immediately investigated . . . We discovered . . . the pink oval tablets with FP/20MG imprints.").

[14] Exh. 16, Email re. CIT-18 FAX to Investigational sites (w/ attachment) at 1 ("[A] copy of the FAX that went out to all CIT-MD-18 Pediatric Investigational sites this morning is attached[.]").

[15] *Id.* at 2 (directing patients already randomized to continue on with study).

[16] Exh. 17, Email re. Letter to FDA for CIT-18 (w/attachment) at 2 ("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.").

[17] Exh. 18, Email responses re. Letter to FDA for CIT-18 at 1.

[18] *Id.*

[19] *Id.*

[20] Exh. 19, Letter from T. Varner (Forest) to R. Katz (FDA) at 1.

[21] *Id.*

[22] *Id.*

the FDA it would do, the results would be negative.[23] But, Forest reneged on its promise to the FDA. When it submitted the final study report to the FDA in April 2002, Forest included the unblinded patients in the primary efficacy analysis and buried, in an appendix, the results of the primary efficacy analysis excluding the unblinded patients.[24] In the narrative section of the report, Forest explained that there had been a dispensing error where nine patients received pink-colored pills, but the patients "were otherwise blinded."[25] This is in stark contrast to Dr. Flicker's unequivocal pronouncement that the integrity of the blind was unmistakenly violated. In its submission to the FDA, Forest did not disclose that the investigators were unblinded or that the medication dispensed was Forest-branded, dose-stamped, oval-shaped commercial Celexa tablets. When the FDA reviewed the results of MD-18, it copied and pasted the language from the final study report and parroted the claim that pink pills were dispensed but were "otherwise blinded."[26] Forest's deception worked—the FDA had no idea that the nine patients were actually unblinded[27] and that the study, when properly analyzed, was negative across the board.

Before the MD-18 study report was even written or given to the FDA, Forest started promoting the "positive" results of MD-18 to physicians. Forest issued a press release emphasizing the importance of the positive MD-18 study in a field, i.e., SSRI treatment of pediatric depression, which had consistently failed to produce positive results[28]; paid Dr. Karen Wagner (an investigator on the study) to present the false "positive" results of the study at various academic conferences and, directly, to physicians in CME programs and in-person off-label promotion meetings[29]; and published the false results of MD-18 in a ghostwritten

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[23] *See* Exh. 20, Email re. CIT-MD-18 at 1 ("We need to generate Tables 4.1A and 4.1B for ITT population, excluding the 9 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?").

[24] *See* Exh. 21, Email re. Notes from conference call Oct 4 (w/attachment) at 2 ("[S]ome citalopram table[t]s were not blinded. The 9 patients who received unblinded medication were included in the main analyses; a secondary 'Post-hoc analysis of the ITT subpopulation' was done. Refer to these analyses briefly in methods and results and reference the reader to the appendix table."); Exh. 9, Excerpts of Study MD-18 Rpt. at pgs. 70, 244 (unblinded results).

[25] *Id.* at pg. 44.

[26] Exh. 22, Review and Evaluation of Clinical Data by Dr. Earl Hearst, FDA at 11. All but two words of Dr. Hearst's medical review of MD-18 were copied and pasted from the final study report.

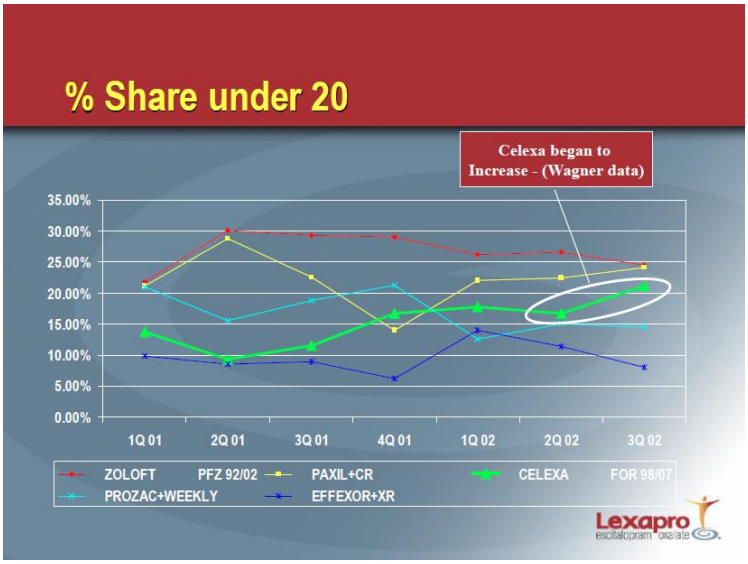
[27] Exh. 8, 2017 Depo. of T. Laughren at 154:6-23 ("18 Q Okay. So it was your understanding that the patients, despite receiving different color tablets, were still blinded, correct? . . . THE WITNESS: Well, that -- that was -- that was my assumption, correct.").

[28] Exh. 23, 2001 Forest Press Release at 2-3 ("This study is significant because few studies involving any antidepressant have shown efficacy compared to placebo in the treatment of depression in children and adolescents . . . Citalopram is now one of the few therapies for which we have data showing safety and efficacy for this population." (quoting Dr. Karen Wagner)).

[29] Exh. 24, Email re. Ped data at 2 ("[W]e would like to wrap some PR and CME around this data"); Exh. 25, Email re. ACNP pediatrics abstract at 1 ("John wants GCI to start working a release and any other way they can spin this data."); Exh. 26, Emails re. ACCAP meeting at 1

manuscript and then instructed its sales force to use the publication to promote the use of Celexa and Lexapro in children.[30] None of these presentations and publications disclosed the unblinding issue. It was buried.

The impact of the off-label promotion of the false data was known to Forest, as demonstrated in the following slide taken from Forest's internal marketing plan[31] discussing its anticipated launch of Lexapro:



When Forest's off-label promotion was finally exposed by the USAO in 2010 and Forest was forced to settle and plead guilty to the crime, Forest did not disclose its fraud related to MD-18. Instead, Forest represented to the USAO and DOJ that MD-18 was positive, militating its misconduct in suppressing the dissemination of Study 94404. Thus, Forest's false assertion that MD-18 was a positive study formed, in part, the basis of the USAO's negotiated settlements with Forest. These documents and testimony clearly demonstrate that Forest made material misrepresentations to the USAO and FDA about this issue and, in fact, continues to do so to this

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("You should discuss with GCI bringing her [Dr. Wagner] in for media training prior to the start of the CME program."); Exh. 27, Emails re. ACCAP Meeting at 3 ("We spoke with Karen Wagner today about the current state of affairs regarding the pediatric data. . . She . . . reminded us that if we want to appeal to the PCP and Pediatric audiences, we need to publish in a place that provided the appropriate readership . . . She also said that the lack of data regarding the use of Celexa for pediatrics is limiting it to 'last choice' among physicians - she just wanted to make sure we understood the marketing advantages of the data.").

[30] *See, e.g.*, Exh. 28, Selection of Call Notes at 7, 16-17 ("discussed cx used in children . . . and results of dr wagner study regarding cx use for children and adolescents . . . Brought up the Wagner study and sent study to Dr. asked Dr if it would make a difference to use Lx in that age group since Cx has done well.").

[31] Exh. 29, Lexapro Tactical Presentation at pg. 12; *see also id.* at pgs. 10-14 (discussing strategies to increase under 20 market).

very day. When Dr. William Heydorn was deposed, the former Forest scientist responsible for preparing the MD-18 final study report and a named author on MD-18's publication with Dr. Wagner, he admitted "I wish we had done things a little differently . . . probably should have been more forthcoming[.]"[32]

PART I: THE PLACEBO EFFECT AND STUDYING ANTIDEPRESSANT EFFICACY

All drugs are susceptible to the placebo effect—the effect a drug has on a patient that has nothing to do with the medicinal properties of the drug but is caused by the very act of getting medical attention.[33] The belief that one is possibly experiencing medical treatment, by itself, can create significant and measurable improvement for many conditions.[34]

In 1962, reeling from news of birth defects caused by a drug called thalidomide, Congress amended the Food Drug and Cosmetic Act (the Kefauver Harris Amendment, Pub. L. No. 87-781, 76 Stat. 780 (1962)). Before a drug could be sold as an effective medication, the drug maker would be required to prove the drug could outperform placebo or, in other words, demonstrate that the benefit patients receive from a drug could not simply be duplicated by administration of placebo.[35]

Today, a drug's efficacy is determined using double-blind randomized controlled trials ("DBRCTs").[36] A DBRCT involves the systematic comparison of patients taking a drug and patients taking a placebo.[37] Patients enrolled in the clinical trials are randomly assigned into two groups. One group takes the drug and the other takes a placebo. However, neither the investigators nor the patient know which group each patient is in. Once the study is complete, the benefit observed in the two groups is compared, and if the patients taking the drug meaningfully outperform the patients in the placebo group, the clinical trial is considered positive.[38] If the drug does not outperform placebo, it is called negative.

As its name suggests, a DBRCT involves three elements, all of which are designed to limit bias: (1) double-blind (2) randomized (3) controlled trials.[39] First, the trial must be double-blind. This means neither the investigator nor the patient know whether the pill ingested by the patient

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[32] Exh. 11, 2016 Depo. of W. Heydorn at 307:24-308:15.

[33] Exh. 30, U.S. Food and Drug Administration (FDA), *Guidance for Industry, E 10 Choice of Control Group and Related Issues in Clinical Trials*, at 4 (May 2001).

[34] *Id.*

[35] *See* 21 C.F.R. § 314.126.

[36] *In re Neurontin Mktg. & Sales Practices Litig.*, 712 F.3d 21, 47-49 (1st Cir. 2013).

[37] *See* FDA, *supra* note 33, at 4-5.

[38] *Id.* at 5.

[39] Exh. 31, Food and Drug Administration (FDA), *Guidance for Industry, E9 Statistical Principles for Clinical Trials*, at 10-14 (Sept. 1998).

is the active drug or placebo.[40] If either the investigator or the patient is unblinded, it invalidates the data since there is no way to determine whether the effects observed are caused by the drug or caused by the placebo effect (for the patient and investigator). Second, the trial must be randomized.[41] Patients assigned to the drug or control group must be randomly assigned. Otherwise, the distribution of patients would, itself, inject bias into the study. Finally, the trial must be controlled. This means the drug must be compared to a control group, i.e., a placebo pill.[42]

Before a DBRCT is conducted, a study protocol is generated.[43] The protocol specifies the study's endpoints—the primary and secondary measures that determine whether the drug works—and the conduct / procedures of the study. In nearly all DBRCTs, before a study will be considered positive, the primary endpoint must statistically outperform placebo. This means that the difference between the drug and placebo must be large enough to conclude the difference was not a result of chance. Conventionally, and for the purposes of the DBRCTs discussed in this memorandum, to be considered statistically significant, the endpoint must have a p-value (a statistical measure) less than 0.05.[44]

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[40] *Id.* at 10 ("Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on."); *see* FDA, *supra* note 33, at 4 (listing possible ways bias enters a trial without blinding). In the context of clinical trials related to depression, this factor is particularly important where a patient's depression is assessed by an investigator based on the patient's answers to specified questions about how they feel. If either the investigator or the patient knows they are receiving the drug, that knowledge will likely influence their assessment.

[41] FDA, *supra* note 39, at 12 ("In combination with blinding, randomization helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.").

[42] *Id.* at 18.

[43] *Id.* at 3 ("For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins."). The protocol must be followed religiously. *See* Exh. 32, Ravindra B. Ghooi, et al., *Assessment and classification of protocol deviations*, 7 PERSPECTIVES CLIN. RES. 3, 132-36 (July-Sept. 2016) (discussing importance of following protocols and how deviating from them can lead to misleading study results); Exh. 33, Stephen L. George & Marc Buyse, *Data fraud in clinical trials*, 5 CLIN. INVEST, 2 161-173 (2015) (discussing how falsification of data, i.e., misrepresenting important events in a clinical trial, are the most egregious types of misconduct).

[44] Exh. 34, Food and Drug Administration (FDA), *DRAFT Guidance for Industry, Multiple Endpoints in Clinical Trials*, at 4-5 (Jan. 2017) (discussing the typical use of a p-value of less than 0.05).

PART II: CELEXA PEDIATRIC CLINICAL TRIALS

There were two pediatric trials conducted on Celexa: Study 94404 and MD-18. And, as discussed below, both were negative for efficacy on every primary and secondary endpoint.

I. Celexa Study 94404 Was a Negative Clinical Trial

Celexa Study 94404 was conducted in Europe by Forest's partner, Lundbeck, and was submitted to the FDA on March 21, 2002.[45] The study involved 244 depressed adolescents, aged 13-18.[46] The study had one primary endpoint and nine secondary endpoints.[47] As illustrated in Table 1, all endpoints were negative.

Table 1 – Celexa Study 94404 Efficacy Results[48]

Endpoint	P-Value	Result
Change in Kiddie-SADS-P Total Score over Time (Primary)	N/A	Negative
Change from Baseline in Kiddie-SADS-P Total Score	0.791	Negative
Kiddie-SADS-P Response	1.000	Negative
Change from Baseline in MADRS Total Score	0.853	Negative
MADRS Response	0.865	Negative
MADRS Remission	0.867	Negative
Beck's Depression Inventory (BDI)	0.863	Negative
Global Assessment of Functioning (GAF)	0.933	Negative
Life Event Scale	N/A	Negative
Expressed Emotions	N/A	Negative

Forest learned that Study 94404 was negative on July 16, 2001.[49] This was approximately around the time Forest also learned about the results of MD-18. Forest made a deliberate decision to suppress the results of 94404 while promoting the results of MD-18.[50] Dr. William

[45] Exh. 35, Excerpts of Study 94404 Rpt. at *1.

[46] *Id.* at *11 (pg. 47 of 345).

[47] *Id.* at *8-10 (pgs. 42-44 of 345).

[48] *Id.* at *12-23 (pgs. 58-69 of 345) (data listed in text).

[49] Exh. 36, Letter from Lundbeck to Forest (w/attachment), at 1; Exh. 37, Email re. 94404 Headline results at 1-2 ("94 404 citalopram vs placebo in the treatment of adolescent depression have been unblinded and unfortunately with a negative result. It was not possible to detect a significant difference between the two treatment groups.").

[50] *See* Exh. 3, Criminal Information ¶ 70 ("FOREST PHARMACEUTICALS aggressively publicized and promoted the results from the positive Forest study, while at the same time FOREST PHARMACEUTICALS did not publicize or disclose the results of the negative study to persons outside the FDA or the Danish company which sponsored the negative study. As a

Heydorn, a former Senior Medical Writer at Forest, explained:

> Q. Were you aware of anyone at Forest Labs who shared the view that it would be best if the positive data of CIT-MD-18 Was in the marketplace before the negative data of 94404 was out in the marketplace?
> . . .
> A. Yes.
> . . .
> Q. And who did you understand to share that view?
> A. I think most of the individuals associated with the citalopram project held that view.
> . . .
> Q. Was it your understanding at the time that you were working at Forest Labs that positive data would be better than negative data in terms of marketing Celexa?
> . . .
> A. Yes.
> Q. And that positive data being put out in the marketplace over negative data would be better for the sales of Celexa?
> . . .
> A. I certainly wasn't in the sales and marketing department, but that would be my understanding, yes.[51]

The investigators at Lundbeck were eager to get the results of 94404 published, but Forest and Lundbeck wanted to make sure the "positive" results of MD-18 were in the public domain.[52] Thus, for three years, the results of Study 94404 remained concealed. Then, in 2004, the New York Times published an article criticizing Forest for publishing MD-18 without mentioning the negative results of Study 94404.[53] This prompted an immediate response from Forest where it issued a press release disclosing the results of Study 94404.[54] Study 94404, however, did not get published until 2006—five years after Forest and Lundbeck obtained the results.[55]

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result, doctors and psychiatrists received incomplete and misleading information concerning all available known data pertaining to the efficacy of using Celexa to treat depression in children and adolescents.").

[51] Exh. 38, Excerpts of 2007 Depo. of W. Heydorn at 77:23-80:5.

[52] Exh. 39, Email re. Publications at 1-2 ("I just wanted to check on the status for the Wagner pediatric manuscript . . . investigators in the Lundbeck sponsored study seem eager to submit a manuscript on their study (they are working on it - we have not yet seen any draft) and I wanted to make sure that the positive data are in the public domain before their negative data get out.")

[53] Exh. 40, Barry Meier, *Medicine's Data Gao – Journals in a Quandary; A Medical Journal Quandary: How to Report on Drug Trials*, NY TIMES (June 21, 2004).

[54] Exh. 41, Press Release, Forest Laboratories, Inc., *Forest Discusses Disclosure of Citalopram Clinical Trial Data in Children and Adolescents* (June 24, 2004).

[55] Exh. 42, Anne-Liis von Knorring, et al, *A Randomized, Double-blind, Placebo-controlled*

II. Celexa Study MD-18 Was a Negative Clinical Trial, but Forest Misled the FDA about the Results

Celexa Study MD-18 was conducted by Forest in the United States. It involved 174 pediatric patients diagnosed with depression, aged 7-17.[56] The final study report for MD-18 was submitted to the FDA on April 8, 2002.[57] MD-18 had one primary and four secondary endpoints.[58] As illustrated in Table 2, all five endpoints were negative. For those patients who actually completed MD-18, i.e., "observed cases," the results were also negative (p-value of 0.167).[59]

Table 2 – Celexa Study MD-18 Efficacy Results[60]

Endpoint	P-Value	Result
Change from Baseline in CDRS-R at 8 Weeks (LOCF) (Primary)	0.052*	Negative
Change from Baseline in CDRS-R at 8 Weeks (Observed Cases)	0.167	Negative
CGI Improvement at 8 Weeks	0.257	Negative
Change from Baseline in CGI Severity at 8 Weeks	0.266	Negative
Change from Baseline in CGAS at 8 Weeks	0.309	Negative
Change from Baseline in K-SADS-P Depression Module at 8 Weeks	0.105	Negative

**P-value based on data excluding 9 patients who were unblinded during the study.*

In any DBRCT, data collected from the patients must be double-blind. The protocol for MD-18 stated that: "*Any patient for whom the blind has been broken will immediately be discontinued from the study and no further efficacy evaluations will be performed.*"[61] Dr. William Heydorn, the primary author of the final study report for MD-18,[62] confirmed that, pursuant to the protocol, unblinded patients were to be excluded from any efficacy analysis.[63] And, this makes sense. Efficacy in a depression trial is based on an investigator's subjective assessment of a patient's subjective responses to questions on a depression questionnaire. If either the patient or investigator knows whether the patient is taking a real drug or a placebo, it could very well influence the patient's answers and the investigator's subjective scoring. Indeed, the FDA has identified multiple types of bias associated with blinding:

Study of Citalopram in Adolescents with Major Depressive Disorder, 26 J. CLIN. PSYCHOPHARMACOLOGY 3, 311-15 (2006).

[56] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 38.

[57] *Id.* at pg.1.

[58] *Id.* at pgs. 49-50.

[59] *Id.* at pg. 111.

[60] *Id.* at pgs. 101-104, 111, 244.

[61] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 328.

[62] Exh. 38, Excerpts of 2007 Depo. of W. Heydorn at 42:13-44:13.

[63] Exh. 11, 2016 Depo. of W. Heydorn at 107:13-107:21.

- Subjects on active drug might report more favorable outcomes because they expect a benefit or might be more likely to stay in a study if they knew they were on active drug.
- Observers might be less likely to identify and report treatment responses in a no-treatment group or might be more sensitive to a favorable outcome or adverse event in patients receiving active drug.
- Knowledge of treatment assignment could affect vigor of attempts to obtain on-study or follow-up data.
- Knowledge of treatment assignment could affect decisions about whether a subject should remain on treatment or receive concomitant medications or other ancillary therapy.
- ***Knowledge of treatment assignment could affect decisions as to whether a given subject's results should be included in an analysis.***
- Knowledge of treatment assignment could affect choice of statistical analysis.

Blinding is intended to ensure that subjective assessments and decisions are not affected by knowledge of treatment assignment.[64]

Forest told the FDA, DOJ, and USAO that MD-18 was a positive study because, even though all of the secondary endpoints were negative (as well as the observed cases analysis), Forest claimed the primary endpoint reached statistical significance. This, however, was untrue. As discussed in detail below, the first nine patients randomized into MD-18 were unblinded because of a packaging error. Under the protocol, these initial nine patients should not have been included in the efficacy analysis. And, without these patients included, MD-18 was negative on *every* endpoint, including the primary endpoint. Internal documents and the testimony of former employees demonstrate that Forest deliberately misled the FDA about the extent of the unblinding and that MD-18, when properly assessed, is negative.

A. General Overview of MD-18 Study

Dr. Paul Tiseo, Joan Barton, and Dr. Charles Flicker oversaw MD-18.[65] Dr. Tiseo was the Medical Monitor for MD-18, Ms. Barton was the Clinical Trial Manager of MD-18, and Dr. Flicker was Dr. Tiseo and Ms. Barton's supervisor, overseeing all of the clinical trial programs related to Celexa and Lexapro.[66] Dr. Tiseo was responsible for the overall conduct of the

[64] Exh. 30, FDA, *supra* note 33, at 4 (emphasis added).

[65] *See* Exh. 43, Excerpts of Study MD-18 Protocol at pg. 334; Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 168:1-169:12; 170:5-14; Exh. 11, 2016 Depo. of W. Heydorn at 29:14-32:2.

[66] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 334; Exh. 11, 2016 Depo. of W. Heydorn at 29:14-32:2.

study.[67] Above Dr. Flicker was Dr. Ivan Gergel and, above him, was Dr. Lawrence Olanoff.[68] After MD-18 was completed, Dr. Tiseo left Forest, and Dr. William Heydorn took responsibility for drafting and publishing the results of MD-18 in both the final study report and subsequent academic publication.[69]

When a child was enrolled in the study, the child and their parent were dispensed medication at different pre-specified intervals as reflected below:

Visit 1	Week -1	Patient dispensed 1 bottle containing 10 placebo pills.
Visit 2	Week 0	Patient randomized. Dispensed 1 bottle containing 10 pills.
Visit 3	Week 1	Patient dispensed 1 bottle containing 10 pills.
Visit 4	Week 2	Patient dispensed 2 bottles containing 10 pills.
Visit 5	Week 4	Patient dispensed 1 bottle containing 40 pills.
Visit 6	Week 6	Patient dispensed 1 bottle containing 40 pills.
Visit 7	Week 8	Study completed.[70]

At Visit 1 (week -1), each patient was put through a one-week placebo screening period, also known as a placebo run-in.[71] During this period, the patient was given one week of medication in a 10-pill bottle containing placebo pills.[72] This period was single-blinded—meaning the patient did not know the pills were placebo, only the investigator knew.[73]

At Visit 2 (week 0), patients were assessed to see how they responded to the 1 week placebo-screening period.[74] If they responded, they were not allowed to enter the randomized portion of the trial.[75] The remaining patients were randomized into either the placebo or Celexa group. At this point, each patient's baseline was established.[76] The randomization was supposed to be double-blind, meaning neither the patient nor the investigator knew which group the patient was assigned to. Each patient was given another 10-pill bottle containing either blinded-placebo or

[67] Exh. 11, 2016 Depo. of W. Heydorn at 29:14-32:2; Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 168:1-169:12; 170:5-14.

[68] Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 168:1-169:12; 170:5-14.

[69] Exh. 38, Excerpts of 2007 Depo. of W. Heydorn at 42:13-44:13; Exh. 11, 2016 Depo. of W. Heydorn at 29:14-32:2.

[70] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 326.

[71] *Id.* at pgs. 323-26.

[72] *Id.*

[73] *Id.*

[74] *Id.*

[75] *Id.* at 318 ("Patients must have a Children's Depression Rating Scale-Revised (CDRS-R) score of 40 or greater at both the Screening and Baseline visits.")

[76] *Id.* at pgs. 323-26.

blinded-Celexa.[77]

At Visit 3 (week 1), the investigator conducted another round of assessments to see how, if at all, the patient was responding to treatment.[78] As part of this process, each patient was required to return unused medication and the investigator was required to count the number of remaining pills in the bottle to ensure compliance.[79] At the end of the visit, the patients were dispensed a new 10-pill bottle to last until the next visit, the following week.[80]

At Visit 4 (week 2), like at Visit 3, more assessments were done and the pills were counted. The patients were then dispensed two 10-pill bottles to last the next two weeks.[81]

At Visit 5 (week 4), the patients were given another round of assessments and the pills were counted.[82] At this half-way point in the trial, the investigators were permitted to increase the patient's dose by double if the patient was not responding.[83] If so, the patient was expected to take two pills instead of one each day.[84] Accordingly, at Visit 5 (week 4), each patient was given a 40-pill bottle, which would last two weeks until the next visit.[85]

At Visit 6 (week 6), more assessments and pill counts were conducted and the patients were dispensed another 40-pill bottle to last two more weeks.[86]

At Visit 7 (week 8) the study was completed and the final assessments were performed. The success of each patient was determined by a comparison of the patient's improvement (or lack of improvement) between Visit 2 (week 0) and Visit 7 (week 8).[87]

B. At the Beginning of the Trial, a Packaging Error Caused Nine Patients, and their Investigators, to Become Unblinded

Shortly after MD-18 began enrolling patients, Forest learned of a packaging error. According to Dr. Tiseo, two "investigational sites called in to report that some of their patients were receiving white tablets and others were receiving pink tablets."[88] Forest investigated and,

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[77] *Id.*
[78] *Id.*
[79] *Id.*
[80] *Id.*
[81] *Id.*
[82] *Id.*
[83] *Id.*
[84] *Id.*
[85] *Id.*
[86] *Id.*
[87] *Id.*
[88] Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1; *accord* Exh. 11, 2016

"it was discovered that a number of bottles of 'active' medication were mistakenly packed with the pink-colored commercial Celexa® tablets instead of the standard white citalopram tablets used for blinded clinical studies."[89]

According to an investigation by the clinical supply group within Forest, the 10-pill bottles to be used in the Celexa group did not contain the standard white blinded pills, but contained pink, oval-shaped, Forest-branded, and dose-stamped commercial Celexa® tablets.[90] See photo below.

To correct the packaging error, Dr. Tiseo ensured "all sites were notified of this error by telephone and by fax."[91] In the fax, Dr. Tiseo informed each investigational site about the packaging error and told each site that the pink pills they were seeing in the patients already randomized were "pink-colored commercial Celexa® tablets instead of the standard white citalopram tablets used for blinded clinical studies."[92] Dr. Tiseo explained that "dispensing these tablets would ***automatically unblind the study***."[93] Dr. Tiseo instructed each investigational site to immediately return the unblinded medication for repackaging.[94] However, for those patients already randomized, i.e., already receiving the commercial Celexa tablets, Dr. Tiseo instructed

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Depo. of W. Heydorn at 197:18-198:14 (verifying that the handwriting belongs to Charles Flicker); Exh. 44, Emails re. Urgent CIT-MD-18 at *1 (When notified of the findings by a site, *due to seeing white and pink tablets*, all supplies were returned and the 10ct bottles re-packaged with non-trade "white" tablets." (emphasis added)).

[89] Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1.

[90] Exh. 15, Memo re. CIT-MD-18 (Deviation Report) at 1-2.

[91] Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1; *accord* Exh. 16, Email re. CIT-18 FAX to Investigational sites (w/ attachment) at 1 ("[A] copy of the FAX that went out to all CIT-MD-18 Pediatric Investigational sites this morning is attached. All sites have also been contacted by telephone and given verbal instructions on how to proceed[.]").

[92] Exh. 16, Email re. CIT-18 FAX to Investigational sites (w/ attachment) at 2.

[93] *Id.* (emphasis added).

[94] *Id.* at 4.

each site to keep using the unblinded medication.[95]

The problem, however, is that for those patients already randomized into the study, the patients and the investigators were unblinded. The investigators brought the packaging error to Forest's attention because some patients were receiving white pills and some were receiving pink ones. When Dr. Tiseo told investigators the pink pills were commercial Celexa tablets, even if the patients somehow did not know the Forest-branded tablets were the active drug, the investigators knew the patients getting the pink pills were getting Celexa and the patients getting white pills were getting inert placebos. Dr. Flicker admitted this during his deposition: "[I]f an investigator were to look . . . at returned medication and he saw that the tablets were pink . . . then I would think the investigator would be able to draw the conclusion that the patient was on active drug."[96] Dr. Heydorn also conceded: "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 . . . unmistakenly compromised? . . . It does raise questions about the integrity of the blind, yes."[97]

Additionally, there is strong evidence that the patients randomized into the Celexa group were also, individually, unblinded. First, the average improvement of the blinded patients in the study taking Celexa was 21.3 points on the CDRS scale.[98] However, the average improvement for the unblinded patients given commercial Celexa for the first four weeks was 30.5 points.[99] This 50% greater improvement in the unblinded Celexa patients, versus the blinded Celexa patients, is strong evidence that those patients or investigators were, in fact, unblinded.

Second, the patients in the Celexa group who were given the commercial Celexa tablets would have been exposed to different color and shaped pills throughout the trial. Specifically, the pink tablets were only located in the 10 pill bottles, which were only dispensed during the four weeks after randomization. The last four weeks of trial used the 40-pill bottles, which contained the standard, blinded, white pills. However, prior to being randomized, every patient was given white placebo pills during the one week placebo run-in period. So, this means, these patients would have been given white pills for one week, pink commercial Celexa pills for four weeks, then white placebo-looking pills for four weeks.[100] This is illustrated in the diagram on the next page.[101]

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[95] *Id.*

[96] Exh. 45, 2016 Depo. of C. Flicker at 278:24-279:6.

[97] Exh. 11, 2016 Depo. of W. Heydorn at 202:13-19.

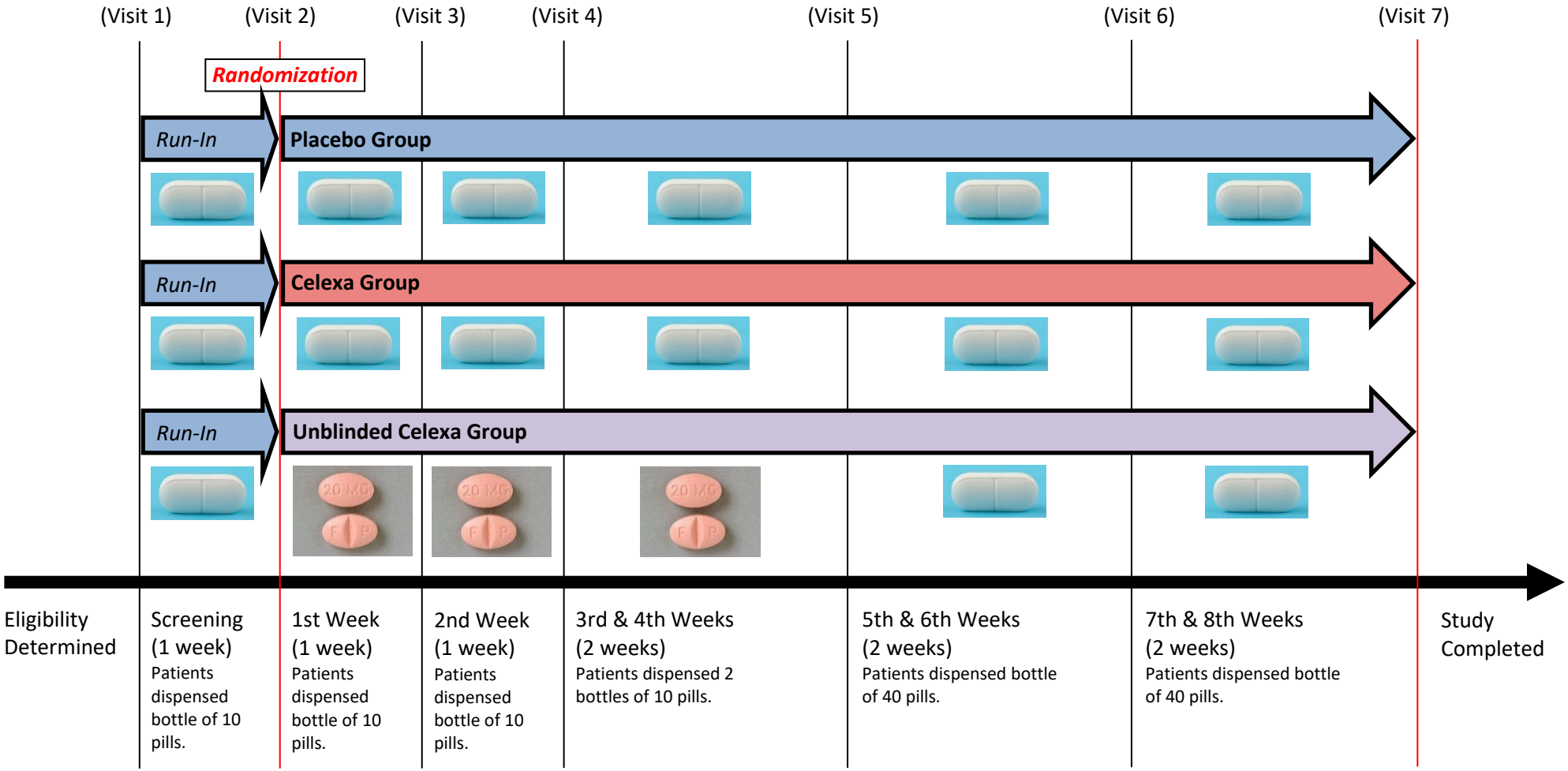
[98] Exh. 46, J. Jureidini Expert Report at 5.

[99] *Id.*

[100] *See* Exh. 47, J. Glenmullen Expert Rpt. at 24 (discussing how the dispensing process for these unblinded Celexa patients occurred).

[101] *Id.*

Celexa Study Dispensing Diagram



Average Change from Baseline

Placebo Group: Improved 16.4 points

Celexa Group: Improved 21.3 points

Unblinded Celexa Group: Improved 30.5 points

According to the protocol for MD-18, "*[a]ny patient for whom the blind has been broken will immediately be discontinued from the study and no further efficacy evaluations will be performed.*"[102] This means any unblinded patients should have been excluded from the study efficacy evaluations. Dr. Heydorn confirmed this fact: "[P]er the protocol, ***those patients should have been excluded*** because they were unblinded, correct? . . . ***Yes***."[103]

Internal Forest documents confirm these patients were, in fact, considered unblinded by the Forest scientists and statisticians working on MD-18. For example, Ms. Barton sent an email to Drs. Tiseo and Flicker on December 6, 2000, inquiring about whether MD-18 would need to have additional patients enrolled due to the fact "the study drug was unblinded."[104] In another email, dated August 10, 2001, Jane Wu, a biostatistician working on MD-18, explained they needed to generate tables "excluding the 9 patients who were unblinded at the beginning of the study."[105] In another email, dated April 5, 2002, Julie Kilbane was finalizing the submission of MD-18 and sent an email explaining that "[s]ome of the supplies were unblinded for this study[.]"[106] Within Forest, there was no ambiguity about whether these patients were actually "unblinded."

C. Forest Knowingly Misled the FDA about the Nature of the Unblinding by Using, As Forest Regulatory Affairs Manager Put It, "Masterful Euphemisms" to "Protect Medical and Marketing"

After correcting the packaging error to prevent further "automatic" unblinding, Forest debated whether to notify the FDA of the problem. Dr. Tiseo drafted an initial version of a letter to send to the FDA.[107] Dr. Flicker reviewed it and advised not sending any letter, but, if Forest did send a letter, he advised giving considerably less detail.[108] After incorporating Dr. Flicker's comments, Dr. Tiseo circulated a draft version of the letter to various Forest executives and regulatory personnel, including Lawrence Olanoff, Ivan Gergel, Amy Rubin, Tracey Varner, Julie Kilbane, and Dr. Flicker.[109] The draft letter stated that the dispensed medication could have

[102] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 328.

[103] Exh. 11, 2016 Depo. of W. Heydorn at 227:5-10, 228:20-24, 244:11-17.

[104] Exh. 48, Email re. CIT-MD-18 Study Drug at 1.

[105] Exh. 20, Emails re. CIT-MD-18 at 1.

[106] Exh. 44, Emails re. Urgent CIT-MD-18 at *2.

[107] Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1; Exh. 11, 2016 Depo. of W. Heydorn at 197:18-198:14 (verifying that the handwriting belongs to Charles Flicker).

[108] Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1 ("Reconsider no letter otherwise I recommend much less narrative[.]").

[109] Exh. 17, Email re. Letter to FDA for CIT-18 (w/attachment) at 1 ("Attached please 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.").

"unblinded the study."[110] Dr. Tiseo solicited comments from the group.[111]

Amy Rubin, who worked in Regulatory Affairs, edited the letter, changing the language from stating that the dispensing error could have "unblinded the study" to stating the error had the "potential to cause patient bias."[112] Ms. Rubin's edit drew criticism from Dr. Flicker who felt Ms. Rubin's edits were not up front: "***Altho 'potential to cause bias' 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.***"[113] This criticism, however, did not prompt Ms. Rubin to correct the language of the letter. Instead, Ms. Rubin responded: "Thanks for the compliement [sic]. ***Part of my job is to create 'masterful' euphemisms to protect Medical and Marketing.***"[114] For Ms. Rubin, misleading the FDA was not only acceptable, it was *part of her job*.[115]

And, she did her job well. The letter ultimately sent to the FDA on March 20, 2000, contained the misleading "masterful euphemism" language.[116] The letter did *not* disclose that the patients dispensed the pink pills were "automatically unblinded" as Dr. Tiseo stated to the investigators or that, as Dr. Flicker noted, the integrity of the blind was "unmistakenly violated." The smokescreen was up.

As part of the MDL litigation, Plaintiffs deposed Dr. Thomas Laughren, the former Director of Psychiatric Drug Products in the Division of Neuropharmacological Drug Products at the FDA. He personally reviewed the final study report for MD-18 while at the FDA and, ultimately, was the man at the FDA who approved Lexapro for use in adolescents in 2009.[117] Dr. Laughren departed the FDA in 2013 and, within months, was working as a testifying expert for various pharmaceutical companies, including Forest.[118] In fact, Dr. Laughren was hired as a testifying expert *for Forest* to provide opinions about the *pediatric efficacy* of Celexa and Lexapro and whether the drugs can increase the risk of suicidal behavior in children.[119] Notwithstanding Dr. Laughren's unseemly transition from regulating Forest at the FDA to working for Forest, he was shown the euphemism emails and other documents, and he took offense to Forest's conduct:

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[110] *Id.* at 2 ("[D]ue 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.").

[111] *Id.* at 1 ("please review and send your comments back to me within the next few days.")

[112] Exh. 18, Email responses re. Letter to FDA for CIT-18 at 1-2.

[113] *Id.* at 1.

[114] *Id.*

[115] *Id.*

[116] Exh. 19, Letter from T. Varner (Forest) to R. Katz (FDA) at 1.

[117] Exh. 8, 2017 Depo. of T. Laughren at 401:24-402:8 ("[Y]ou're actually the one who ultimately signed off finally on Lexapro's approval for adolescents, right? A Yes."); Exh. 49, Lexapro Approval Letter for Adolescents at 3 (signed by Dr. Laughren).

[118] Exh. 8, 2017 Depo. of T. Laughren at 81:1-83:14.

[119] *Id.*

[Q]. [D]oes 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"?

[A]. ***Yeah, no, that's – that's concerning, I would say.*** . . .

[Q.] 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"?

[A]. ***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.

. . .

[Q.] 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"? . . .

[A.] ***What -- what concerns me is -- is that -- you know, what was represented to FDA was not precisely what happened.***[120]

D. Despite Misrepresenting the Unblinding to the FDA, Forest Promised to Exclude the Data from the Patients from Its Primary Efficacy Analysis

While the March 20, 2000 letter to the FDA misrepresented the nature of the unblinding to the FDA, it also stated: "For reporting purposes, ***the primary efficacy analysis will exclude the eight potentially unblinded patients***, with a secondary analysis including also to be conducted."[121] This sentence was added by Dr. Flicker to the original draft of the letter.[122] Dr. Flicker, consistent with his view that the integrity of the blind was unmistakenly violated, knew the data from these patients was corrupted. So, Forest promised the FDA, consistent with the express wording of the MD-18 study protocol, that the unblinded patients would not be counted in the primary efficacy analysis and that, instead, "[a] full complement of 160 patients will be enrolled under standard double-blind conditions."[123] Dr. Flicker acknowledged: "[Y]ou were suggesting that the nine patients subject to the dispensing error were not standardly double-blinded, correct? . . . I think it does suggest that."[124] Importantly, this promise to exclude the unblinded patients from the primary efficacy analysis was made *before* Forest knew the results of the primary efficacy endpoint turned on the inclusion of those patients.

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[120] *Id.* at 205:14-21, 206:14-23, 207:21-208:4 (emphasis added).

[121] Exh. 19, Letter from T. Varner (Forest) to R. Katz (FDA) at 1 (emphasis added).

[122] Exh. 13, Draft FDA Letter with C. Flicker Handwritten Comments at 1.

[123] Exh. 19, Letter from T. Varner (Forest) to R. Katz (FDA) at 1.

[124] Exh. 45, 2016 Depo. of C. Flicker at 294:13-23.

E. Forest Reneged on its Promise to Exclude the Unblinded Patients from the Primary Efficacy Results and, Again, Misrepresented the Unblinding in MD-18's Final Study Report

The protocol for MD-18 only required the enrollment of 160 patients.[125] However, accounting for the unblinded patients, the study would need to randomize at least 169 patients total so that Forest would have a full-complement of patients under standard double-blind conditions. Forest ultimately randomized 174 patients into the study, including nine of the unblinded patients.[126] So, for purposes of powering the study with sufficient patients, MD-18 did not require the data from the unbinded patients.[127]

After the MD-18 data was collected, however, Forest reneged on its promise to exclude the unblinded patients from the primary efficacy analysis. Without any consultation with the FDA, Forest slipped the unblinded patients into the primary efficacy analysis—combining the data from the unblinded patients with the blinded cohort—and prepared a secondary "post-hoc" analysis excluding the patients and put it in an appendix.[128] Including these unblinded patients into the results was "substantial."[129] With the unblinded patients in the study, the primary endpoint reached statistical significance, but with the unblinded patients excluded—as Forest promised the FDA—***all primary and secondary endpoints were negative***. Had Forest done what it promised, the study would have been negative. In fact, Forest's corporate representative conceded that MD-18 is a negative study when the unblinded patients are excluded.[130] So did Dr. Heydorn, the primary author of the MD-18 study report:

> Q. By excluding these nine patients, the P-value went from a statistically significant .038 to a statistically insignificant .052 on the CDRS-R rating scale after 8 weeks, correct?
>
> [A]. Yes.
>
> Q. ***So, in other words, this P-value shows citalopram versus placebo was negative for the primary outcome measure for MD-18, right?***

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[125] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 318 ("The study population will be equally stratified between children (aged 7 to 11) and adolescents (ages 12 to 17). A total of 160 patients will be randomized to double-blind treatment.")

[126] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 64 ("A total of 174 patients received double-blind study drug, of whom 89 received citalopram and 85 received placebo."

[127] *Id.* at pg. 62 ("Assuming an effect size (treatment group difference relative to pooled standard deviation) of 0.5, a sample size of 80 patients in each treatment group was used[.]").

[128] *Id.* at pg. 63.

[129] Exh. 11, Depo. of W. Heydorn at 88:3-17 (Dr. Heydorn admitting that including the patients made an "important substantial difference" and that those patients were not needed to power the study).

[130] Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 294:10-295:20 ("If they were removed from the study, I understand that the result would have been negative.").

[A]. ***Yes.***[131]

Indeed, Dr. Heydorn admitted that, if these patients were unblinded, the fact that the study was negative without them "undermine[s] the assertions that Study 18's outcome was positive for showing Celexa significantly improved major depression disorder in children and adolescents[.]"[132] When Dr. Heydorn was shown the internal documents demonstrating that the integrity of the blind was unmistakenly violated, he conceded Forest was not honest with the FDA, that Forest misled people about the results of MD-18, and that he would have written the study report differently:

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 know. 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***.
. . .
Q. Would you have changed anything in the final study report?
A. ***If I were the only one involved in writing it, I probably would have written it somewhat differently***.[133]

When Dr. Heydorn's testimony was presented to Dr. Laughren, he testified:

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?
[A]. ***That's what he's saying.***
Q. And he's the man who actually was responsible for the final study report for Study MD-18, right?
[A]. He appears to have been, yes.
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?***

[131] Exh. 11, 2016 Depo. of W. Heydorn at 86:22-87:9.

[132] *Id.* at 112:14-112:20.

[133] *Id.* at 308:16-309:6 (emphasis added).

[A]. ***Yes.***[134]

The original draft of the MD-18 study report was prepared by a company called PharmaNet, a contract research organization.[135] Before the first draft of the report was prepared, Dr. Flicker, Dr. Heydorn, and two biostatisticians from Forest met with PharmaNet to discuss how the report should be prepared.[136] The notes of the meeting illustrate Forest's general strategy in dealing with the unblinded patients:

> Dosing error – some citalopram table[t]s were not blinded. The 9 patients who received unblinded medication were included in the main analyses; a secondary "Post-hoc analysis of the ITT subpopulation" was done. ***Refer to these analyses briefly in methods and results and reference the reader to the appendix table.***[137]

Thus, from the outset, Forest intended to bury the impact of the unblinded data by referring "to these analyses briefly" and referencing "the reader to the appendix table" on page 244 (of 2,135). It is also worth noting that, even here, in this meeting, Forest was once again stating that the drugs "were not blinded" and that the 9 patients "received unblinded medication." As shown below, this clear admission of unblinding was *deliberately* removed from the final study report sent to the FDA.

In the final study report for MD-18, there are four references to the unblinded patients and *all* of them are misleading or factually false. The first reference is in a section of the Study Report titled "Blinding" where it states:

> Because of a drug packaging error, the citalopram or placebo tablets initially dispensed to 9 patients at 3 study centers were distinguishable in color, although otherwise blinded (see Section 7.0). When this error was identified at the beginning of the study period, all study medication shipments were replaced in full with tablets of identical color to remove any potential for unblinding.[138]

This paragraph is riddled with inaccuracies and misstatements. First, the placebo tablets initially dispensed were not distinguishable in color—only the Celexa group received the pink pills, which is why the investigators were unblinded. If both the placebo and Celexa pills had been pink, then the investigators would not necessarily have known which patients were assigned to each group. Second, they were not just distinguishable in color—the pink pills were Forest-stamped, dose-stamped, commercial Celexa tablets. The failure of Forest to disclose that the drug dispensed was commercial branded Celexa is misleading in the extreme. Third, when this

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[134] Exh. 8, 2017 Depo. of T. Laughren at 263:9-264:5 (emphasis added).

[135] Exh. 11, 2016 Depo. of W. Heydorn at 237:2-15.

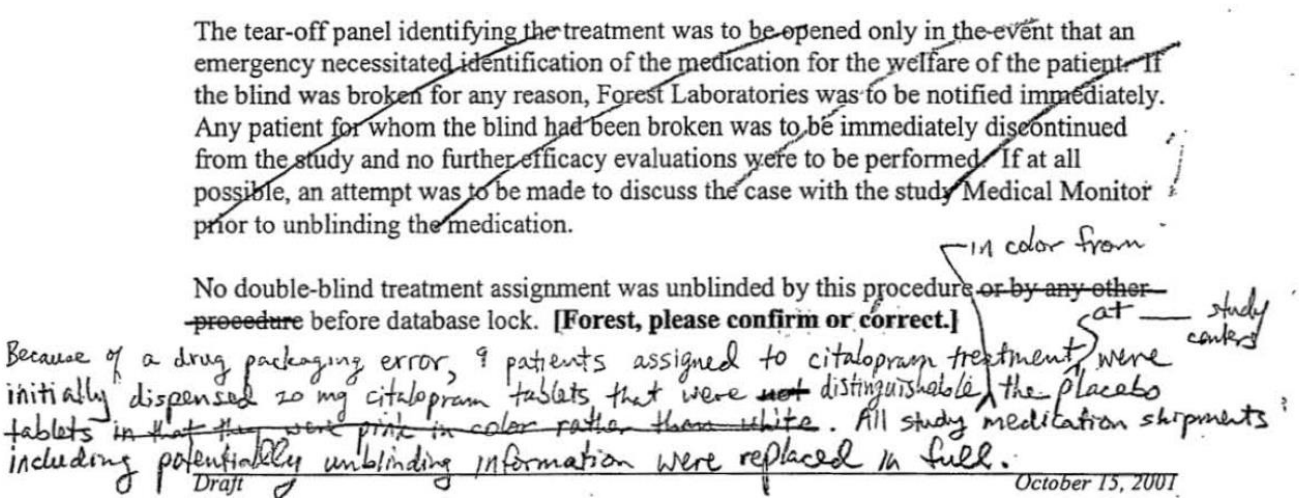
[136] *Id.* at 236:15-237:6; Exh. 21, Email re. Notes from conference call Oct 4 (w/attachment) at 1 ("Attached are my notes from the conference call with the CRO on the peds study.").

[137] Exh. 21, Email re. Notes from conference call Oct 4 (w/attachment) at 2 (emphasis added).

[138] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 44.

error was identified, the medication for those patients not yet randomized was replaced, but for the nine patients already in the study, Forest *did not* replace their medications.[139] Forest instructed each site to continue using the multicolor pills for those patients already randomized to placebo.[140] That means those Celexa patients received white pills for the screening period, pink pills for the first four weeks, and then white pills for the last four weeks. This paragraph falsely stated that these patients' medication was replaced "to remove any potential for unblinding" and this is simply not true.

Notably, in the original draft of the MD-18 study report prepared by PharmaNet, a section of the study report contained the language from the original protocol, specifying that "[a]ny patient for whom the blind had been broken was to be immediately discontinued from the study and no further efficacy evaluations were to be performed."[141] Dr. Flicker, however, crossed this language out and inserted the language that ultimately made its way into the final study report:


The tear-off panel identifying the treatment was to be opened only in the event that an emergency necessitated identification of the medication for the welfare of the patient. If the blind was broken for any reason, Forest Laboratories was to be notified immediately. Any patient for whom the blind had been broken was to be immediately discontinued from the study and no further efficacy evaluations were to be performed. If at all possible, an attempt was to be made to discuss the case with the study Medical Monitor prior to unblinding the medication.

No double-blind treatment assignment was unblinded by this procedure ~~or by any other procedure~~ before database lock. **[Forest, please confirm or correct.]**

in color from

at study centers

Because of a drug packaging error, 9 patients assigned to citalopram treatment were initially dispensed 20 mg citalopram tablets that were ~~not~~ distinguishable the placebo tablets ~~in that they were pink in color rather than white~~. All study medication shipments including potentially unblinding information were replaced in full.

Draft October 15, 2001

The second reference to the dispensing error is in the section titled "Changes in the Conduct of the Study and Planned Analysis" and it reads:

> Nine patients (Patients 105, 113, 114, 505, 506, 507, 509, 513, and 514) were mistakenly dispensed 1 week of medication with potentially unblinding information (tablets had an incorrect color coating). Therefore, in addition to the analysis specified in Section 6.4.1 for the primary efficacy parameter, a post-hoc analysis was performed on an ITT subpopulation that excluded these 9 patients.[142]

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[139] Exh. 16, Email re. CIT-18 FAX to Investigational sites (w/ attachment) at 3 ("Patients already randomized . . . will proceed through the study normally a . . . DO NOT ship their remaining drug back to Forest. Keep all of their drug at your site and continue to use it as you would ordinarily. Return only the units of drug for your non-randomized patients.").

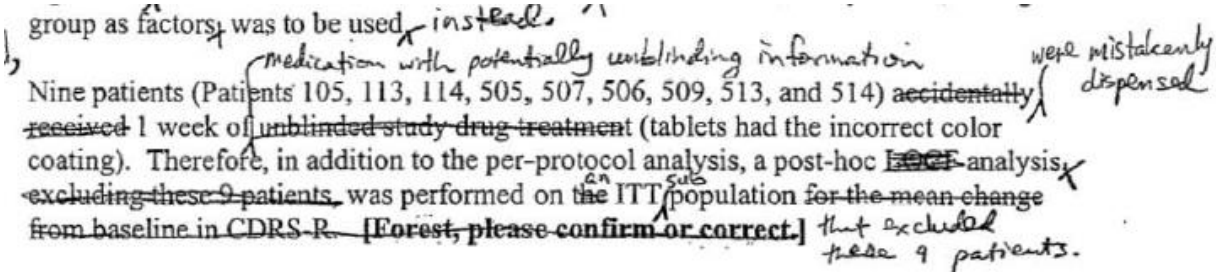
[140] *Id.*

[141] Exh. 50, Draft of MD-18 Study Report w/ C. Flicker Comments at 26.

[142] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 63.

This paragraph is also misleading and factually incorrect. First, these nine patients were not dispensed *one* week of medication with potentially unblinding information. These patients received unblinded drug for the first four weeks, not just one week.[143] When this point was shown to Dr. Heydorn, he admitted the statement about one week was not true: "A. It does say one week of medication, yes. . . . Q. So that's not actually true, right, with respect to patients 113 and 513, correct? . . . ***It would appear not to be true, yes.***"[144] And, since the investigators were unblinded, the patients were technically unblinded for the entire study. Second, once again, Forest stated there was an incorrect color coating, even though the pink pills were actually Forest-stamped, dose-stamped, commercial Celexa tablets. Third, Forest stated that it was providing "a post-hoc analysis" excluding these nine patients. But, again, this directly contradicts the letter Forest sent to the FDA when the unblinding occurred: "For reporting purposes, the primary efficacy analysis will exclude the eight potentially unblinded patients, ***with a secondary analysis including them also to be conducted.***"[145]

Finally, the phrase "potentially unblinding information" is deeply misleading. Ironically, this was Dr. Flicker's phraseology—the same person who, back in March 2000, characterized "potential to cause bias" as a "masterful stroke of euphemism" and felt that the "integrity of the blind was unmistakenly violated."[146] In the original draft of the MD-18 study report, it stated: "Nine patients . . . accidently ***received 1 week of unblinded study drug treatment***[.]"[147] Note, there was no "potential" or uncertainty about whether the patients received unblinded study drug treatment. However, in November 2001, when Dr. Flicker edited the first draft of the report, he crossed out this language and added the "potentially" language:[148]


group as factors was to be used instead.
medication with potentially unblinding information
were mistakenly dispensed
Nine patients (Patients 105, 113, 114, 505, 507, 506, 509, 513, and 514) ~~accidentally received~~ 1 week of ~~unblinded study drug treatment~~ (tablets had the incorrect color coating). Therefore, in addition to the per-protocol analysis, a post-hoc ~~LOCF~~ analysis ~~excluding these 9 patients~~ was performed on ~~the~~ an ITT sub population ~~for the mean change from baseline in CDRS-R.~~ **~~[Forest, please confirm or correct.]~~** that excluded these 9 patients.

So, Dr. Flicker stated that the "integrity was unmistkenly violated" in 2000, and then, a year

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[143] Indeed, investigators were not notified of the problem until Dr. Tiseo sent out the facsimile on March 2, 2000. *See* Exh. 16, Email re. CIT-18 FAX to Investigational sites (w/ attachment) at 1. At that point in time, three patients had already been in the study for over a month, and the rest had been in the study for over two weeks. Exh. 9, Excerpts of Study MD-18 Rpt. at pg.1214-15, 1235-37 (listing the dates of each unblinded patients' various assessments). The statement that these patients only received incorrectly colored drug for one week is plainly false.

[144] Exh. 11, 2016 Depo. of W. Heydorn at 176:3-20 (emphasis added).

[145] Exh. 19, Letter from T. Varner (Forest) to R. Katz (FDA) at 1.

[146] Exh. 18, Email responses re. Letter to FDA for CIT-18 at 1 (emphasis added).

[147] Exh. 50, Draft of MD-18 Study Report w/ C. Flicker Comments at 44 (emphasis added).

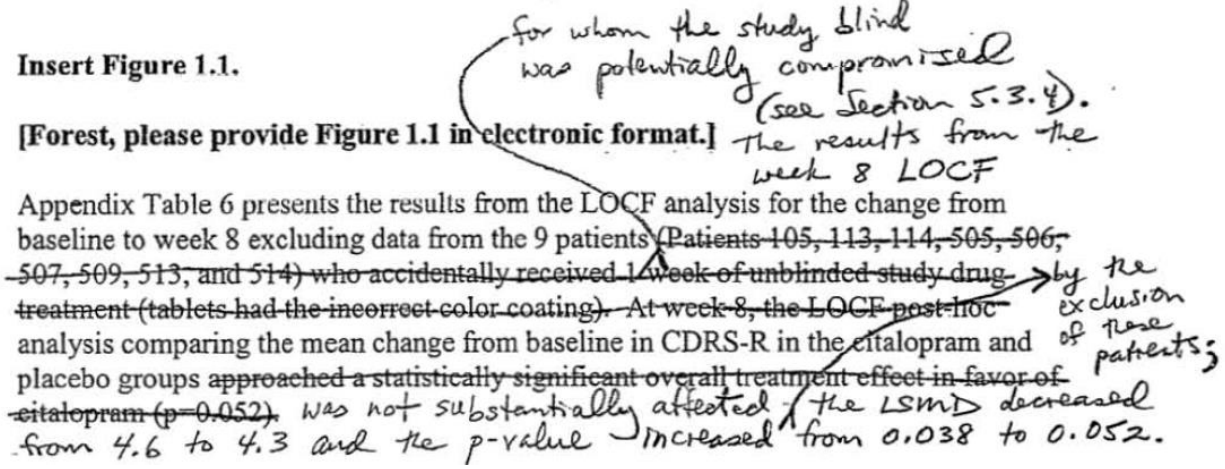
[148] *Id.*

later, after he learned that the unblinded patients were needed to obtain a positive result on the primary endpoint, he characterized it as "potentially unblinding information."

The third reference to the unblinding is in the section discussing the primary efficacy endpoint. It reads:

> Appendix Table 6 presents the results from the LOCF analysis for the change from baseline to Week 8 excluding data from the 9 patients for whom the study blind was potentially compromised (see Section 5.3.4). The results from the Week 8 LOCF analysis comparing the mean change from baseline in CDRS-R in the citalopram and placebo groups was not substantially affected by the exclusion of those patients; the LSM difference decreased from 4.6 to 4.3 and the p-value increased from 0.038 to 0.052.[149]

This is also misleading. And, once again, this is the handiwork of Dr. Flicker. The original draft of the study report stated: "Appendix Table 6 presents the results from the LOCL analysis for the change of baseline t week 8 excluding data from the 9 patients . . . who ***accidently received 1 week of unblinded study drug treatment***[.]"[150] Dr. Flicker crossed out this language and crafted some masterful euphemisms of his own:[151]



What makes this paragraph so misleading—aside from suggesting these patients were not actually unblinded—is that Dr. Flicker stated that the exclusion of the unblinded patients did not substantially affect the results of the study. But that is just not true. Excluding the unblinded patients makes the primary endpoint no longer statistically significant, i.e., negative.[152] It changes the entire result of the endpoint and, by extension, the study. Dr. Heydorn testified:

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[149] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 70.

[150] Exh. 50, Draft of MD-18 Study Report w/ C. Flicker Comments at 49 (emphasis added).

[151] *Id.*

[152] Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 294:10-295:20.

[Q]. So with the dispensing error patients excluded from the MD-18 primary efficacy outcome measure, Celexa failed to significantly outperform placebo in treating pediatric depression, right?
[A]. That appears to be the case.
Q. ***That would be an important substantial difference, wouldn't it?***
[A]. Yes.[153]

The final reference to the unblinding was in the section of the report titled, "Validity."[154] It reads:

> The study was designed to provide a valid, prospectively randomized, double-blind comparison of the treatment effects of citalopram and placebo. A medication packaging error partially compromised the study blind for 9 of the 174 patients. Post-hoc analysis excluding these patients supported the results from the intent-to-treat analysis.[155]

This section of the report was also drafted by Dr. Flicker.[156] And, like the previous sections, it misstates the effect of excluding the unblinded patients from the trial on the overall results. Thus, all the sections in the final study report addressing the unblinding issue were drafted by Dr. Flicker and none of them state, as he previously stated in his email, that the integrity of the blind was unmistakenly violated. The report was deliberately misleading or, at least in Dr. Flicker's own words, not up front.

F. The FDA Never Fully Considered the Unblinding Issue and a Reasonable Regulator at the FDA Could Review this *New* Information and Conclude Study MD-18 Was Negative

Forest submitted the MD-18 Study Report to the FDA as part of an application seeking a pediatric indication for Celexa. Ultimately, the FDA denied the application, stating there was insufficient evidence that Celexa was effective in treating pediatric depression.[157] A careful review of the FDA's analysis of MD-18, however, reveals that the FDA was misled about the unblinding situation and, ultimately, the results of the study.

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[153] Exh. 11, 2016 Depo. of W. Heydorn at 87:19-88:6.

[154] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 83.

[155] *Id.*

[156] Exh. 50, Draft of MD-18 Study Report w/ C. Flicker Comments at 67.

[157] Exh. 51, Letter from R. Katz (FDA) to T. Varner (Forest) at 1-2 ("[A] single positive study is not sufficient, in our view, to support this new claim in pediatric MDD . . . the history of predominantly negative placebo-controlled trials in pediatric MDD argues against the extrapolation of the MDD claim from adults to pediatric patients on the basis of the adult data alone, or even on the basis of one positive study in pediatric patients, along with positive adult data.").

MD-18 was reviewed by Dr. Laughren and Dr. Earl Hearst.[158] Dr. Laughren was the Team Leader of Psychiatric Drug Products and Dr. Hearst was the primary medical reviewer.[159] Normally, clinical trials are reviewed by more than one medical reviewer and the FDA conducts a statistics review, designed to verify the statistics presented by the drug sponsor.[160] Dr. Laughren explained that "[t]he -- 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."[161] However, because the FDA and Forest understood that Celexa would not be approved for children due to the negative result of Study 94404, the FDA determined "there was no need for a statistics review of the efficacy data."[162] Instead, the FDA only did a medical review of Study 94404 and MD-18.

Dr. Hearst's primary medical review of MD-18 concluded, based on the information in the final study report, that MD-18 was positive.[163] Regarding the unblinding issue, Dr. Hearst copied and pasted the text from the final study report—the report Dr. Heydorn conceded he would have written differently had he known about the unblinding issue.[164] Dr. Hearst copied verbatim: "[b]ecause of a drug packaging error, the citalopram or placebo tablets initially dispensed to 9 patients at 3 study centers were distinguishable in color, although otherwise blinded."[165] Indeed, all but *two words* of Dr. Hearst's review of MD-18 consists of sections copied and pasted from the final study report, suggesting the FDA relied heavily on the accuracy of the report. And, by copying and pasting from the study report, Dr. Hearst parroted Forest's assertion that the data from these unblinded patients was not actually unblinded. Dr. Laughren acknowledged that Dr. Hearst appeared to have copied and pasted from the final study report and conceded this was not the approach he endorsed:

> Q. And that is a verbatim copy and paste which was in Dr. Hearst's medical review, correct?
> [A]. Yes . . .That -- that does look like it's – it's identical language.
> [Q]. 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?

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[158] Exh. 52, T. Laughren, Memo. re. Recommendation for Non-Approval at 1.

[159] *Id.* ("The primary review of the clinical efficacy and safety data was done by Earl Hearst, M.D., from the clinical group.").

[160] Exh. 8, 2017 Depo. of T. Laughren at 95:10-96:3.

[161] *Id.* at 95:19-22.

[162] Note also Laughren Depo. at 94:1-95:6.

[163] Exh. 22, Review and Evaluation of Clinical Data by Dr. Earl Hearst, FDA at 2.

[164] *Compare id.* at 11 ("Because of a drug packaging error, the citalopram or placebo tablets initially dispensed to 9 patients at 3 study centers were distinguishable in color, although otherwise blinded.") *with* Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 44 ("Because of a drug packaging error, the citalopram or placebo tablets initially dispensed to 9 patients at 3 study centers were distinguishable in color, although otherwise blinded[.]").

[165] Exh. 22, Review and Evaluation of Clinical Data by Dr. Earl Hearst, FDA at 11.

A. No, I -- I -- I did not do that.
Q. Why not?
A. ***Because I preferred to reach my own conclusions.***[166]

Dr. Laughren also prepared a memorandum, which included a review of MD-18.[167] Although Dr. Laughren advised against a pediatric indication for Celexa, he stated in reference to MD-18 that "I agree with Dr. Hearst that this is a positive study in support of the efficacy in pediatric MDD."[168] With regard to the unblinding issue, he remarked that "[t]here was a packaging error resulting in tablets being distinguishable for drug and placebo for 9 patients (***although still blinded***)."[169] When asked about this sentence, Dr. Laughren testified that, based on the information from the final study report for MD-18, it was his understanding that the patients received different color pills but were *still blinded*:

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?***
[A]. I – I'm assuming that I made that statement based on something that I had seen in -- in the supplement.
Q. Okay. So it was your understanding that the patients, despite receiving different color tablets, were still blinded, correct?
[A]. Well, that -- that was -- that was my assumption, correct.
Q. If in fact the patients were unmistakenly unblinded, that is not what you understood at the time that you wrote this memorandum, correct?
[A] 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.***[170]

Thus, in the absence of clear statements such as "the blind was unmistakenly violated," Dr. Laughren believed the study report's assertion that the patients were not really unblinded and, thus, their inclusion in the primary endpoint analysis was not a cause for concern. After showing Dr. Laughren the internal documents where numerous Forest employees stated, in no uncertain terms, that the nine patients were unblinded, Dr. Laughren agreed that the final study report for MD-18 misrepresented what happened with regard to the unblinding:

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?

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[166] Exh. 8, 2017 Depo. of T. Laughren at 278:9-278:16 (emphasis added).

[167] Exh. 52, T. Laughren, Memo. re. Recommendation for Non-Approval at 1.

[168] *Id.* at 3.

[169] *Id.*

[170] Exh. 8, 2017 Depo. T. Laughren at 154:6-155:9.

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.[171]

Dr. Laughren also testified that the information presented to him during his deposition was "new information" that he did not consider when he reviewed MD-18 at the FDA:

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?
[A]. It -- ***it certainly would have been my preference that -- that Forest be more transparent with FDA about the issue of unblinding***. . . .
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?
[A]. ***It -- it isn't my judgment at this point***. . . . ***So, I mean I -- that – that's for FDA to decide at this point.*** . . . Whether or not FDA -- and ***I also told you that, in retrospect, I would have had a statistical review done on -- on 18.***
. . .
And it's – it's up to FDA to decide whether or not, you know, based on this -- on this, you know, <u>new information</u>, which I think is probably <u>new information from FDA because I wasn't aware of it at the time.</u> But it's not my call.[172]

According to Dr. Laughren, the information about the unblinding of the patients constituted "new information" that was not available to him—and was in fact misrepresented to him—while at the FDA.[173] And, even though it was no longer his "call," Dr. Laughren agreed that a

[171] *Id.* at 205:4-13.

[172] *Id.* at 397:9-398:12.

[173] Dr. Laughren also testified that he did not believe the new information would have changed his judgment that MD-18 was a "positive" study, because even though all the secondary endpoints were negative and the p-value for the primary efficacy endpoint went above 0.05 with the unblinded patients excluded, he testified it was "close enough." *Id.* at 147:7-148:11, 168:21-169:5. This opinion, however, strains credibility. Back in 2013, before the unblinding issue was unearthed, Dr. Laughren was deposed as an expert for Forest and he *specifically* testified that exclusion of the unblinded patients rendered MD-18 negative: "Q. ***[I]f these patients were removed, this would no longer be a positive study?*** A. ***That's correct.***" Exh. 53, Excepts of

reasonable regulatory person at the FDA could review this *new* information and conclude that MD-18 was negative:

> 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?
>
> [A]. 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.***[174]

G. Forest Also Misled the FDA about the Results of the Secondary Endpoints

Forest did not limit its deception to the unblinding issue—Forest also misled the FDA about the secondary endpoints in the study. There were four secondary endpoints: (1) GGI-I at 8 weeks; (2) change from baseline in CGI-S at 8 weeks; (3) change from Baseline in CGAS at 8 Weeks; and (4) change from Baseline in K-SADS-P Depression Module at 8 Weeks.[175] There is no dispute that all of the secondary endpoints in the study were negative at 8 weeks, meaning none of the secondary measures were statistically significant ($p<0.05$).[176] Forest admits they were negative.[177] And yet, in the final study report for MD-18, under the section titled "Efficacy Conclusions" Forest stated:

> Significant differences ($p<0.05$), indicative of greater improvement in citalopram patients than placebo patients, were also observed on the CGI-I, CGI-S, and CGAS. Statistically significant effects were not found as consistently across study timepoints for the secondary efficacy parameters as for the primary efficacy parameter, but numerically greater improvement in the citalopram group was observed on every efficacy parameter at every clinic visit in both the LOCF and OC analyses.[178]

2013 Depo. T. Laughren at 301:20-302:2 (emphasis added). Indeed, Forest and Dr. Heydorn both agree that MD-18, with the unblinded patients excluded, is negative. Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 294:10-295:20 ("***If they were removed from the study, I understand that the result would have been negative.***" (emphasis added)); Exh. 11, 2016 Depo. of W. Heydorn at 87:11-87:14 (same). Dr. Laughren's "close enough" opinion is an after-the-fact attempt to justify his conclusion that MD-18 was positive—a conclusion that formed the basis of *his* approval of Lexapro for use in adolescents in 2009. To admit that the study would be negative while excluding the unblinded patients would force him to concede that he made a mistake in approving Lexapro for use in adolescents.

[174] Exh. 8, 2017 Depo. of T. Laughren at 402:18-403:2 (emphasis added).

[175] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 321, 329.

[176] Exh. 9, Excerpts of Study MD-18 Rpt. at pgs. 101-104.

[177] Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 188:4-20 (confirming, on behalf of Forest that all secondary endpoints were negative).

[178] Exh. 9, Excerpts of Study MD-18 Rpt. at 72.

This is misleading because it suggests that the CGI-I, CGI-S, and CGAS were statistically significant "indicative of greater improvement in citalopram" when, in fact, they were ***all*** negative at week 8, i.e., the pre-specified secondary endpoints. Internal documents indicate that this was a deliberate strategy. Specifically, when Forest contracted with PharmaNet to prepare the first draft of the MD-18 study report, they had a conference on October 4, 2001, where Dr. Heydorn, Dr. Flicker, Dr. Jin, and Dr. Wu from Forest attended.[179] Notes from the conference call indicate Forest knew the secondary endpoints were negative, but wanted to spin the data by focusing on earlier time points in the study when the secondary endpoints were positive:

> For secondary efficacy measures – no significant difference at the week 8 LOCF analysis. The[re] are some significant findings early on in treatment. Forest looking at individual patient listings to see if there are any clues as to why week 8 findings were not positive. For now, ***emphasize the positive findings at earlier time points for the secondary efficacy variables***.[180]

Then, when PharmaNet prepared the first draft of the study report, it stated in the section titled "Efficacy Conclusions" that:

> All other efficacy parameters showed a consistent numerical trend in favor of citalopram treatment, but ***failed to reach statistical significance at week 8.*** Except for the CGI-I responder score, all other parameters with evaluations at week 6 reached statistical significance in favor of citalopram treatment at this timepoint. The by-visit evaluations for these parameters show a marked improvement in the placebo scores at the week 8-timepoint, suggesting a placebo effect. No explanation is currently available for this observation. This large placebo effect may be, in part, responsible for ***the lack of statistical significance in favor of citalopram at week 8.***[181]

However, Dr. Flicker crossed out this language and handwrote the language that, for the most part, ended up in the final study report.[182] Notably, Dr. Flicker also attempted to change the definitions of the secondary efficacy parameters to make them incorporate earlier time points, as opposed to week 8.[183] For example, in the original protocol for MD-18, which Dr. Flicker signed, it stated that "the endpoints for the secondary objectives are the CGI-Improvement score, and change from baseline in the CGI-Severity score, K-SADS-P (depression module) score and CGAS score at Week 8.[184]" And, PharmaNet faithfully described these objectives in terms of

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[179] Exh. 21, Email re. Notes from conference call Oct 4 (w/attachment) at 1.

[180] *Id.* at 2.

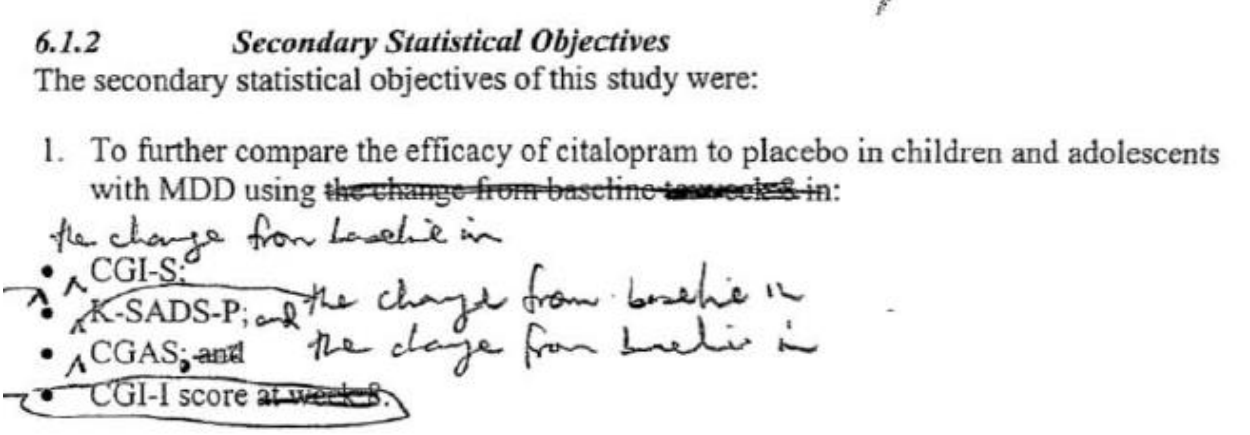
[181] Exh. 50, Draft of MD-18 Study Report w/ C. Flicker Comments at 51-52.

[182] *Id.*

[183] *Id.* at 35-36, 38.

[184] Exh. 43, Excerpts of Study MD-18 Protocol at pg. 321, 329.

week 8 in its original draft.[185] However, Dr. Flicker crossed out "week 8" in his editing, suggesting that the endpoint was not at week 8, but at any time period during the study:[186]



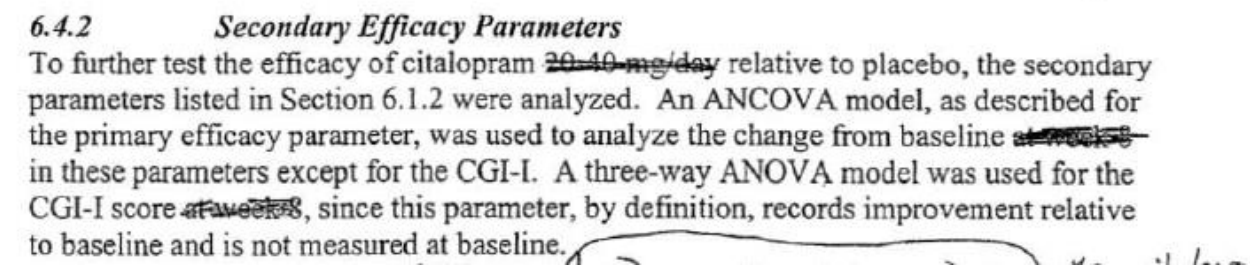
6.1.2 Secondary Statistical Objectives

The secondary statistical objectives of this study were:

1. To further compare the efficacy of citalopram to placebo in children and adolescents with MDD using ~~the change from baseline to week 8 in~~: the change from baseline in

- CGI-S;
- K-SADS-P; and the change from baseline in
- CGAS; ~~and~~ the change from baseline in
- CGI-I score ~~at week 8~~.

Then, in the section describing the Secondary efficacy parameters, once again Dr. Flicker crossed out any reference to week 8:[187]



6.4.2 Secondary Efficacy Parameters

To further test the efficacy of citalopram ~~20-40 mg/day~~ relative to placebo, the secondary parameters listed in Section 6.1.2 were analyzed. An ANCOVA model, as described for the primary efficacy parameter, was used to analyze the change from baseline ~~at week 8~~ in these parameters except for the CGI-I. A three-way ANOVA model was used for the CGI-I score ~~at week 8~~, since this parameter, by definition, records improvement relative to baseline and is not measured at baseline.

This elimination of "week 8" from these sections indicates that Dr. Flicker was deliberately attempting to redefine the efficacy parameters so that Forest's focus on earlier time points, i.e., not at week 8, would appear to be consistent with the study protocol.

The impact of this deception on the FDA's review of MD-18 is striking. Normally, as Dr. Laughren explained, the FDA does not pay much heed to the words used in the final study report: "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.***"[188] That, however, did not happen here. Instead, Dr. Hearst, who conducted the primary medical review of MD-18 lifted, verbatim, the section of the final study report dealing with the secondary endpoints into his medical review:

[185] Exh. 50, Draft of MD-18 Study Report w/ C. Flicker Comments at 35.

[186] *Id.*

[187] *Id.* at 38.

[188] Exh. 8, 2017 Depo. of T. Laughren at 68:18-69:4 (emphasis added).

Table 3 – Comparison of MD-18 Study Report & Dr. Heart Medical Review	
Exh. 9, MD-18 Final Study Report, pg. 72	**Exh. 22, Hearst Medical Review, pg. 11**
Significant differences ($p<0.05$), indicative of greater improvement in citalopram patients than placebo patients, were also observed on the CGI-I, CGI-S, and CGAS. Statistically significant effects were not found as consistently across study timepoints for the secondary efficacy parameters as for the primary efficacy parameter, but numerically greater improvement in the citalopram group was observed on every efficacy parameter at every clinic visit in both the LOCF and OC analyses.	Significant differences ($p<0.05$), indicative of greater improvement in citalopram patients than placebo patients, were also observed on the CGI-I, CGI-S, and CGAS. Statistically significant effects were not found as consistently across study timepoints for the secondary efficacy parameters as for the primary efficacy parameter, but numerically greater improvement in the citalopram group was observed on every efficacy parameter at every clinic visit in both the LOCF and OC analyses.

This is Dr. Hearst's *only* discussion of the results of the secondary endpoints—the only medical reviewer of MD-18—and it was lifted, verbatim, from Forest's study report. When Dr. Laughren was shown this data, he admitted that Forest's spin on the secondary endpoints had made its way into the FDA official medical review:

> [Q]. 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 <u>not giving a complete picture</u>.***
> Q. And it appears that that ***<u>spin</u> that Forest put into the final study report made it into Dr. Hearst's report, correct?***
> [A]. It -- it appears to have, yes.[189]

In Dr. Laughren's review of MD-18—the only other person within the FDA to review MD-18—his discussion of the secondary endpoints was even more inaccurate than Dr. Hearst's. He stated: "Results also significantly favored citalopram over placebo on most secondary outcomes" even though every secondary endpoint was negative.[190] Dr. Laughren could not remember what he was thinking when he wrote the statement:

> [Q]. 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?
> [A]. Correct.

[189] Exh. 8, 2017 Depo. of T. Laughren at 279:6-17 (emphasis added).

[190] Exh. 52, T. Laughren, Memo. re. Recommendation for Non-Approval at 3.

Q. You're referring here, I assume, to the earlier time points when there were statistically significant results in the secondary endpoints, correct?

[A]. 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.***

[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?

[A]. 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.

[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?

[A]. That is -- that appears to be correct, yes.

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.***[191]

Thus, from the outset, Forest had an objective—avoid disclosing that all the secondary endpoints were negative and, instead, focus on the secondary measures that reached statistical significance at various earlier time points. This "spin" was successful. Not only did the primary medical reviewer at the FDA, Dr. Hearst, copy and paste that spin into his review, but his supervisor, Dr. Laughren went even further by stating that most of the secondary endpoints supported efficacy even though they were all negative. Like a cascade, starting with Forest's deliberate decision of obscure the secondary endpoints, the deception made its way into the FDA's own "independent" reviews.

PART III: FOREST USED FALSE RESULTS FROM MD-18 TO PROMOTE PEDIATRIC USE OF CELEXA AND LEXAPRO

That Forest off-label promoted Celexa for use in children prior to September 2002 is an undisputed fact.[192] However, starting in December 2001, Forest began aggressively using the

[191] Exh. 8, 2017 Depo. of T. Laughren at 279:21-282:2 (emphasis added).

[192] Exh. 65, Tr. of Arraignment on Information at 16:10-14, 20:18-25 ("MR. STEGER: . . . The United States would have further demonstrated that beginning in 1998 and continuing thereafter through at least September, 2002, Forest promoted Celexa for use in treating children and adolescents suffering from depression, even though Celexa was not FDA approved for pediatric use. . . . THE COURT: Then likewise the allegations that were made by both counsel, are these

"positive" results of MD-18 to promote the use of Celexa and, later, Lexapro for use in children.[193] Specifically, Forest wanted the data presented at a scientific conference so it could reference the presentation in various types of promotional activities including continuing medical education ("CME") programs.[194] On September 21, 2001, John MacPhee of Forest outlines what he wanted to accomplish with the MD-18 pediatric data: get the pediatric data from MD-18 published as soon as possible so that Forest can use the data in CME programs for marketing.[195]

A few weeks later, on October 15, 2001, Jeffery Lawrence of Forest wrote to Mary Prescott at the medical communications company, BSMG/Weber Shandwick, asking about the status of MD-18 manuscript and explaining that "we would like to wrap some PR and CME around this data[.]"[196] In response, Ms. Prescott explained "I don't know that any decision has been made about who is going to write the manuscript (not to be confused with who is going to be the author[s] of the manuscript. . . . But, for reasons I'll list below, I think it would make sense to have a first draft prepared in-house . . . or here, if Bill Heydorn's group is swamped[.]"[197] She went on to explain that "I've heard through the grapevine that not all the data look as great as the primary outcome data. For these reasons (speed and greater control) I think it makes sense to prepare a draft in-house that can then be provided to Karen Wagner (or whomever) for review and comments."[198] She advised that "[r]egarding PR, it will be possible to generate some PR around the presentation of the data . . . and especially if published in a top-tier journal like JAMA -- Forest can expect substantial media coverage."[199] This prompted Mr. Lawrence to email Dr. Paul Tiseo, the researcher overseeing MD-18: "Have you heard anything else about the Pediatric data? When we last talked, you mentioned some of the measures didn't look that great[.]"[200]

Then, on October 31, 2001, Christina Goetjen of Forest reported back about the company's

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facts true? MR. WEINSTEIN: They're consistent with what I believe the facts to be. THE COURT: Okay. So essentially the corporation is pleading guilty to these charges because it is guilty and for no other reason? MR. WEINSTEIN: That's correct.").

[193] *See, e.g.*, Exh. 55, Email re. ACP-ASIM at 1 ("[W]e may try a bridging strategy. That is, we don't have esc. [Lexapro] data on pediatrics yet, but what if we talk about Celexa and relate it to Esc. [Lexapro]"); *see also* Exh. 10, Email re. Stop the Presses at 1-2 ("I believe several of us are quite anxious to get our hands on this data! When, Bill Heydorn, WHEN ?!!").

[194] Exh. 24, Email re. Ped data at 2 ("[W]e would like to wrap some PR and CME around this data" . . . Regarding PR, it will be possible to generate some PR around the presentation of the data at ACNP . . . once the data are presented at a meeting, you can reference that presentation in other materials. . .).

[195] *Id.* at 4.

[196] *Id.* at 3.

[197] *Id.* at 1-2.

[198] *Id.*

[199] *Id.*

[200] *Id.*

attempt to enlist Dr. Wagner.[201] Apparently, Dr. Wagner agreed to help and began advising Forest about the marketing advantages of the data:

> We spoke with Karen Wagner today about the current state of affairs regarding the pediatric data. . . . She . . . reminded us that if we want to appeal to the PCP and Pediatric audiences, we need to publish in a place that provided the appropriate readership (something JAMA would've done.) She also said that the lack of data regarding the use of Celexa for pediatrics is limiting it to "last choice" among physicians - ***she just wanted to make sure we understood the marketing advantages of the data. I assured her we got it.***
>
> She is excited about our Pediatric Regional CME series and will be a fundamental part of speaker selection. She knows that she and Jeff will be working closely as I will be on maternity leave.[202]

In response, Mr. MacPhee explained "my feeling is that the fact that we are last for ped use is the very reason we can't wait to disseminate data[.]"[203] Ms. Goetjen assured Mr. MacPhee that Dr. Wagner "is committed to our aggressive timeline as she understands the urgency to get this data in front of our audience as soon as possible if we're going to maximize the impact."[204] Ultimately, they all agreed to have BSMG write the first draft: "Bill thought it would be best if BSMG wrote the first draft... Karen Wagner also realizes that we want this done quickly[.]"[205] Forest enlisted Natasha Mitchner, an admitted ghostwriter.[206] Notably, a week after these decisions were made, Mr. Lawarance specifically asked for an Excel file of all "the Celexa targets who are pediatricians, and or Pediatric Psychiatrists."[207]

In December 2001, Dr. Wagner traveled to the annual convention of the American College of Neuropsychopharmacology (ACNP) in Hawaii and presented the "positive" results of MD-18.[208] Her presentation, which was ghost-authored by Ms. Mitchner, did not mention or discuss the negative results of 94404, it did not discuss the fact that every secondary efficacy endpoint for MD-18 was negative, and it did not disclose that MD-18's primary efficacy measure only achieved statistical significance by including data from unblinded patients.[209] Instead, she presented the "positive" results of the primary endpoint, stating that MD-18 was evidence that Celexa was effective in children.[210]

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[201] Exh. 27, Emails re. ACCAP Meeting at 2-3.

[202] *Id.* (emphasis added).

[203] *Id.*

[204] *Id.*

[205] *Id.*

[206] Exh. 57, Excerpts of Depo. of N. Mitchner at 47:19-48:5.

[207] Exh. 54, Emails re. Pediatric Targets at 1.

[208] Exh. 56, Email re. Wagner Hot Topics slides (w/attachment) at 1.

[209] *Id.* at 6.

[210] *Id.* at 12.

With the "positive" data presented at a scientific conference, Forest immediately started using the false data to promote the efficacy of Celexa in children. For example, Forest issued a press release about Dr. Wagner's ACNP presentation, describing the "positive" results of MD-18.[211] Forest contracted with a company called GCI "to start working a release and any other way they can spin this data[.]"[212] Ms. Goetjen explained that Forest wanted to issue the press release so it could "put a promotional spin on it and . . . issue additional PR when it is published[.]"[213]

In the release, Dr. Wagner is quoted: "This study is significant because few studies involving any antidepressant have shown efficacy compared to placebo in the treatment of depression in children . . . Citalopram is now one of the few therapies for which we have data showing safety and efficacy for this population."[214] The press release made no mention of Study 94404, MD-18's negative secondary endpoints, or the unblinding issue, i.e., it had Forest's "promotional spin" on it.

Forest then paid Dr. Wagner to travel around the country and tell physicians, in meetings and formal CME programs, that Celexa was effective in children based on the results of MD-18. Forest sponsored a CME program which was hosted and presented by Dr. Wagner, where she cited and discussed the "positive" data from the ACNP presentation to support the message that Celexa was safe and effective in children.[215] Forest sales representatives were specifically instructed to invite physicians to the CME program—a program for which she played a major role in selecting speakers.[216] And, like her ACNP presentation, her CME presentation did not disclose Study 94404, the negative secondary endpoints for MD-18, or the unblinding issue.[217] Instead, the presentation ended with a multiple choice question: "Which of the following medications has been shown to be more effective than placebo in the treatment of depression in children and adolescents?"[218] The only available correct answer: Celexa.[219] This marketing was successful, as illustrated in Forest's marketing plan, showing pediatric prescriptions rose after the

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[211] Exh. 23, 2001 Forest Press Release at 2-3.

[212] Exh. 61, Emails re. ACNP pediatrics abstract at 1.

[213] Exh. 62, Emails re. ACNP Press Releases at 1.

[214] Exh. 23, 2001 Forest Press Release at 2-3.

[215] Exh. 58, Excerpts of Dr. Wagner's CME Program at 2-3.

[216] *See, e.g.*, Exh. 28, Selection of Call Notes at 7, 16-17 ("discussed cx used in children . . . and results of dr wagner study regarding cx use for children and adolescents . . . Brought up the Wagner study and sent study to Dr. asked Dr[.] if it would make a difference to use Lx in that age group since Cx has done well."). Plaintiffs are in possession of numerous specific examples of Forest sales representatives inviting physicians to this CME program, but those call notes are still, technically, under seal.

[217] Exh. 58, Excerpts of Dr. Wagner's CME Program at 2-3.

[218] *Id.* at 7-8.

[219] *Id.* at 10.

"Wagner data" was promoted.[220]

In 2004, the MD-18 data was officially published. However, in the years leading up to its publication, Forest tightly managed how the data was presented. For example, in an email discussing the company's publication approach, Dr. Heydorn proposed using a "brief report" because "[a]s a Brief Report, we feel we can avoid mentioning the lack of statistically significant positive effects at week 8 or study termination for secondary endpoints."[221] And then again, in September 2002, the original draft manuscript mentioned a lack of efficacy in children under 12, but Dr. Heydorn instructed Ms. Prescott to "remove/revise the statement about the lack of efficacy in children [sic], since the results on that point have been pulled out."[222]

When the manuscript finally was published in 2004, it stated that Dr. Wagner was the primary author and did not disclose the ghostwriters.[223] And then, years later, after the criminal plea by Forest related to this conduct became public, the journal issued a statement about the Wagner publication, stating that the authors did not properly disclose the fact that commercial writers were used.[224] In the note, it states that Dr. Wagner claimed she was "not aware that Dr. Heydorn was working with a commercial writer."[225] This was false. There are multiple instances of Dr. Wagner communicating directly with the ghostwriters. Indeed, Dr. Heydorn confirmed during his deposition that Dr. Wagner was aware the manuscript was written by ghostwriters.[226]

To this very day, Forest and Dr. Wagner still cite to and rely on MD-18 as evidence of Celexa's efficacy, even though it only achieved a positive outcome by inappropriately including data from unblinded patients.[227] And, Forest was only able to achieve that result by misdirecting the FDA and misleading the USAO. Indeed, prescribing guidelines for pediatric psychiatry still provide misleading and false information on Celexa in the treatment of pediatric depression based on Forest-sponsored publications.

Importantly, the USAO only criminally prosecuted Forest for off-label promotion for Celexa between 1998 and 2002, and settled civil claims for Celexa and Lexapro through 2005. It turns out, however, that this conduct continued until, at least, 2009. Gerard J. Azzari was the National

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[220] Exh. 29, Lexapro Tactical Presentation at pg. 12.

[221] Exh. 59, Emails re. Second Draft of Pediatric Manuscript at 1.

[222] Exh. 60, Emails re. Citalopram at 1.

[223] Exh. 63, Karen Wagner, et al., *A Randomized, Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents*, 161 AM. J. PSYCH. 6, 1079-83 (June 2004).

[224] Exh. 64, Robert Freedman & Michael D. Roy, *Editor's Note*, 166 AM. J. PSYCH. 8, 942-43 (Aug. 2009).

[225] *Id.* at 943.

[226] Exh. 11, 2016 Depo. W. Heydorn at 312:24-313:16.

[227] *See, e.g.*, Exh. 79, Aaron Levin, *Child Psychiatrists Look at Specialty From Both Macro, Micro Perspectives*, 51 PSYCH. NEWS 12, 1-38, 23 (June 2017) (Dr. Wagner referenced and quoted, espousing the false assertion that MD-18 was positive).

Director of Sales at Forest between 1997 and 2005 and Senior Vice President of Sales between 2005 and 2010.[228] Between 1997 and 2010, he oversaw and directed a substantial portion of Forest's sales force, i.e., the Forest sales representatives who promoted Celexa and Lexapro to physicians.[229] During his deposition, Plaintiffs asked Mr. Azzari whether it was true that Celexa was promoted off-label between 1998 and 2002, and he admitted it was.[230] Then, he admitted that this misconduct continued with Celexa and Lexapro through 2009:

> Q. So I am going to ask you again, based on your knowledge and experience between 2002 and 2009, did Forest sales representatives engage in off-label promotion of Lexapro for use in pediatric patients?
>
> A. Could I talk to counsel about this question?
>
> Q. Not while it's pending. I'm asking you for your answer based on your knowledge and experience. . . . Let me state it again, because I want you to understand what I am asking you.
>
> A. OK, yes, yes, yes.
>
> Q. ***Based on your knowledge and experience and your years at Forest, between 2002 and 2009, did Forest sales representatives engage in off-label promotion of Lexapro for use in pediatric patients?***
>
> A. ***I have knowledge that representatives may have presented Celexa or Lexapro inappropriately.***
>
> Q. ***Between 2002 and 2009?***
>
> A. ***Yes.***
>
> Q. ***And you know that, you have knowledge of that related to Lexapro, correct?***
>
> A. ***Yes.***
>
> Q. And that's based on your knowledge that child specialists were on Lexapro call panels between 2002 and 2009, correct?
>
> A. No. ***My commentary was that individuals may have inappropriately presented Celexa or Lexapro to physicians.***[231]

[228] Exh. 66, 2016 Depo. G. Azzari at 20:18-21:15.

[229] *Id.* at 21:17-26:5.

[230] *Id.* at 235:7-235:13.

[231] *Id.* at 236:1-237:22 (emphasis added).

PART IV: THE LEXAPRO PEDIATRIC TRIALS

There were two pediatric trials conducted on Lexapro: MD-15 and MD-32. And, as discussed below, MD-15, the only Lexapro study to test both children and adolescents, was negative across the board. MD-32, which only tested adolescents, was considered positive from a statistical perspective, but is suspect from a clinical efficacy perspective.

I. Lexapro Study MD-15 Was a Negative Clinical Trial

The FDA denied the pediatric application for Celexa on September 23, 2002 because:

> [T]he results from one of your two studies, Study 94-404, failed to demonstrate the efficacy of Celexa in pediatric patients with MDD. While we consider the second study, Study CIT MD-18, to be positive, a single positive study is not sufficient, in our view, to support this new claim in pediatric MDD. . . . [T]he history of predominantly negative placebo-controlled trials in pediatric MDD argues against the extrapolation of the MDD claim from adults to pediatric patients on the basis of the adult data alone, or even on the basis of one positive study in pediatric patients, along with positive adult data.[232]

Shortly after, in December 2002, Forest commenced a double-blind placebo-controlled pediatric clinical trial of Lexapro: Study MD-15. MD-15 evaluated 264 children and adolescents between the ages of 6-17.[233] And, like Study 94404 and MD-18, every primary and secondary endpoint was negative for efficacy:

Table 4 – Lexapro Study MD-15 Efficacy Results[234]

Endpoint	P-Value	Result
Change from Baseline in CDRS-R at week 8- LOCF (Primary)	0.310	Negative
CGI Improvement at Week 8- LOCF	0.169	Negative
Change from Baseline in CGI Severity at Week 8- LOCF	0.057	Negative
Change from Baseline in CGAS at Week 8- LOCF	0.065	Negative
Analysis of CDR-R Response Rate at Week 8- LOCF	0.317	Negative
Analysis of CGI-I Response Rate at Week 8 - LOCF	0.144	Negative

II. Lexapro Study MD-32 Was a "Positive" Clinical Trial for Adolescents, but Did Not Show a Meaningful Difference between Lexapro and Placebo

[232] Exh. 51, Letter from R. Katz (FDA) to T. Varner (Forest) at 1.

[233] Exh. 67, Excerpts of MD-15 Study Rpt. at pg. 1 (Initiation date of December 9, 2002).

[234] *Id.* at pgs. 100-105 (showing every primary, secondary, and additional efficacy analyses were negative).

After Forest obtained the negative results of MD-15 in 2004 (in addition to Study 94404 and MD-18), Forest was concerned about conducting further pediatric trials. So, Forest obtained an agreement from the FDA, before the protocol for MD-32 was even written, that if Forest could obtain a positive result for adolescents in another Lexapro trial, the FDA would approve an adolescent indication.[235] This agreement, however, was specifically contingent on MD-18 being considered a positive study.[236] So, as one Forest executive put it, "everything hinges on SCT-32."[237]

To that end, Forest commenced MD-32 in April 2005, which was completed in May 2007.[238] The trial evaluated 316 adolescents (only 259 completed the trial), between the ages of 12-17.[239] In stark contrast to every other pediatric clinical trial of Celexa and Lexapro, MD-32 achieved statistical significance on both primary and secondary endpoints—although the observed cases analyses on the primary endpoint, i.e., those patients who completed the study, were negative.[240]

MD-32 has several problems. First, the study was designed to detect a statistical significance, even with clinically insignificant differences between Lexapro and placebo. It is widely acknowledged that "[s]tatistically significant effects are not necessarily clinically meaningful effects."[241] This distinction between statistical and clinical significance exists because statistical significance is a species of statistics and clinical significance focuses on real-world effects. Clinical significance is 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 cost, a change in the patient's management."[242] Thus, it is entirely possible to achieve a statistically significant result, even if the difference is trivial, by overpowering a study, i.e., increasing the sample size. As Dr. Laughren of the FDA acknowledged:

> 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?
>
> . . .

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[235] Exh. 68, Letter from FDA re. Forest's Questions at 1 ("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.").

[236] *Id.*

[237] Exh. 73, Email re. DRAFT Lexapro Road Map at 1.

[238] Exh. 69, Excerpts of MD-32 Study Rpt. at 1.

[239] *Id.* pgs. 50, 158.

[240] *Id.* at pg. 158.

[241] Exh. 70, Richard S. Keefe, et al., *Defining a Clinically Meaningful Effect for the Design and Interpretation of Randomized Controlled Trials,* 10 INNOV. CLIN. NEUROSCI. 5-6 Suppl. A, 4S-19S (May-June 2013).

[242] *Id.* at 7S.

> [A]. There's no question that . . . 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.[243]

Efficacy in each of the pediatric clinical trials, including MD-32, was measured by comparing the level of depression, as established using a rating scale, at the beginning of the trial with the level of depression at the end of the trial. Then, Forest compared the results in the drug arm with the results in the placebo arm to see if there was any benefit from the drug beyond a placebo effect. In MD-32, both the Lexapro and placebo patients improved, but the difference in improvement between the Lexapro and placebo groups was only 3.4 points—out of a scale that goes up to 113 points.[244] This means patients taking Lexapro improved an additional 3.4 points on the depression rating scale than patients taking a sugar pill. This difference of 3.4 points, while statistically significant, is so small that no patient or doctor would be able to tell the difference in real life.[245]

There are also questions about whether MD-32 was properly conducted. When the patients were randomized into the study, the Lexapro group started with a baseline score that was statistically significantly higher than the placebo group, i.e., 1.6 points.[246] This indicates there was selection bias (not true randomization in the Lexapro and placebo groups). On average, patients in the Lexapro group were 1.6 points worse than the placebo patients, which means there was more "room" for improvement.[247]

Forest claims that a difference of 1.6 at baseline is not clinically significant, so it does not affect the study.[248] However, if so, then a difference of 3.4 at the end of the study is also not clinically significant. One physician who peer reviewed the study manuscript commented: "It was not clear why the authors consider the baseline difference in the CDRS-R (~2 points) between the two treatment groups as not clinically significant even though it was statistically significant. This is confusing as the authors' then note that a CDRS-R treatment difference between the groups of ~2pts, which is statistically significant, shows efficacy."[249]

Finally, even if one disregards the methodological problems with MD-32, the results hardly provide substantial evidence of efficacy. There are two primary ways to quantify clinical

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[243] Exh. 8, 2017 Depo. of T. Laughren at 375:5-17.

[244] Exh. 69, Excerpts of MD-32 Study Rpt. at pg. 58.

[245] *See* Exh. 47, J. Glenmullen Expert Rpt. at 17 ("But, while statistically significant, the difference was too small to be clinically meaningful.").

[246] Exh. 69, Excerpts of MD-32 Study Rpt. at pg. 54; Exh. 71, Graham J. Emslie, et al., *Escitalopram in the Treatment of Adolescent Depression: A Randomized Placebo-Controlled Multisite Trial,* 48 J. AM. ACAD. CHILD ADOLESC. PSYCH. 7, 721-29, 725 (July 2009).

[247] Exh. 71, Emslie *supra* note 246 at 725.

[248] *Id.*

[249] Exh. 72, MD-32 Reviewer comments at 8.

significance. The first is called the Cohen effect size.[250] "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 is deemed large if it is >0.8, small if it is <0.5, and moderate if it falls between those values."[251] The second is known as the number needed to treat ("NNT"). The NNT reflects the number of people who need to be treated with the drug before one additional person improves more than taking a placebo.[252] "[T]he NNT is a meaningful, well-accepted, common-sense measure[.]" *Id.* On the NNT scale, if the number is less than 2, then the drug is considered highly effective. *Id.* If the NNT is greater than 4, then it is less effective, since one would need greater numbers of patients taking the drug before a person fared better than placebo.[253]

In MD-32, the effect size was 0.27 and the NNT was 8.75.[254] These are, by all objective measures, appalling numbers. This prompted one researcher reviewing Study MD-32 "to wonder whether the restrictive entry criteria in conjunction with the small effect size limit the utility of escitalopram in the real world of adolescent MDD. Are these results statistically significant but clinically not meaningful?"[255] And another stated "this is a relatively small ES [effect size]. Given this small ES, there were no data to see if this level of change had any quality of life meaning."[256] Considering this is the only statistically positive study for Celexa or Lexapro, obtained under questionable circumstances, and was limited to adolescents, the results are small" and unreliable. Standing alone, MD-32 provides scant, if any, evidence of true efficacy.

PART V: FOREST LEVERAGED THE FALSE RESULTS OF MD-18 TO OBTAIN AN ADOLESCENT INDICATION FOR LEXAPRO

In 2004, Forest sent a request to the FDA inquiring whether "a positive study with escitalopram using a conventional acute treatment design . . . along with the previous positive study with citalopram (Study CIT-MD-18) be adequate to support an indication for acute treatment in pediatric patients aged 12 - 17 years?"[257] Relying on the false claim that MD-18 was positive, Forest wanted to know whether an additional positive study in adolescents would be enough to obtain an adolescent indication for Lexapro. In response, the FDA stated: "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."[258] Thus, if Forest could obtain a positive adolescent clinical trial for Lexapro, the FDA agreed to give Lexapro an adolescent indication. This promise, however, was based on a belief that MD-18 was

[250] Exh. 70, Keefe *supra* note 241, at 11S; *accord* Exh. 8, 2017 Depo. of T. Laughren at 296:16-298:12.

[251] Exh. 70, Keefe *supra* note 241, at 11S.

[252] *Id.* at 11S.

[253] *Id.*

[254] Exh. 71, Emslie *supra* note 246 at 726, 727.

[255] Exh. 72, MD-32 Reviewer comments at 9.

[256] *Id.* at 8.

[257] Exh. 68, Letter from FDA re. Forest's Questions at 1.

[258] *Id.*

a positive study. As Dr. Laughren explained:

> 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. Okay. If MD-18 was negative -- okay, just assume that for a second -- would the FDA have made this agreement? . . .
>
> [A]. No. I don't -- I don't believe so. That would be my impression that – that we would not have -- have reached that agreement.[259]

Ultimately, Forest was able to obtain a statistically positive result in MD-32, as discussed above. Forest then, in 2008, submitted the results of MD-32 and MD-18 as part of a supplemental new drug application seeking an adolescent (12-17) indication for Lexapro. Since the FDA had already promised to approve the application, its review of the data was barebones.

However, before delving into the FDA's review of this supplemental application, it is important briefly to discuss the FDA's original review of MD-18, again. MD-18 involved both children (7-11) and adolescents (12-17).[260] However, the study was not powered to measure just children or adolescents.[261] And, after getting the results, Forest conducted several statistical analyses of the data and stated, repeatedly, that "[s]imilar effects were seen in the children and adolescent subgroups, as evidenced by the lack of a treatment-by-age group interaction[,]" that "the magnitude of the treatment effect was similar in the child and adolescent subgroups[,]" and that "[t]he magnitude of the mean citalopram-placebo differences on the efficacy ratings was numerically higher in the adolescents than in the children, but no significant treatment-by-age group interactions were observed, indicating that the citalopram treatment effect was not age dependent."[262] And, this lack of treatment-by-age difference was seen across every primary and secondary endpoint.

Despite this, when Dr. Laughren prepared his memorandum in 2002—when both Forest and

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[259] Exh. 8, 2017 Depo. of T. Laughren at 368:24-369:9.

[260] Exh. 9, Excerpts of Study MD-18 Rpt. at pg. 38.

[261] Exh. 21, Exh. 21, Email re. Notes from conference call Oct 4 (w/attachment) at 2 "Note that study was not powered to look at differences within the two subgroups (children and adolescents)."

[262] Exh. 9, Excerpts of Study MD-18 Rpt. at pgs. 69, 72, 83.

the FDA knew the FDA would not be approving a pediatric indication for Celexa[263]—he noted that the observed treatment effect in the study was primarily coming from the adolescent subgroup.[264] When Dr. Laughren was asked about this during his deposition, he explained "[i]t's something that I -- that I generally do. I -- you know, I explore a little bit more."[265] It was, as he put it, an "exploratory" analysis and was not a prespecified hypothesis.[266] Thus, there was no statistical analysis done on the data to determine whether the difference between children and adolescents was statistically significant:

> Q. 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.[267]

It is also important to note, as discussed above, that when MD-18 was reviewed by the FDA, there was no statistical review done on the study[268] and Dr. Hearst, quite literally, copied and pasted his entire MD-18 analysis from Forest's final study report for MD-18.

However, when MD-18 was resubmitted to the FDA in 2008 as part of Forest's application for an adolescent indication for Lexapro—an application the FDA had already agreed to approve before Forest even started enrolling patients in MD-32—the FDA did not conduct any significant rereview of the data, but relied exclusively on Dr. Hearst's and Dr. Laughren's prior reviews of MD-18.

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[263] Exh. 8, 2017 Depo. of T. Laughren at 94:23-95:4 ("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.").

[264] Exh. 52, T. Laughren, Memo. re. Recommendation for Non-Approval at 3 ("[I]t appears that the positive results for this trial overall are coming largely from the adolescent Subgroup.").

[265] Exh. 8, 2017 Depo. of T. Laughren at 283:5-8.

[266] *Id.* at 284:10-21.

[267] *Id.* at 284:24-285:14.

[268] Exh. 52, T. Laughren, Memo. re. Recommendation for Non-Approval at 1 ("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.").

Specifically, the primary review of the supplemental application was done by Dr. Roberta Glass,[269] the team leader review was done by Dr. Ni Khin,[270] the statistical review was done by George Kordzakhia,[271] and the overall review and final approval was issued by Dr. Laughren.[272]

Dr. Glass, as the primary reviewer, did not conduct any in-depth analysis of MD-18. Rather, Dr. Glass assumed that MD-18 was already positive, as she specifically noted that "[t]he sponsor reached an agreement with FDA that a pediatric claim for escitalopram, an isomeric version of citalopram, could be obtained with the support of one positive pediatric study in escitalopram in addition to the one positive study in citalopram."[273] According to Dr. Laughren, Dr. Glass was focused only on MD-32, not MD-18:

> 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?
>
> . . .
>
> [A]. That's correct.[274]

This superficial approach to reviewing MD-18 is reflected in her report. Dr. Glass simply copied and quoted Dr. Laughren's analysis, which included data from the unblinded patients, stating: "The study is positive for the primary efficacy variable of change from baseline of the CDRS-R total Score (p=0.038). . . . As Dr. Laughren noted in his memo of 9/16/02, '…it appears that the positive results for this trial are coming largely from the adolescent subgroup.'"[275] Indeed, Dr. Glass copied and pasted Dr. Laughren's exploratory analysis into her review.[276] And, like Dr. Laughren, there is no statistical analysis of the difference between children and adolescents or any discussion about the fact the study report specifically stated that the differences were not driven by age. Dr. Glass also never mentioned or discussed the effect of the unblinding—indeed, there is no indication she was even aware of it or its significance. When Dr. Laughren was shown this data during his deposition, he agreed:

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[269] Exh. 74, Roberta Glass, *Clinical Review*, FDA.

[270] Exh. 75, Ni Khin, *Memorandum re. Recommendation of Approval Action for Lexapro*, FDA.

[271] Exh. 76, George Kordzakhia, *Statistical Review and Evaluation*, FDA at 1, 3 (indicating that the statistical review were done on MD-32)

[272] Exh. 77, T. Laughren, *Recommendation for Approval Action for Lexapro*, FDA; Exh. 49, Lexapro Approval Letter for Adolescents at 3.

[273] Exh. 74, Glass *supra* note 269 at 8; see also *id.* at 9 ("On November 16, 2004, the Division confirms that one additional positive acute treatment study with escitalopram in adolescents, in addition to Study CIT-MD-18, is adequate evidence to support a labeling claim that escitalopram is an effective acute treatment of MDD in adolescents. Thus, Study SCT-MD-32 in adolescent patients was initiated in February 2005.").

[274] Exh. 8, 2017 Depo. of T. Laughren at 381:6-12.

[275] Exh. 74, Glass *supra* note 269 at 22.

[276] *Id.* at 23.

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. ***It does not appear that she did a comprehensive clinical review of MD-18 at this point; is that right?***

. . .

[A]. ***That's likely the case, yes.***[277]

And, Dr. Khin likewise conducted a superficial review of MD-18—again, predicated on the fact that the FDA had already determined that MD-18 was positive. Dr. Khin explained: "In this review cycle, our review of efficacy was focused on the positive results from one placebo controlled short-term study (study SCT-MD-32) in our evaluation of the efficacy and safety of escitalopram in the acute treatment of MDD in adolescents."[278] Dr. Laughren explained:

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?

[A]. I -- I don't -- I don't know that I would call that marching orders. . . . 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. . . . [T]hey appeared at least to have been relying upon the agreement that the FDA reached with Forest in 2004.

A. I think that's fair.[279]

Consistent with that approach, Dr. Khin specifically stated that she relied on Dr. Hearst's (the

[277] Exh. 8, 2017 Depo. T. Laughren at 382:13-383:16 (emphasis added).

[278] Exh. 74, Khin *supra* note 270 at 2.

[279] Exh. 8, 2017 Depo. of T. Laughren at 387:5-388:2.

FDA reviewer who copied and pasted from Forest's final study report) and Dr. Laughren's reviews: "I would refer to the clinical review by Dr. Earl Hearst dated 9/12/02 and a memorandum by Dr. Thomas Laughren dated 9/16/02 regarding their reviews of materials submitted under supplemental NDA for citalopram on 04/18/2002. I will briefly summarize their interpretation of results from the Study 18 . . . below."[280] Then, Dr. Khin proceeded to copy and paste Dr. Laughren's *exploratory* analysis from 2002—the very analysis that was never subjected to any statistical analysis.[281] And, she made her conclusion relying on the Hearst and Laughren analyses: "Based on prior clinical review by Dr. Hearst and Dr. Laughren's memo, we should be able to count on positive efficacy results from citalopram study 18 in the same aged population for acute treatment of MDD."[282] Dr. Laughren confirmed this:

> Q. So it appears that Dr. K[h]in is relying heavily, if not exclusively, on Dr. Hearst and yourself's analysis of Study MD-18.
>
> [A]. That's correct. Now, of course, this is the team leader review. It's not the primary review.[283]

This reliance on Dr. Laughren's exploratory review was raised during his deposition as well:

> 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? . . .
>
> [A]. I -- I doubt that I was thinking ahead that far.
>
> Q. Fair enough. ***In retrospect, it seems that that's exactly what happened.***
>
> A. ***That's true.***[284]

Finally, Dr. Kordzakhia conducted the FDA's statistics review for the supplemental application.[285] But, that statistics review, like Dr. Glass's and Dr. Khin's reviews, was limited to MD-32.[286] This means, for a second time, MD-18 evaded any meaningful statistical review. Dr.

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[280] Exh. 74, Khin *supra* note 270 at 3.

[281] *Id.* at 6 ("Summary of primary efficacy results by age group for Study CIT-MD-18 - LOCF (data extracted from Dr. Laughren's memo dated 9/16/2002)"; *see id.* at 5 ("Please see Table 2 in section 5.1.3 regarding summary of primary efficacy results by age group for Study CIT-MD-18 (LOCF data extracted from Dr. Laughren's memo dated 9/16/2002)").

[282] *Id.* at 6-7.

[283] Exh. 8, 2017 Depo. of T. Laughren at 389:12-18.

[284] *Id.* at 392:12-393:1 (emphasis added).

[285] Exh. 76, Khin *supra* note 270.

[286] *Id.* at 1, 3 (indicating that the statistical review were done on MD-32).

Laughren admitted this was not typical:

> Q. 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? . . .
>
> [A]. It's prob- -- it's probably not typical.
> . . .
>
> 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? . . .
>
> [A]. ***In -- in retrospect, I think I -- I would have preferred that.***[287]

Ultimately, Dr. Laughren approved the supplemental application and Lexapro was indicated for adolescent depression in March 2009.[288] And, subsequently, Forest continued to aggressively market and sell Lexapro for use in adolescents throughout the United States, albeit now it was "legal." Dr. Laughren, however, admitted that, if MD-18 was a negative study, he would not have approved the adolescent indication for Lexapro:

> Q. If MD-18 was in fact negative, would you ever have approved Lexapro for use in adolescents? . . .
>
> [A]. 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.
> . . .
>
> 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. . . .
>
> Q. ***And you're saying you wouldn't have approved it if there was only one study, positive Study 32, right?*** . . .
>
> [A]. ***That's correct.***[289]

[287] Exh. 8, 2017 Depo. of T. Laughren at 384:4-385:7.

[288] Exh. 49, Lexapro Approval Letter for Adolescents at 3, at 1-2.

[289] Exh. 8, 2017 Depo. of T. Laughren at 401:15-402:16 (emphasis added).

And, while Dr. Laughren defended his decision to approve Lexapro for adolescents during his deposition, he admitted that the FDA, even today, could re-review this data and conclude that MD-18 was negative and, thus, rescind the Lexapro approval for adolescents:

> 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?*** . . .
>
> [A]. 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.[290]

When one considers that Forest's corporate representative admitted, under oath, that MD-18 is negative when the unblinded patients are removed,[291] and the mountain of evidence showing these patients were, in fact, unblinded,[292] the scope of the fraud comes into view—by misleading the FDA about the unblinding in MD-18 using "masterful euphemisms"[293] and deliberately misleading language, Forest bamboozled the FDA into approving Lexapro for use in adolescents. And, now, the man responsible for allowing this mischarge of science—indeed, the godfather of all modern antidepressants,[294] Dr. Laughren—started a company called Psychopharm

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[290] *Id.* at 402:18-403:2 (emphasis added).

[291] Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 294:10-295:20 ("If they were removed from the study, I understand that the result would have been negative.").

[292] Exh. 16, Email re. CIT-18 FAX to Investigational sites (w/ attachment) at 2 ("[D]ispensing these tablets would automatically unblind the study."); Exh. 18, Email responses re. Letter to FDA for CIT-18 at 1 ("[T]he integrity of the blind was unmiatakenly violated."); Exh. 20, Email re. CIT-MD-18 at 1 ("We need to generate Tables . . . excluding the 9 patients who were unblinded at the beginning of the study."); Exh. 21, Email re. Notes from conference call Oct 4 (w/attachment) at 2 ("[S]ome citalopram tables were not blinded. The 9 patients who received unblinded medication were included in the main analyses[.]"); Exh. 11, 2016 Depo. W. Heydorn at 155:2-24, 157:18-21, 218:6-13 ("Q. So with respect to the nine patients who received the pink tablets, the study was unblinded with respect to them automatically, correct? . . . THE WITNESS: I guess yes. . . . Q. So they were unblinded as well, correct? . . . THE WITNESS: With respect to those patients, I would assume so. . . Q. Now, having seen this e-mail from Dr. Flicker and the fax from Dr. Tiseo, would you agree that the patients who were subject to the dispensing error were actually unblinded? . . .THE WITNESS: I don't know for a fact, but that's the implication from these letters, yes."); Exh. 46, J. Jureidini Expert Report at 5 (showing that the results from the unblinded Celexa patients were 50-60% greater in than blinded Celexa patients).

[293] Exh. 18, Email responses re. Letter to FDA for CIT-18 at 1.

[294] Exh. 8, 2017 Depo. T. Laughren at 27:23-28:7 ("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

Consulting, where he touts having "29 years of experience at the FDA in ***assisting pharmaceutical companies with psychiatric drug development programs***," and "hope[s] to ***continue in this effort*** as an independent consultant."[295]

PART VI: FOREST USED THE FALSE ASSERTION THAT MD-18 WAS POSITIVE AND THE FDA'S APPROVAL FOR LEXAPRO TO NEGOTIATE REDUCED PENALTIES IN USAO CASE

When the USAO negotiated Forest's criminal plea, civil settlement, and CIA, Forest was able to use the "fact" that MD-18 was positive and that the FDA had approved, in March 2009, the adolescent use of Lexapro. As it turns out, however, those two material facts, which clearly limited the ability of the United States to fully prosecute Forest's off-label promotion, were based on outright fraud and deception. Under the terms of the criminal plea, the USAO retains the right to reopen its prosecution if the plea agreement was based on or involved any falsehoods.[296] The information and evidence set forth in this memorandum strongly support the reopening of the USAO's prosecution of Forest, to hold Forest accountable for the fraud perpetrated on the FDA, the USAO, physicians, parents, and the medical/scientific community.

SSRIs? A. Every one of them[.]").

[295] Exh. 78, LinkedIn Profile for T. Laughren & PsychoPharm Consulting, at 1 (emphasis added).

[296] Exh. 2, Plea Agreement at 6.