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April 28, 2017

R. Brent Wisner, Esq.
Baum Hedlund
12100 Wilshire Boulevard, Suite 920
Los Angeles, CA 90025

Dear Mr. Wisner:

This report details my expert opinion in the Celexa and Lexapro Marketing and Sales Practices Litigation. In summary, my opinions are:

1. Celexa and Lexapro Lack Efficacy in Treating Pediatric Patients

Beginning in 1998 when Celexa first entered the United States market and continuing in 2002 when Lexapro entered the market as the company's new patented version of the drug, Forest heavily promoted its antidepressants Celexa and Lexapro off-label for pediatric patients despite the drugs lack of efficacy in this patient population. Celexa and Lexapro are close chemical cousins. In 2010, Forest pled guilty to criminal and civil charges brought by the United States Department of Justice that, for more than a decade, the company had aggressively promoted Celexa and Lexapro off-label for children and adolescents. As part of the guilty plea, Forest paid hundreds of millions of dollars in fines.

While promoting Celexa and Lexapro off-label for pediatric patients, Forest and its Danish affiliate Lundbeck conducted two efficacy studies of Celexa and two later studies of Lexapro in this patient population, hoping to win FDA approval. The four studies included 19 primary and secondary measures of the children's depressions. The studies included a program of regular clinic appointments in which the children received considerable care and attention from doctors, mental health clinicians, clinic staff, and their parents.

In all four studies, Forest's antidepressants offered no clinically significant advantage over placebo, or so-called "sugar pills." In some instances, children treated with placebo did a little better than children treated with Celexa or Lexapro. In only one study

(Lexapro Study 32) did the drug statistically outperform placebo, but the difference was too small to be clinically significant. In real life, clinical practice doctors and patients would not be able to detect such a small, marginal at best, difference between the drug and placebo. Doctors and parents seeing pediatric patients improve on Celexa or Lexapro might think the improvement was due to the drugs, having no idea that all or most of the improvement would have occurred on placebo. Indeed, an argument could be made that this one positive study is an anomaly.

2. Celexa Study 18 (the Wagner Study) Was a Failed, Negative Study

By 2001, Forest and its Danish affiliate Lundbeck had completed the companies' first two double blind, placebo controlled studies of Celexa for children and adolescents, a European study (Celexa Study 94404) and an American study (Celexa Study 18). The European study is also known as the Lundbeck study, since it was conducted by Forest's Danish affiliate. The American study is also known as the Wagner study, since Forest used Dr. Karen Wagner at the University of Texas Medical Branch in Galveston as the lead author of the company's published version of the study. Forest has touted the Wagner study as a positive study, and even used it to gain FDA approval of Celexa's chemical cousin, Lexapro. However, the Wagner study was only positive because Forest inappropriately counted unblinded patients in the company's calculations. When the calculations are done properly, the Wagner study is not positive, Celexa did not significantly outperform placebo. Thus, Forest had no legitimate basis to promote the use of either Celexa or Lexapro for pediatric use.

3. Forest Suppressed Celexa Study 94404 (the Lundbeck Study), Which was a Negative Study

In the Lundbeck Study 94404, Celexa was not effective for treating depressed pediatric patients and had a numerically 2.5 times greater rate of suicidality than patients randomized to placebo. In the Wagner Study 18, Celexa was not significantly better than placebo, but by including patients that had been "unmistakenly unblinded," Forest was able to make Celexa appear to statistically significantly perform better than placebo on the primary efficacy measure, but only marginally so. Forest exaggerated the results of the Wagner study as part of aggressively promoting Celexa and Lexapro for pediatric patients, while suppressing the results of the negative Lundbeck study.

4. The FDA Approved Lexapro For Depressed Adolescents Using Data from the Wagner Study 18

For marketing approval purposes, the FDA generally requires two studies in which patients on the drugs do better than patients on placebo. The difference between the drug and placebo can be small, so long as it is statistically significant, even if it is so small that it is not clinically significant.

In 2009, the FDA approved Lexapro for depressed adolescents on the basis of Celexa Study 18 and Lexapro Study 32. As indicated above, in Lexapro Study 32, the difference between the drug and placebo was statistically significant but clinically insignificant. Celexa Study 18, when properly analyzed, was neither statistically nor clinically significant. The FDA relied on Forest's faulty Celexa Study 18 results and also allowed the company to ignore its other two failed studies (Lexapro Study 15 and Celexa Study 94404). Even with the lack of knowledge that Celexa Study 18 was actually negative, the FDA's approval of Lexapro for adolescents has been controversial. In my opinion, given the available evidence, the approval was not warranted.

5. In 2010, Forest Pled Guilty to Off-Label Marketing Its Antidepressants for Pediatric Patients

In September 2010, Forest pled guilty to both the criminal and civil charges brought by the United States Department of Justice that the company suppressed the Lundbeck study, while using the Wagner study to aggressively promote Celexa and Lexapro off-label for children and adolescents. According to a government press release issued on the day the guilty plea was announced "Forest used illegal kickbacks to induce physicians and others to prescribe Celexa and Lexapro" to children. On related charges, in the guilty plea, Forest acknowledged that it "acted knowingly and corruptly."

Qualifications

A graduate of Harvard Medical School, I am a Clinical Instructor in Psychiatry at Harvard Medical School, was a staff psychiatrist at the Harvard Law School Health Services for twenty years, and have a private practice in Harvard Square. I am Board Certified in Psychiatry by the American Board of Psychiatry and Neurology. I am the author of two books on antidepressants: *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* published in 2000 by Simon & Schuster and *The Antidepressant Solution: A Step-by-Step Guide to*

Overcoming Antidepressant Withdrawal, Dependence, and "Addiction" published by Simon & Schuster's Free Press division in January 2005.[1]

I am a moderate in the debate over the risks and benefits of antidepressant medications. I prescribe antidepressants for patients whose conditions are serious enough to warrant the drugs and have had numerous patients report their beneficial effects. But, I am a critic of the drugs being over-prescribed for mild, even trivial, conditions and of patients not being adequately warned of their side effects. I testified at the FDA's February 2004 and December 2006 hearings on antidepressant-induced suicidality.

Since the publication of *Prozac Backlash,* I have become a national spokesperson for the appropriate, measured use of psychiatric medications. I have been interviewed on numerous national television and radio shows including NBC's The Today Show, ABC News' 20/20, ABC's Good Morning America, ABC's World News Tonight, ABC's Primetime Live, CNN, Fox News, PBS, Court TV, and National Public Radio for my expertise on antidepressants. My work has been the subject of many reviews and articles including in the *New York Times* and *The New Yorker* magazine.[2] Among the honors I have received for writing *Prozac Backlash* is the American College for Advancement in Medicine's (ACAM's) Annual Achievement Award in Medicine in May 2001. I received the award at ACAM's 2001 annual convention and delivered the convention's keynote address, the Linus Pauling Lecture. My *curriculum vitae* is enclosed with this report as Exhibit 1.

Materials Reviewed for this Report

Appendix A lists the internal Forest documents, deposition testimony, and exhibits I had available to me, considered, reviewed or relied upon in preparing this report. I will supplement my report if it becomes appropriate to do so. I have also reviewed relevant medical literature on antidepressant medications and drawn on my extensive knowledge and experience prescribing these drugs to patients.

In the past four years, I have given testimony in the following cases:

For my work on this case I am compensated at the hourly rate of $800. In the past four years, I have given testimony in the following cases: Barth v Netolicky on October 2, 2014; Brown v Forest Labs et al on March 11, 2013 and May 14, 2013; Henry v Kahnert on July 10, 2013; Elmore v Janssen on August 12, 2013; Teters v Bristol-Myers Squibb on October 25, 2013; Delahoussaye v Concepcion on November 22, 2013; Amedia v United States of America on April 15, 2014 and August 25, 2014; Muzichuck v Forest Labs on

July 1, 2014 and July 28, 2015; Herrera and Lowry v Eli Lilly on November 25, 2014 and August 4, 2015; the United States of America ex rel John King and Tammy Drummond Individually et al v Solvay SA et al on February 27, 2015; Dolin v GlaxoSmithKline on March 16, 2015 and March 29-30, 2017; Hexum and Herrera v Eli Lilly on April 22, August 4, and August 11, 2015; Hagen Brown and Ali v Eli Lilly on June 1, 2015 and August 27, 2015; Batoh v McNeill on June 26, 2015; Bane vs Nguyen on July 8, 2015; United States of America ex rel Richard Templin and James Banigan v Organon and Omnicare on August 31, 2015; Wheeler v Eli Lilly on April 27, 2016; Risperdal and Invega Product Liability Class vs Janssen Pharmaceuticals on June 10, June 27, and July 5, 2016; Reis v Cronin on September 8, 2016

1. Celexa and Lexapro Lack Efficacy in Treating Pediatric Patients

Beginning in 1998 when Celexa first entered the United States market and continuing in 2002 when Lexapro entered the market as the company's new patented version of the drug, Forest heavily promoted its antidepressants Celexa and Lexapro off-label for pediatric patients. Celexa and Lexapro are close chemical cousins. In 2010, Forest pled guilty to criminal and civil charges brought by the United States Department of Justice that, for more than a decade, the company had aggressively promoted Celexa and Lexapro off-label for children and adolescents.[3] As part of the guilty plea, Forest paid hundreds of millions of dollars in fines.[4]

While promoting Celexa and Lexapro off-label for pediatric patients, Forest and its Danish affiliate Lundbeck conducted two efficacy studies of Celexa and two later studies of Lexapro in this patient population, hoping to win FDA approval.[5] The four studies included 19 primary and secondary measures of the children's depressions.[6] The studies included a program of regular clinic appointments in which the children received considerable care and attention from doctors, mental health clinicians, clinic staff, and their parents.

In all four studies, Forest's antidepressants offered no clinically significant advantage over placebo. In only one study (Lexapro Study 32) the drug statistically significantly outperformed placebo, but the difference was too small to be clinically significant. In real life, clinical practice doctors and patients would not be able to detect such small, marginal at best, differences between the drugs and placebo. Doctors and parents seeing pediatric patients improve on Celexa or Lexapro might think the improvement was due to the drugs, having no idea that all or most of the improvement would have occurred on placebo.

Forest and Lundbeck were aware that, historically, most studies have found antidepressants are not effective for pediatric patients. According to the June 19, 1996 protocol for Celexa Study 94404:[7]

> Tricyclic antidepressants have been studied in double-blind trials without proving any significant differences versus placebo; amitriptyline, imipramine, desimipramine, and nortriptyline.

The Study 94404 protocol also stated:[8]

> The first controlled study with a [newer] SSRI, Prozac, showed considerable improvement of symptoms *both* for active drug and placebo. The high placebo response in teenagers could explain why studies cannot demonstrate significant effect of an active drug [emphasis added].

Thus, Forest knew a number of older tricyclic antidepressants had been studied in pediatric patients but were found to be no more effective than an inactive placebo and that the SSRI Prozac had been studied but failed to show efficacy in this population. In antidepressant studies, pediatric patients typically have high placebo response rates: their improvement on an inactive placebo is comparable to their improvement on an antidepressant. This is because pediatric patients are even more suggestible and responsive to placebo than adults.

In pharmaceutical company studies, pediatric patients actually receive more than just a placebo pill or an active drug: In an intensive program of regular clinic visits they receive considerable care, concern, and attention from the researchers conducting the studies and from their parents who also participate.

Forest's Four Efficacy Studies in Pediatric Patients

Forest and its Danish affiliate Lundbeck conducted four efficacy studies in pediatric patients, two Celexa studies followed by two later Lexapro studies. The term pediatric patients is typically used to refer to children and adolescents under the age of 18. And when the term "children" is used inter-changeably with the phrase pediatric patients, it includes adolescents.

All four of Forest's pediatric studies were double-blind, placebo-controlled, randomized studies. Placebo-controlled means roughly half the pediatric patients received an active drug while the other half received inactive placebo pills. Randomized means the patients were randomly assigned to the active drug versus placebo groups. Double blind means the pills were identical and neither the researchers nor the patients were supposed to know who was receiving the active drug versus placebo. Table 1 lists Forest's four pediatric studies.[9] Celexa Study 94404 was conducted in Europe while the later three studies were conducted in the United States.

Table 1

Forest's Pediatric Efficacy Studies

Drug	Study No.	Dates	Length (weeks)	No. Patients	Ages	Suicidal or Hospitalized	Early Placebo Responders
Celexa	94404	1996-2001	12	233	13-18	Included	Included
Celexa	18	2000-2001	8	174	7-17	Excluded	Excluded
Lexapro	15	2002-2004	8	261	6-17	Excluded	Excluded
Lexapro	32	2005-2007	8	311	12-17	Excluded	Excluded

Duration

As seen in Table 1, all four of Forest's pediatric studies were short-term studies prospectively designed to assess efficacy, that is, how well the drugs worked by comparison with placebo. Celexa Study 94404 was the longest; the children were treated for 12 weeks. The other three studies were considerably shorter, treating children for only eight weeks.

Size

All four of Forest's pediatric studies were large studies, Celexa Study 18 was the smallest with 174 patients. Lexapro Study 32 was the largest with 311 patients. The first and last studies—Celexa Study 94404 and Lexapro Study 32—focused on adolescents, while the other two studies—Celexa Study 18 and Lexapro Study 15—included younger-aged children.

Dose

In Celexa Study 94404, the pediatric patients were started on 10 mg/d and their dose could be titrated to 20, 30, or 40 mg/d.[10] In Celexa Study 18, the children were started on 10 mg/d and their dose could be adjusted to either 20 or 40 mg/d.[11] Thus, the maximum dose in both Celexa studies was 40 mg/d. In both Lexapro studies, the children were started on 10 mg/d, which could be titrated to 20 mg/d.[12]

Suicidal Patients

As seen in Table 1, only Celexa Study 94404 included suicidal patients. Indeed, almost one-third of the patients had a history of a suicide attempt.[13] In Forest's other three studies—Celexa Study 18, Lexapro Study 15, and Lexapro Study 32—patients with active suicidal thoughts, patients who had made a serious suicide attempt within the

previous year, and patients who had ever been hospitalized because of a suicide attempt were excluded.[14]

Hospitalized Patients

Celexa Study 94404 also included hospitalized patients. About one-third of the patients had previously been treated for depression, about 20% had a history of psychiatric hospitalization, and about 14% were hospitalized when they began the study.[15] Forest's other three studies excluded hospitalized patients; only patients well enough to be treated on an outpatient basis were allowed into the studies.[16]

Early Placebo Responders

Celexa Study 18, Lexapro Study 15, and Lexapro Study 32 also excluded early placebo responders. To identify pediatric patients who quickly responded to placebo, Forest first treated all of the patients for a week *prior* to officially starting the studies in a "one-week single-blind placebo lead-in" phase.[17] Single-blind means the researchers knew all the children were receiving placebo, but the children did not; the children thought they could be receiving either the active drug or placebo. At the end of the one-week placebo lead-in phase, children whose depression scores had quickly improved were not allowed to continue in the actual study. Instead, these, early placebo responders were excluded from the studies. [18]

Identifying and removing early placebo responders weakens the performance of the placebo group in the actual study by excluding patients who are strong placebo responders.[19] Excluding early placebo responders is a technique pharmaceutical companies sometimes use to bias studies in favor of their drugs.[20] Forest excluded early placebo responders from Celexa Study 18, Lexapro Study 15, and Lexapro Study 32, biasing the studies in favor of the company's drugs.[21] Only the first study, Celexa Study 94404 did not have a placebo lead-in phase and did not exclude strong, early placebo responders.

Representative Patients

Since Celexa Study 94404 included suicidal patients, hospitalized patients, and early placebo responders, this first study was more representative of the range of patients who could be prescribed Forest's antidepressants in real world clinical practice. By contrast, Celexa Study 18, Lexapro Study 15, and Lexapro Study 32 were limited to highly selected patients. Indeed, according to confidential, internal Forest emails comparing the original two Celexa studies:[22]

> Whereas the European study [i.e., Celexa Study 94404] included patients as one would be likely to encounter in daily life, and therefore was actually a better study in terms of treatment "effectiveness," the USA trial [i.e., Celexa Study 18] applied more stringent inclusion criteria and in that sense resembles classic [pharmaceutical company] clinical trials [studies] with "ideal" patients no one ever sees on one's doorstep.

I agree with the assessment that Celexa Study 94404 was superior to the other three studies of highly selected patients not representative of the general pediatric patient population seeking psychiatric treatment for depression. Studies need to be representative in order for their results to be generalizable to the real world patient population who may be treated with the drugs.[23]

Primary Clinical Measure

Table 2 lists the primary clinical measurement scales used in Forest's four pediatric studies.[24] The FDA requires pharmaceutical companies to designate the primary measure before a study is conducted, in the study protocol. Typically, the studies also use a number of secondary measurement scales to provide corroborating, or supporting, evidence.

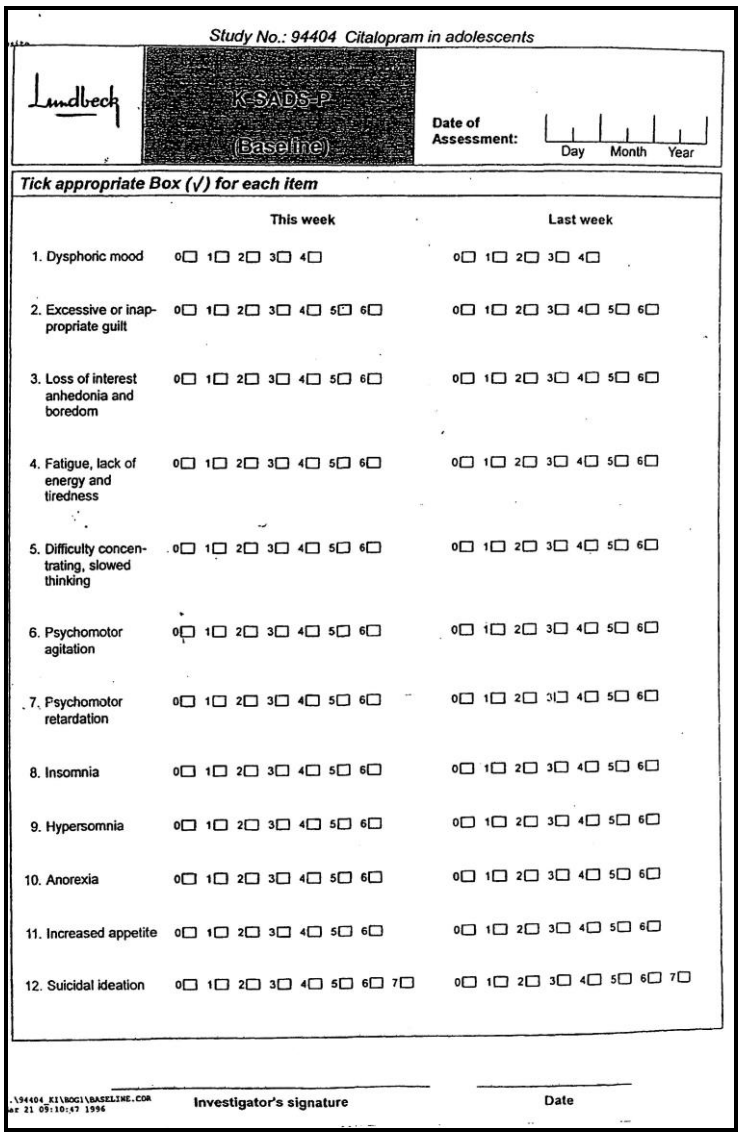
Table 2
Primary Clinical Measurement Scale

Drug	Study	Primary Measure
Celexa	94404	K-SADS-P
Celexa	18	CDRS-R
Lexapro	15	CDRS-R
Lexapro	32	CDRS-R

As seen in Table 2, the primary efficacy measure in Celexa Study 94404 was the depression module of the Schedule of Affective Disorders and Schizophrenia for School-Aged Children—Present, abbreviated Kiddie-SADS-P. Figure 1 reproduces the scale, which assesses 12 items including depressed (dysphoric) mood, boredom, agitation, sleep disturbance, change in appetite, and suicidal thoughts (ideation).[25] Each of the items is rated on a scale from zero to four, six, or seven. The total score ranges from 0 to 71. The primary efficacy measure in Celexa Study 94404 was the change in the mean K-SADS-P score from the beginning (the baseline score) to the end of the 12-week study.

Figure 1

The K-SADS-P



Study No.: 94404 Citalopram in adolescents

Lundbeck

K-SADS-P

(Baseline)

Date of Assessment: Day Month Year

Tick appropriate Box (√) for each item

	This week	Last week
1. Dysphoric mood	0☐ 1☐ 2☐ 3☐ 4☐	0☐ 1☐ 2☐ 3☐ 4☐
2. Excessive or inappropriate guilt	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
3. Loss of interest anhedonia and boredom	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
4. Fatigue, lack of energy and tiredness	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
5. Difficulty concentrating, slowed thinking	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
6. Psychomotor agitation	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
7. Psychomotor retardation	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
8. Insomnia	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
9. Hypersomnia	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
10. Anorexia	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
11. Increased appetite	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐
12. Suicidal ideation	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐	0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

\94404_K1\BOG1\BASELINE.COR
Apr 21 09:10:47 1996

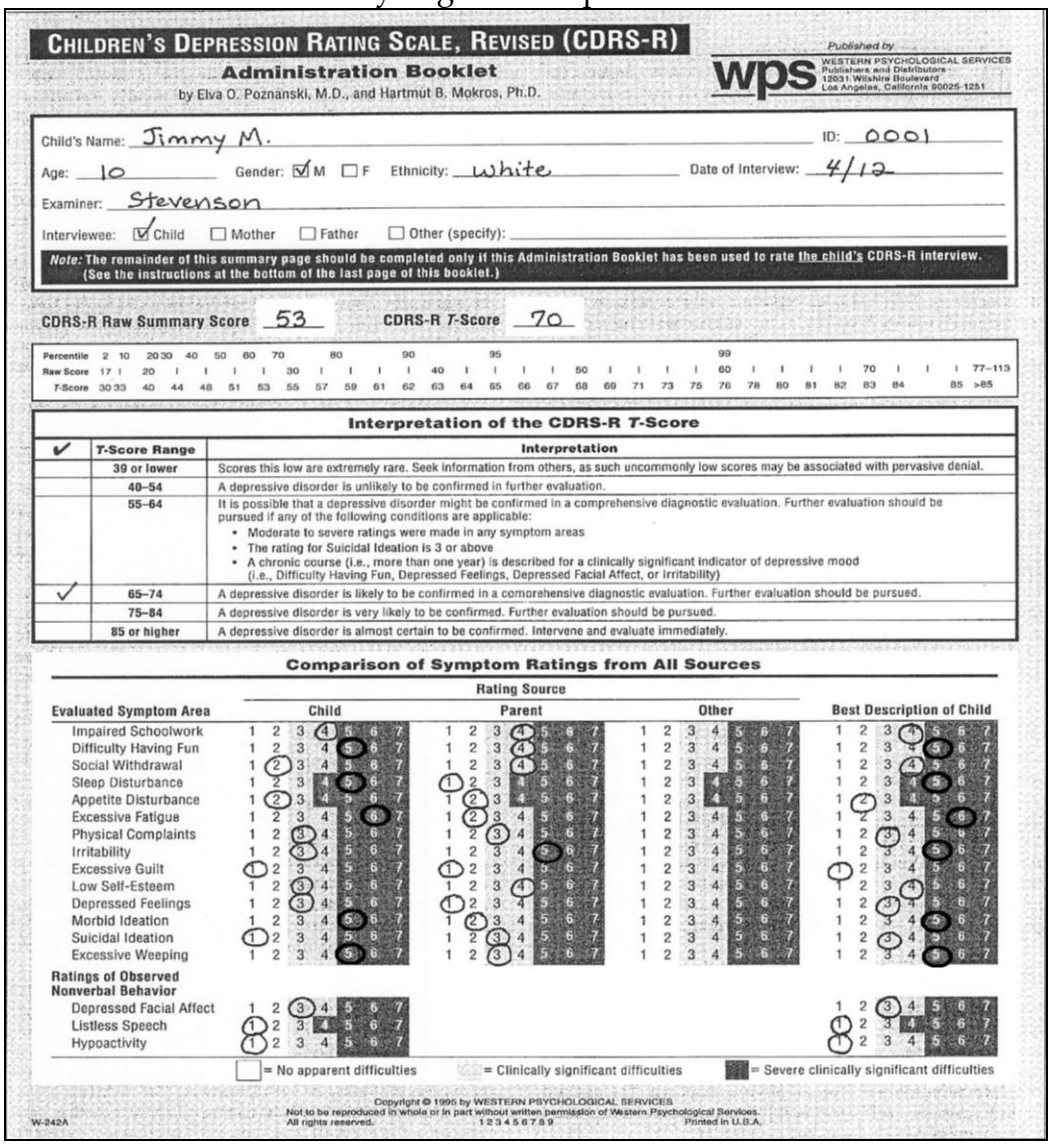
Investigator's signature

Date

As seen in Table 2, Forest changed the primary measurement scale in its later three studies to the Children's Depression Rating Scale—Revised, or CDRS-R. Figure 2 reproduces the CDRS-R scale, which assesses 17 items ranging from impaired schoolwork and difficulty having fun to depressed feelings, morbid thoughts, and suicidal thoughts.[26] Fourteen of the items are rated on a scale from one to seven, while three are rated on a scale from one to five.[27] The total score ranges from 17 to 113[28]

Figure 2

Summary Page of Completed CDRS-R



CHILDREN'S DEPRESSION RATING SCALE, REVISED (CDRS-R)

Administration Booklet

by Elva O. Poznanski, M.D., and Hartmut B. Mokros, Ph.D.

Published by WPS WESTERN PSYCHOLOGICAL SERVICES Publishers and Distributors 12031 Wilshire Boulevard Los Angeles, California 90025-1251

Child's Name: Jimmy M. ID: 0001

Age: 10 Gender: ☑ M ☐ F Ethnicity: White Date of Interview: 4/12

Examiner: Stevenson

Interviewee: ☑ Child ☐ Mother ☐ Father ☐ Other (specify):

Note: The remainder of this summary page should be completed only if this Administration Booklet has been used to rate the child's CDRS-R interview. (See the instructions at the bottom of the last page of this booklet.)

CDRS-R Raw Summary Score 53 CDRS-R *T*-Score 70

Percentile	2	10	20	30	40	50	60	70	80	90	95	99	
Raw Score	17	20	30	40	50	60	70	77–113					
T-Score	30	33	40	44	48	51	53	55	57	59	61	62	63	64	65	66	67	68	69	71	73	75	76	78	80	81	82	83	84	85	>85

Interpretation of the CDRS-R *T*-Score

✓	*T*-Score Range	Interpretation
	39 or lower	Scores this low are extremely rare. Seek information from others, as such uncommonly low scores may be associated with pervasive denial.
	40–54	A depressive disorder is unlikely to be confirmed in further evaluation.
	55–64	It is possible that a depressive disorder might be confirmed in a comprehensive diagnostic evaluation. Further evaluation should be pursued if any of the following conditions are applicable: • Moderate to severe ratings were made in any symptom areas • The rating for Suicidal Ideation is 3 or above • A chronic course (i.e., more than one year) is described for a clinically significant indicator of depressive mood (i.e., Difficulty Having Fun, Depressed Feelings, Depressed Facial Affect, or Irritability)
✓	65–74	A depressive disorder is likely to be confirmed in a comprehensive diagnostic evaluation. Further evaluation should be pursued.
	75–84	A depressive disorder is very likely to be confirmed. Further evaluation should be pursued.
	85 or higher	A depressive disorder is almost certain to be confirmed. Intervene and evaluate immediately.

Comparison of Symptom Ratings from All Sources

Evaluated Symptom Area	Rating Source: Child	Parent	Other	Best Description of Child
Impaired Schoolwork	4	4		4
Difficulty Having Fun	5	4		5
Social Withdrawal	2	4		4
Sleep Disturbance	5	1		5
Appetite Disturbance	2	2		2
Excessive Fatigue	6	2		6
Physical Complaints	3	3		3
Irritability	3	5		5
Excessive Guilt	1	1		1
Low Self-Esteem	3	4		4
Depressed Feelings	3	1		3
Morbid Ideation	3	2		3
Suicidal Ideation	1	3		3
Excessive Weeping	5	4		5
Ratings of Observed Nonverbal Behavior				
Depressed Facial Affect	3			3
Listless Speech	1			1
Hypoactivity	1			3

☐ = No apparent difficulties ▒ = Clinically significant difficulties ■ = Severe clinically significant difficulties

W-242A

As seen in Figure 2, in the CDRS-R, both the child and parent can be separately interviewed to assess how the child is doing. The researcher picks the score for each item (the child's or the parent's score) that in the researcher's judgment best describes the child, adding them up to obtain a total composite score.[29] The primary efficacy measure in Celexa Study 18, Lexapro Study 15, and Lexapro Study 32 was the change in the mean CDRS-R score from baseline to the end of the eight-week study.

Secondary Clinical Measures

Table 3 lists the secondary measurement scales used in Forest's pediatric studies.[30] The secondary measures are meant to provide corroboration, or support, for the results of the primary measure.

Table 3

Secondary Measurement Scales

Drug	**Study**	**Primary Measure**	**Secondary Measures**
Celexa	94404	K-SADS-P	K-SADS-P Response MADRS MADRS Response MADRS Remission BDI GAF LES EE
Celexa	18	CDRS-R	K-SADS-P CGI Severity CGI Improvement CGAS
Lexapro	15	CDRS-R	CGI Severity CGI Improvement CGAS
Lexapro	32	CDRS-R	CGI Improvement

Pharmaceutical companies have been criticized for merely measuring improvement in depression scores in antidepressant studies, since patients' scores may improve a small amount, leaving the patients still quite depressed. As a result, some studies have tried to define specific thresholds for response or remission. As seen in Table 3, in Celexa Study 94404 some of the secondary measures assessed response and remission rates. Response on the K-SADS-P scale was defined as the proportion of patients who achieved a score of 2 or less on the depressed mood and anhedonia items of the scale.[31] Response on the Montgomery Asberg Depression Rating Scale (MADRS) was defined as at least a 50% reduction in the patient's depression score.[32] Remission on the MADRS scale was defined as achieving a score of 12 or less.[33] Celexa Study 94404 also used several other secondary measures including the Beck Depression Inventory (BDI), the Global Assessment of Functioning (GAF) scale, and the Life Event Scale (LES).[34]

Altogether, the scales assessed over 100 items, or dimensions, of depression and the patients' lives.

As seen in Table 3, no single measurement scale was used in all four studies. In Celexa Study 18, Forest changed the primary measure to the CDRS-R and used the K-SADS-P as a secondary measure. In Celexa Study 18, the three other secondary measures were also new: the Clinical Global Impressions Severity (CGI Severity) score, the Clinical Global Impressions Improvement score (CGI Improvement), and the Children's Global Assessment Scale (CGAS). In Celexa Study 18, Forest did not re-use any of the secondary measures used in Celexa Study 94404. And, Forest dropped the K-SADS-P as a secondary measure in both Lexapro Study 15 and Lexapro Study 32. Indeed, by the time Lexapro Study 32 was conducted, Forest had eliminated all but one secondary, supporting measure. And, in the later three studies, Forest did not include any threshold measures of response or remission as primary or secondary assessments.

In Celexa Study 94404, the patients' parents were evaluated for Expressed Emotions (EE), an assessment of their attitudes and feeling toward their depressed children.[35] In Celexa Study 18, Lexapro Study 15, and Lexapro Study 32, the primary measure, the CDRS-R scale, could be repeated with the parents as another assessment of how the child was doing. In addition, the pediatric patients received complete medical, psychiatric, family, and social histories; physical exams; electrocardiograms; vital signs, height, and weight; and blood tests.[36] The assessments were performed according to a predetermined schedule at the screening appointment, baseline evaluation, and at the end of weeks one, two, five, nine and 12 in Celexa Study 94404 and at the end of weeks one, two, four, six, and eight in the three shorter studies.[37]

Thus, the pediatric patients in Forest's studies were not just dispensed a supply of pills: the active drug or placebo. Rather, they received a substantial amount of care and attention from doctors, mental health clinicians, clinic staff, and their parents who brought them to the appointments and also participated in the study. The studies entailed a program of regular clinic appointments providing considerable clinic staff and parental attention to the pediatric patients plus an active or inactive pill.

Premature Withdrawals

One benchmark of antidepressant studies is the percentage of patients who are treatment failures, dropping out prematurely because they did not feel they were benefitting enough, because of intolerable side effects, or for other reasons. In the first Celexa Study 94404, more than a third of the pediatric patients prematurely withdrew from the study, as seen in Table 4.[38] This was true for the patients treated with Celexa or

placebo. Since Celexa Study 94404 was the most representative of the general population of pediatric patients seeking treatment for depression, one can generalize that more than a third of pediatric patients would not tolerate Celexa or Lexapro even for a short time, up to 12 weeks. The other three studies—Celexa Study 18, Lexapro Study 15, and Lexapro Study 32—were all shorter studies of highly selected patients. As seen in Table 4, fewer of these highly selected patients dropped out of treatment prematurely, but the results are not generalizable because the patients were so highly selected and not representative of the general population of pediatric patients.

Table 4

Percent of Patients Who Prematurely Withdrew from the Studies

Drug	Study	Placebo	Drug	Total
Celexa	94404	34%	35%	34%
Celexa	18	21%	20%	21%
Lexapro	15	14%	22%	18%
Lexapro	32	15%	19%	17%

Two standard methods are used to account for the depression scores of patients who drop out of studies prematurely: last observation carried forward, or LOCF, and observed cases, or OC. In the LOCF method, when patients drop out, their last score is carried forward *as though* they remained in the study until the end. The strength of the LOCF method is that it accounts for all the patients who entered the study. The weakness is that, for patients who drop out, the data carried forward is not real: one is assuming, or pretending, their scores would have remained unchanged. The more patients who drop out, the more artificial and meaningless the results become. In the OC method, the scores of only those patients who finish the study are counted. The advantage of the OC method is that all the data counted is real. The disadvantage of the OC method is that it ignores the patients who drop out either because the drug was ineffective, because of side effects, or for other reasons. Once again, the more patients who drop out, the more artificial and meaningless the results become.

When pharmaceutical companies specify the primary measurement scale in a study's protocol, they also designate either the LOCF or OC method as the primary method of accounting for the scores of patients who drop out prematurely. However, typically the results are computed using both the LOCF and OC methods since they each have strengths and weaknesses. In Celexa Study 94404, the primary measure was the mean change in scores on the K-SADS-P depression scale using the OC method to account for patients who dropped out of the study.[39] In Celexa Study 18, Lexapro Study 15, and Lexapro Study 32, the primary measure was the mean change in scores on the CDRS-R

depression scale using the LOCF method to account for patients who withdrew prematurely.[40]

Statistical Significance

The results of antidepressant studies are evaluated for statistical significance. A result is statistically significant if it is unlikely to have occurred by chance. In statistics, the probability that a result occurred by chance is called the p-value. By convention, a p-value of 0.05 or less is typically used as the threshold for statistical significance; that is, the likelihood the results were due to chance is 5% or less. Both the LOCF and OC methods of accounting for the scores of patients who dropped out of the study are used when assessing statistical significance.

Table 5 summarizes the statistical significance of the primary results of Forest's four pediatric studies.[41] In Celexa Study 94404, placebo outperformed Celexa by a small margin, but the difference was not statistically significant. In Celexa Study 18, when Forest improperly included the unblinded patients, Celexa appeared to outperform placebo by a small margin. The difference was statistically significant by the LOCF method; the p-value was 0.038.[42] However, when the results are analyzed properly without the unblinded patients, the study is not statistically significant. The p-value becomes 0.052.[43] As discussed in detail in a later section of this report, Forest improperly counted the unblinded patients and misleadingly asserted that Celexa Study 18 was a positive study in Celexa's favor.[44]

Table 5

Primary Results—Statistical Significance

Drug	Study	Primary Measure	Statistically Significant Difference?	
			OC	LOCF
Celexa	94404	K-SADS-P	No	No
Celexa	18	CDRS-R	No	No
Lexapro	15	CDRS-R	No	No
Lexapro	32	CDRS-R	No	Yes

Even when Forest inappropriately counted the unblinded patients, the result of Celexa Study 18 was not statistically significant by the OC method, the p-value was 0.167, indicating that the misleading statistical significance by the LOCF method was dependent on the particular method, or formula used.[45] In other words, the results of Celexa Study 18 even when inappropriately including the unblinded patients were not robust enough to be statistically significant by both tests.

As seen in Table 5, in Forest's first Lexapro study, Lexapro Study 15, the small difference between the drug and placebo was not statistically significant using either the LOCF or OC method.

In Forest's last pediatric study, Lexapro Study 32, the difference between the drug and placebo was statistically significant using the LOCF method; the p-value was 0.022.[46] However, the result was not statistically significant using the OC method, the p-value was 0.071, evidence that the result using the LOCF method was marginal at best.[47] Still, on the basis of the statistically significant finding using the LOCF method, Forest asserted that Lexapro Study 32 was a positive study in Lexapro's favor. But, while statistically significant, the difference was too small to be clinically meaningful. Once again, this was a statistically significant, clinically insignificant difference. Given this is the only statistically significant finding out of all of the studies of Celexa and Lexapro (i.e., the study's outcome has not been replicated elsewhere) makes the study dubious, and possibly anomalous.

It is noteworthy that Lexapro Study 32's size (i.e., the number of patients enrolled in the study) was increased from previous studies, which would increase the odds of achieving a statistically significant result. A great deal was riding on the study being positive. In fact, Forest's Executive Director of Clinical Development Psychiatry, Anjana Bose, stated in an email that "everything hinges on SCT-32" being positive in order to gain FDA approval.[48]

Methodological issues and Study 32's marginal efficacy were noted by peer reviewers of the manuscript when submitted to the *Journal of the American Academy of Child and Adolescent Psychiatry* for publication.[49] Graham Emslie, a child psychiatrist at University of Texas Southwestern Medical Center in Dallas was the named lead author. As is customary for peer reviewed medical journals, the manuscript was submitted by the journal to a number of peer reviewers for comment. One document produced by Forest sets forth proposed responses to the reviewer comments. The reviewers' comments themselves are telling:[50]

> Reviewer #1:
>
> Comment 1. I would characterize the effect size on the primary outcome (0.27) as "small to medium" using standard effect size classifications….Would it not be more appropriate to write that the data here suggest that Lexapro is a "mildly", "modestly" or at best "moderately" effective treatment?

> Comment 13. There were some procedures used in this study to ostensibly reduce the placebo response rate [i.e., excluding strong early placebo responders as discussed above] which were apparently unsuccessful [i.e., not successful enough to produce a clinically significant difference between the drug and placebo]….
>
> Reviewer # 5:
>
> Comment 6. The effect size (ES) reported as 0.27 may be comparable to prior reports, however, it should be noted that according to Chen this is a relatively small effect size. Given this small ES, there were no data to see if this level of change had any quality of life meaning [i.e., was clinically significant].
>
> Comment 8. Finally, one has to wonder whether the restrictive entry criteria in conjunction with the small effect size limit the utility of Lexapro in the real world of adolescent depression. Are these results statistically significant but clinically not meaningful? [That is, statistically significant but clinically insignificant.]

Forest's proposed response to reviewer number five's comment 8 was:[51]

> Clearly further research to address some of these issues is warranted.

Based on my review of the documents in this case, I could find no evidence that Forest conducted any further research and no indication Forest informed the FDA of the issues raised by the reviewers.

The distinction between statistical and clinical significance is important. Forest's own consultants have written about the issue. For instance, in a program sponsored by the American Psychiatric Association and Forest Pharmaceuticals, Inc., called "Navigating The Maze: Understanding Methods, Results and Risk in Psychiatry Research," Dr. David Kupfer presented "Assessing Statistical and Clinical Significance in Medical Research," in which he stated:[52]

> Understanding "significance" in drug trials is the key to translating medical research into clinical decision making. Clinical studies are considered "positive" if they are able to detect statistically significant differences between the drug being evaluated, and a placebo or active comparator. Investigators will increase sample size, pool subjects from

> different studies, or combine studies using metaanalysis in the hopes of obtaining results which show statistical significance. However, "statistical significance" is not necessarily equivalent to "clinical significance." Clinical significance requires that the study demonstrate that the difference is powerful enough to impact medical decision making and patient management … [53]

Said Dr. Kupfer:[54]

> Clinical significance requires that the study demonstrate that the difference is powerful enough to impact medical decision making and patient management…. The effect size that would motivate about half of well-informed clinicians to use treatment rather than control in this population.

In a 2013 article entitled "Defining a Clinically Meaningful Effect for the Design and Interpretation of Randomized Controlled Trials" in *Clinical Neuroscience*, Dr. Richard Keefe at the Duke University Medical Center and nine colleagues including Dr. Thomas Laughren, former Team Leader of Psychiatry Drug Products at the FDA and now a consultant to Forest, defined clinical significance as: [55]

> The smallest difference (i.e., effect size) . . . that patients perceive as beneficial and that would mandate . . . a change in the patient's management.

There are two primary ways to quantify clinical significance. The first is called the Cohen effect size.[56] According to Keefe:[57]

> 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.

These Cohen effect size classifications are summarized in Table 6.

Table 6

Cohen Effect Size

Effect Size	Classification
≥ .08	Large
0.79-.5	Medium
.49-.2	Small
≥ .19	Trivial

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.[58] According to Keefe:[59]

> The NNT is a meaningful, well-accepted, common-sense measure.

On the NNT scale, if the number is less than 2, then the drug is considered highly effective.[60] 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.[61] These NNT effect size classifications are summarized in Table 7.

Table 7

Number Needed Treat Effect Size

NNT	Classification
≥ 2	Highly effective
3-7	Moderately effective
≥ 8	Not Effective

The NNT for a particular clinical trial endpoint is calculated using the following equation:

$$NNT = \frac{1}{(Placebo\ response\ rate) - (Treatment\ response\ rate)}$$

Table 9 depicts the clinical effectiveness measured by both Cohen effect size and NNT for the primary endpoint for each of Forest's four pediatric studies. These numbers are based on the published results of each study. Note, the results for Celexa Study 18 include the nine unblinded patients, since Forest included them in the published version of the study. The results would be even lower with the nine patients properly excluded.

Table 9

Effect Sizes

Study	Effect Size	Response Rates	NNT	Clinically Meaningful
Celexa 94404	*Unpublished*	Pla: 61%, Cit: 60%	100	No
Celexa 18	.32	Pla: 24%, Cit: 36%	8.3	No
Lexapro 15	*Unpublished*	Pla: 37.9%, Lex: 45.7%	12.8	No
Lexapro 32	.27	Pla: 48.4%, Lex: 59.1%	9.3	No

In conclusion, as seen in Table 9, none of Forest's four pediatric studies had a clinically meaningful, or clinically significant, result. And, as seen in Table 5, none of Forest's pediatric studies had a statistically significant result using both the OC and LOCF methods of accounting for the scores of patients who dropped out of the studies. None of the studies could rule out chance being responsible for the small difference between the drug and placebo using both standard statistical tests. On the basis of the statistically significant findings using the LOCF method, Forest has asserted Celexa Study 18 (inappropriately including the unblinded patients) and Lexapro Study 32 are positive studies in which the drugs out-performed placebo. But, in both instances, the statistical significance was not supported by the OC method. In both instances, the difference between the active drug and placebo was too small to be clinically significant, too small to be detected in real life clinical practice by doctors, patients, or their parents. And, in the case of Celexa Study 18, the alleged statistically significant findings are based on inappropriate calculations.

2. Celexa Study 18 (the Wagner Study) Was a Failed, Negative Study

As seen in Table 3, Celexa Study 18 had one primary and four secondary endpoints.[62] All four secondary endpoints were negative.[63] Forest maintains that Celexa Study 18 was positive because the primary endpoint was statistically significant, however, Celexa study 18's primary endpoint was actually negative and Forest only obtained an improper statistically significant result using corrupted and invalid data.

In any double blind randomized clinical trial, the data collected from the patients must be double-blind.[64] Indeed, the protocol for Celexa Study 18 states this explicitly:[65]

> Any patient for whom the blind has been broken will immediately be discontinued from the study and no further efficacy evaluations will be performed.

In the final study report for Celexa Study 18, Forest stated:[66]

> Because of a drug packaging error, the Celexa or placebo tablets initially dispensed to 9 patients at 3 study centers were distinguishable in color, although otherwise blinded….

According to Forest's clinical study report, these patients were not actually unblinded (they just received a different colored pill), thus, Forest did not need to discontinue the patients from the study.[67] In the final analysis, Forest inappropriately used the data from these patients to achieve a positive efficacy result for the primary endpoint (the secondary endpoints were negative).[68] But, when these patients are appropriately excluded, the primary endpoint is statistically insignificant and Celexa Study 18 is negative across the board.[69]

These nine patients were, in fact, unblinded and should immediately have been discontinued from the study. Dr. Paul Tiseo, Joan Barton, and Dr. Charles Flicker oversaw Celexa Study 18.[70] Tiseo was the Medical Monitor for Celexa Study 18, Barton was the Clinical Trial Manager. Flicker was Tiseo and Barton's supervisor, overseeing all of the clinical trial programs related to Celexa and Lexapro.[71] Tiseo was responsible for the overall conduct of the study.[72] Shortly after Celexa Study 18 began enrolling patients, Forest learned of a packaging error. According to a March 8, 2000 memo written by Dr. Tiseo:[73]

> [Two] investigational sites called in to report that some of their patients were receiving white tablets and others were receiving pink tablets.

According to Tiseo's memo, Forest investigated and:[74]

> 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.

When Forest learned of the problem:[75]

> On March 2nd [2000] all sites were notified of this error by telephone and by fax.

In the fax, Tiseo informed each investigational site about the packaging error and explained the pink pills were actually:[76]

> Pink-colored commercial Celexa® tablets instead of the standard white Celexa tablets used for blinded clinical studies.

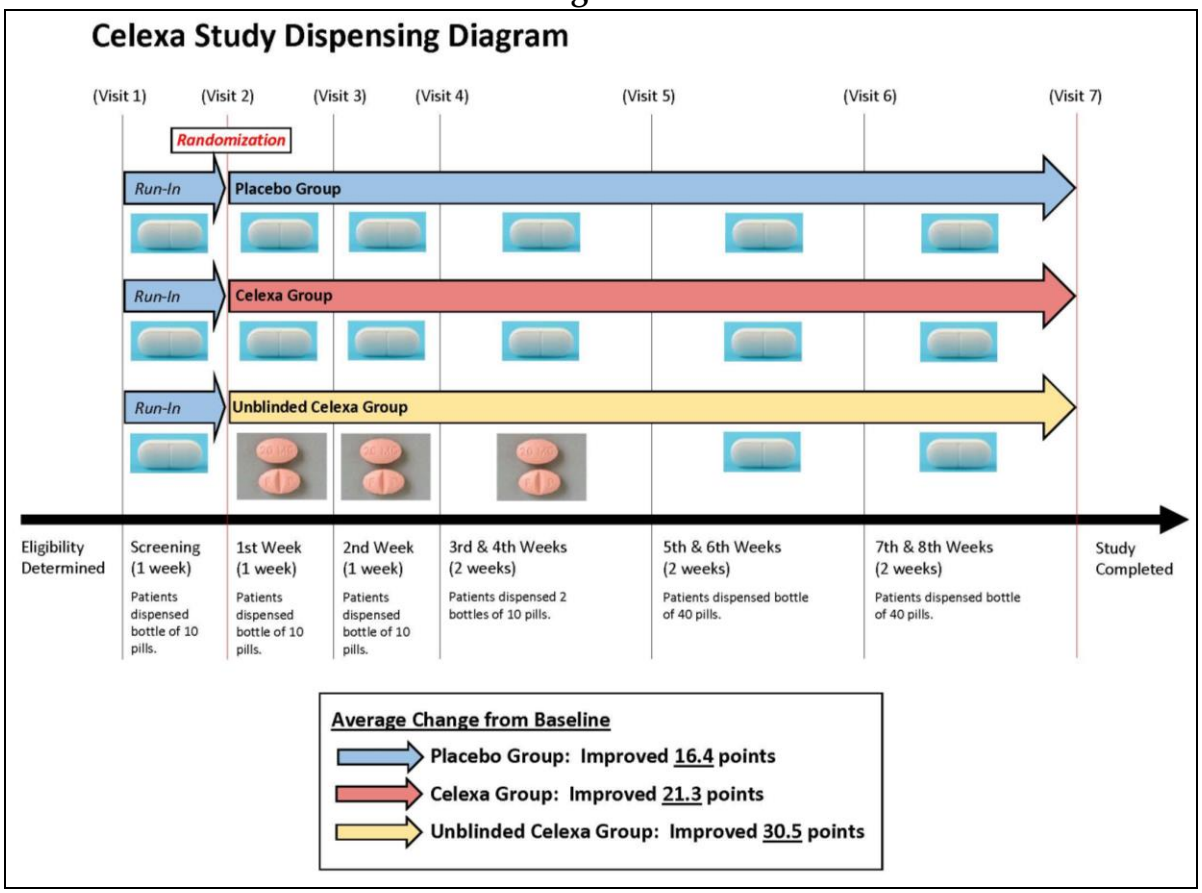
Tiseo informed the investigators:[77]

> Dispensing these tablets would *automatically unblind the study* [emphasis added].

Thus, per Dr. Tiseo, since nine patients had already been dispensed incorrectly color coated pills, those nine patients were automatically unblinded.[78] I agree with Dr. Tiseo. The investigators brought the packaging error to Forest's attention because some patients were receiving white pills, while others were receiving pink ones.[79] When Tiseo told the investigators the pink pills were commercial Celexa tablets, even if the patients did not know the pink tablets were the drug, the investigators knew that those patients getting the pink pills were getting the active drug.[80] The investigator blind was broken.

Figure 3 is a dispensing diagram illustrating breaking the blind in Celexa Study 18.

Figure 3



As seen in Figure 3, all the patients participated in a one-week, placebo run-in phase before the study officially began, before being randomized to Celexa or placebo. All the patients received white, unmarked study pills during the run-in phase. Post-randomization, both the placebo and Celexa patients continued to receive white, unmarked pills. Neither the researchers nor the patients knew who was receiving the active drug versus placebo. The unblinded Celexa group accidentally received pink, commercial Celexa pills, *after* having taken white, unmarked pills for a week. After the problem was discovered halfway through the study, the patients were switched *back* to white, unmarked pills instead of being removed from the study. Thus, the researchers and the patients knew of the mixup. The purpose of the blind is to attempt to minimize bias introduced by researchers and patients knowing who is on the active drug and being susceptible to greater suggestion that they are therefore going to have a more robust response. As seen at the bottom of Figure 3, the unblinded Celexa patients did, in fact, have a more robust response than the blinded Celexa patients.

Forest's biostatistician for the study, Dr. James Jin, has been deposed in this litigation.[81] At his deposition, Dr. Jin admitted any data collected from the nine patients would be corrupted:[82]

> Q: That's corrupted data though isn't it?
> A: There's some data question, yeah agreed.

Numerous internal Forest documents state unequivocally that these patients were, in fact, unblinded. For example, Ms. Barton sent an email to Drs. Tiseo and Flicker on December 6, 2000, inquiring about whether Celexa Study 18 would need to have additional patients enrolled due to the fact "the study drug was unblinded."[83] In an August 10, 2001 email from Jane Wu, another biostatistician working on Celexa Study 18, Wu explained the need to generate tables:[84]

> Excluding the 9 patients who were unblinded at the beginning of the study.

Indeed, Dr. William Heydorn, the Forest scientist who drafted and oversaw preparation of the final study report for Celexa Study 18, admitted the nine patients should have been excluded from the analysis of the study:[85]

> Q: Those patients were unblinded, correct?...
> A: That's what they're saying here, yes….
> Q: And per the protocol, those patients should have been excluded because they were unblinded, correct?...
> A: Yes.
> Q: So with respect to the nine patients who received the pink tablets, the study was unblinded with respect to them automatically, correct?...
> A: I guess yes.

After correcting the packaging error to prevent further "automatic" unblinding, Forest notified the FDA. Drs. Tiseo and Flicker drafted a letter to the FDA and circulated the draft to Forest executives.[86] The letter explained the dispensed medication could have "unblinded" the study but assured the FDA the unblinded patients would *not* be included in the primary efficacy analysis:[87]

> For reporting purposes, the primary efficacy analysis will exclude the potentially unblinded patients….

I agree this would have been the appropriate course for Forest to follow since, according to the study protocol, the nine patients should have been discontinued from the study and excluded from the primary efficacy analysis.[88] The protocol pre-specified the rules to be followed analyzing the data. The rules are pre-specified before a pharmaceutical company knows the results of a study. But, as discussed below, Forest violated the rules after-the-fact, once the company knew the results of the study, and reneged on the assurance to the FDA in the letter.

Amy Rubin worked in Forest's Regulatory Affairs department. When Drs. Tiseo and Flicker circulated the draft letter to Forest executives, Rubin received a copy.[89] Rubin edited the letter, changing the language from stating that the dispensing error could have "unblinded the study" to stating the dispensing error had the "potential to cause patient bias."[90] Ms. Rubin's edit drew criticism from Dr. Flicker:[91]

> 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* (emphasis added).

Dr. Flicker called Rubin's edit a "masterful stroke of euphemism" downplaying the significance of the unblinded patients that was not up front, not honest with the FDA, since the study blind was "unmistakenly violated." Ms. Rubin not only did not change her position, she bragged:[92]

> Thanks for the compliment. Part of my job is to create "masterful" euphemisms to protect Medical and Marketing.

In other words, Forest's liaison department to the FDA apparently considered it their job to defend the company's marketing goals, rather than be up front with the agency. At his deposition, Dr. William Heydorn, who oversaw the company's clinical study report for Celexa Study 18, was asked:[93]

> Q: But they had the obligation to be upfront, truthful and honest with the FDA, correct?...
> A: Yes….
> Q: And this shows that they weren't, correct?...
> A: He apparently had some concerns about this, yes…. It's a misrepresentation of what Charlie Flicker thought should be communicated to the FDA.

Rubin prevailed. The March 20, 2000 letter ultimately sent to the FDA contained her edits, the language Dr. Flicker said was misleading.[94] The letter did not disclose that the patients dispensed the pink pills were "automatically unblinded" as Dr. Tiseo stated in his March 2, 2000 fax to Forest's investigators, the researchers conducting the study for the company.[95] Nor did it disclose the integrity of the blind was "unmistakenly violated," as Dr. Flicker had stated.[96] The letter did, however, concede:[97]

> For reporting purposes, the primary efficacy analysis will exclude…potentially unblinded patients….

Forest recognized the data was corrupted and promised a "full complement of 160 patients" would still be "enrolled under *standard* double-blind conditions [emphasis added]."[98] Thus, even though Forest failed to be straightforward about the unblinding, it would not affect the results because Forest promised—per the protocol—to exclude the unblinded patients from the primary analysis of the study results.

Forest claimed later to have enrolled a complement exceeding 160 patients ostensibly under standard double-blind conditions, not including the unblinded patients Forest promised the FDA to remove from the primary efficacy analysis.[99] (It is uncertain and an open question whether the investigators were unblinded to the entire cohort of patients since they had to replace the bottles of pink tablets with bottles of white tablets, potentially revealing which of the "full complement" were assigned to Celexa.)

After Celexa Study 18 was completed and Forest became aware of the study results, the company did not make good on its promise to the FDA.[100] Forest included the unblinded patients in the primary efficacy analysis—combining the data from the unblinded patients with the blinded cohort. The impact on the study results was significant. Without the unblinded patients, all the primary and secondary endpoints of the study were negative; the study was a failed study. [101] The study results only became slightly positive when the unblinded patients were inappropriately included.[102]

Dr. Heydorn, who was responsible for drafting and finalizing Forest's clinical study report on Celexa Study 18, was never told the nine patients were actually unblinded or that Forest had promised the FDA to exclude those patients from the primary analysis.[103] When Dr. Heydorn was shown the internal Forest documents at his deposition indicating Forest executives knew the nine patients were indeed unblinded, he conceded he would have written the final study report differently:[104]

> Q: Do you have any regrets about your involvement with the CIT-MD-18 [Celexa Study 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* (emphasis added).

Secondary Results

Secondary measures are another check on the results of antidepressant studies. Table 10 summarizes the secondary results of Forest's four pediatric studies.[105]

As seen in Table 10, in Celexa Study 94404 all of the secondary results supported the primary result that there was no statistically significant difference between the drug and placebo.

In Celexa Study 18, all the secondary results supported the primary result that there was no statistically significant difference between the drug and placebo when properly analyzed. All the statistical analyses of the secondary results contradicted rather than supported Forest's improper statistically significant finding for the primary result using the LOCF method. Like Study 18's secondary measurement results, its OC results were not statistically significant even with the unblinded patients included. Thus, each of the additional/secondary efficacy measurements were consistent with the negative primary result that excluded the unblinded patients. This is further evidence that Study 18's primary outcome measure did not statistically significantly outperform placebo and was therefore not a positive study.

In Lexapro Study 15, all the secondary results corroborated the primary result that there was no statistically significant difference between the drug and placebo, not even a small, clinically insignificant difference—between the drug and placebo.

For Lexapro Study 32, Forest eliminated all of the secondary measures but one, the Clinical Global Impressions-Improvement scale. The score on the scale ranges from 1, very much improved, to 7, very much worse.[106] The adjusted difference between Lexapro and placebo was extremely small, less than a third of a point: 0.3.[107] Thus, this very small difference in one secondary result supported the primary result that there was no clinically significant difference between the drug and placebo. The statistical analysis of the secondary result supported the statistical analysis of the primary result by the LOCF method (but not the OC method) that the small difference between the drug and placebo was statistically significant; the p-value was 0.008. Once again, this result demonstrates that statistical significance is clinically meaningless when the difference is so small: a fraction of a point on the measurement scale.

Table 10

Primary and Secondary Results—Active Drug vs. Placebo

Drug	Study	Measure	Clinically Significant Difference?	Statistically Significant Difference?
Celexa	94404	*Primary*		
		1. K-SADS-P	No	No
		Secondary		
		2. K-SADS-P Response	No	No
		3. MADRS	No	No
		4. MADRS Response	No	No
		5. MADRS Remission	No	No
		6. BDI	No	No
		7.GAF	No	No
		8. LES	No	No
Celexa	18	*Primary*		
		9. CDRS-R	No	No
		Secondary		
		10. K-SADS-P	No	No
		11. CGI Severity	No	No
		12. CGI Improvement	No	No
		13. CGAS	No	No
Lexapro	15	*Primary*		
		14. CDRS-R	No	No
		Secondary		
		15. CGI Severity	No	No
		16. CGI Improvement	No	No
		17. CGAS	No	No
Lexapro	32	*Primary*		
		18. CDRS-R	No	Yes
		Secondary		
		19. CGI Improvement	No	Yes

Dose Response Relationship

Typically, if a drug is beneficial, more of the drug produces more benefit. This phenomenon is known by a variety of terms including a dose response relationship, a biological gradient, or a dose-dependent response. As a further check on whether or not Celexa and Lexapro offered any benefit to pediatric patients, Forest analyzed the data looking for evidence of a dose response relationship in its four studies. These analyses looked at the children treated with Celexa or Lexapro whose depression scores improved during the studies to see if there was a correlation between their dose and the degree of improvement. That is: Did the children on higher doses of the drug improve more than children on lower doses? The results of Forest's analyses are summarized in Table 11.[108]

Table 11
Dose-Response Relationship

Drug	Study	Dose Response
Celexa	94404	No
Celexa	18	No
Lexapro	15	No
Lexapro	32	No

As seen in Table 11, there was no evidence of a dose-response relationship in any of Forest's four pediatric studies, additional evidence that Celexa and Lexapro are unlikely to confer benefit to pediatric patients.

Forest's Longer-Term Study 32A

To examine the question of whether Lexapro was effective in longer term treatment, Forest conducted a 16-week, double-blind, placebo-controlled extension of Lexapro Study 32, which had lasted eight weeks, bringing the total length of treatment to 24 weeks, or six months. This longer-term study was called Lexapro Study 32A.[109] Over the course of longer-term treatment, 67% of the pediatric patients on Lexapro were treatment failures, dropping out prematurely.[110] A smaller percentage of patients treated with placebo, 62% dropped out prematurely.[111] Moreover, for those children still in treatment at the end of six months, there was no significant difference—either clinically or statistically—between those treated with Lexapro and those treated with placebo.[112] Thus, longer term, Lexapro was not effective for treating depressed pediatric patients. Within six months, most children were treatment failures, stopping the drug due to lack of efficacy, intolerable side effects, and/or for other reasons. And, for those

children who were able to tolerate the drug for six months, Lexapro offered no significant advantage over placebo.

Summary

In summary, Forest's four studies of Celexa and Lexapro demonstrated that the drugs offer no clinical benefit to pediatric patients. In all 19 primary and secondary measures in the studies, Forest's antidepressants offered no clinically significant advantage over placebo. In only one study did Lexapro slightly outperform the drug, but the difference was too small to be clinically significant. In real life, clinical practice doctors, pediatric patients, and their parents would not be able to detect such small, marginal at best, differences between the drugs and placebo. In real life, doctors and parents seeing pediatric patients improve on Celexa or Lexapro may think the improvement was due to the drugs, having no idea that all or most of the improvement would have occurred on placebo.[113]

3. Forest Suppressed Celexa Study 94404 (the Lundbeck Study)

As seen in Table 12, the Lundbeck 94404 and Wagner 18 studies were both concluded in April 2001. Lundbeck notified Forest of the Lundbeck study's summary results shortly thereafter on July 16, 2001.[114] Karoline Als (Lundbeck Clinical Research Manager) emailed the summary results to Ivan Gergel (Forest Senior VP Scientific Affairs), who forwarded them to Dr. Paul Tiseo (study medical monitor), Julie Kilbane (project manager), Dr. Charles Flicker (Forest Senior Director of CNS research), and Dr. Lawrence Olanoff (Forest VP Scientific Affairs).[115] The email read:[116]

> Please find enclosed the results of study 94404 [the Lundbeck study], *which must be treated strictly confidentially* [emphasis added].

Table 12

The Lundbeck and Wagner Celexa Pediatric Studies

Name	Lundbeck	Wagner
Study Number	94404	18
Dates	1996-2001	2000-2001
Completed	April 2001	April 2001
Age of Patients	13 – 18	7 – 17
No. Celexa Patients	121	89
No. Placebo Patients	112	85
Total No. Patients	233	174
Duration	12 weeks	8 weeks
Suicidal Patients	Yes	No
Hospitalized Patients	Yes	No
Early Placebo Responders	Yes	No
Representative of Pediatric Patients	Yes	No
Efficacy Results	Placebo outperformed Celexa. The small difference was not clinically or statistically significant.	Celexa outperformed placebo (only by including the unblinded patients). According to Forest, the small difference was statistically significant.
Safety Results	Higher rate of suicidal behavior in adolescents taking Celexa	According to Forest, Celexa did not make more pediatric patients suicidal
Reported to FDA	March 21, 2002	April 8, 2002
Publically Announced	Forest suppressed the study. It was revealed in a *New York Times* exposé in 2004.	Forest promoted the study in a December 2001 presentation and press release before the study report was even completed or submitted to the FDA.
Publication Date	June 16, 2006, two years after the *New York Times* exposé.	June 1, 2004

The Lundbeck study, Celexa Study 94404, was a failed study. Indeed, the pediatric patients treated with placebo did slightly better than those treated with Celexa, although the difference was not clinically or statistically significant.[117] Still worse, in the Lundbeck study, there was a higher rate of pediatric patients taking Celexa who experienced suicidality compared to placebo.[118] The percentage of adolescents treated with Celexa who became suicidal was more than double the percentage treated with placebo, 11.6% versus 4.5%.[119] Celexa increased the risk of adolescents becoming suicidal 2.6-fold by comparison to placebo.[120]

As seen in Table 12, Forest suppressed the results of the Lundbeck 94404 study. The company did not take the initiative to publically announce the results, which were only announced years later in a 2004 *New York Times* exposé, as discussed below.[121] By contrast, Forest moved quickly to announce the misleading results of Wagner Study 18, even before the company had completed its full clinical study report to the FDA in 2002 and before publishing the study in 2004.[122]

Forest Quickly Promoted
the Results of the Wagner Study

On December 13, 2001 the misleading results of the Wagner[123] Study 18 were presented at the annual convention of the American College of Neuropsychopharmacology (ACNP).[124] Forest issued a press release announcing the results of the Wagner study to coincide with the conference. According to Forest's misleading press release:[125]

> Celexa was shown to reduce symptoms of depression in adolescents and children with major depressive disorder to a significantly greater extent than placebo….The study also showed that Celexa was well tolerated…."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," said Karen Dineen Wagner, MD, PhD, Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch in Galveston, and the study's lead author. "Celexa is now one of the few therapies for which we have data showing safety and efficacy for this population"….The more common side effects associated with use of Celexa were nausea, influenza-like symptoms, and rhinitis [runny nose].

Forest's press release promoted Celexa as safe (i.e., "well tolerated") for pediatric patients. While exaggerating the efficacy of Celexa in Wagner Study 18 and promoting the drug as safe for pediatric patients, Forest failed to mention the Lundbeck 94404 study.

Wagner's presentation, which was ghost-written by Forest and a contractor, did not mention the negative results of Celexa Study 94404 or the fact that all of the secondary efficacy endpoints for Celexa Study 18 were negative, and it did not disclose the primary efficacy measure for the study only achieved statistical significance by inappropriately including data from unblinded patients.[126] Instead, Forest only had Wagner present the "positive" results of the primary endpoint, misleadingly claiming Study 18 was evidence that Celexa was effective in children.[127]

With the "positive" data presented at a scientific conference, Forest immediately started using the data to promote the efficacy of Celexa in children.[128]

Forest then paid Dr. Wagner to travel around the country promoting Celexa to physicians, in meetings and formal Continuing Medical Education programs, claiming the drug was effective in children based on the corrupted results of Celexa Study 18. Forest sponsored a Continuing Medical Education program hosted and presented by Dr. Wagner, where she cited and discussed the "positive" data from the American College of Neuropsychopharmacology presentation to support the misleading claim Celexa was safe and effective in children.[129] Forest sales representatives were specifically instructed to invite physicians to the company's Wagner Continuing Medical Education program.[130] Like her American College of Neuropsychopharmacology presentation, Wagner's Continuing Medical Education presentation did not disclose Celexa Study 94404, the negative secondary endpoints for Celexa Study 18, nor the unblinding issue.[131] Instead, the presentation ended with a multiple choice question:[132]

> Which of the following medications has been shown to be more effective than placebo in the treatment of depression in children and adolescents?

The alleged correct answer was: Celexa.[133]

The concealment of Celexa Study 94404 in Dr. Wagner's American College of Neuropsychopharmacology presentation and Continuing Medical Education programs was apparently deliberate.[134] According to Dr. Heydorn, who was responsible for Forest's clinical study report for Celexa Study 18, there was a concerted effort to publicize the alleged "positive" data about the pediatric use of Celexa from Study 18 before divulging the negative data from Celexa Study 94404:[135]

> 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. . . . I think most of the individuals associated with the citalopram project held that view….
> Q: And why was it that you would have preferred at the time that the positive data be put in the public domain before the negative data of 94404 was put in that domain?
> A: Clearly from the company's perspective, having the positive data published was a positive move for the compound….

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.

Dr. Heydorn's testimony is corroborated by an internal Forest email, dated November 28, 2002, in which an associate from Lundbeck wrote to him:[136]

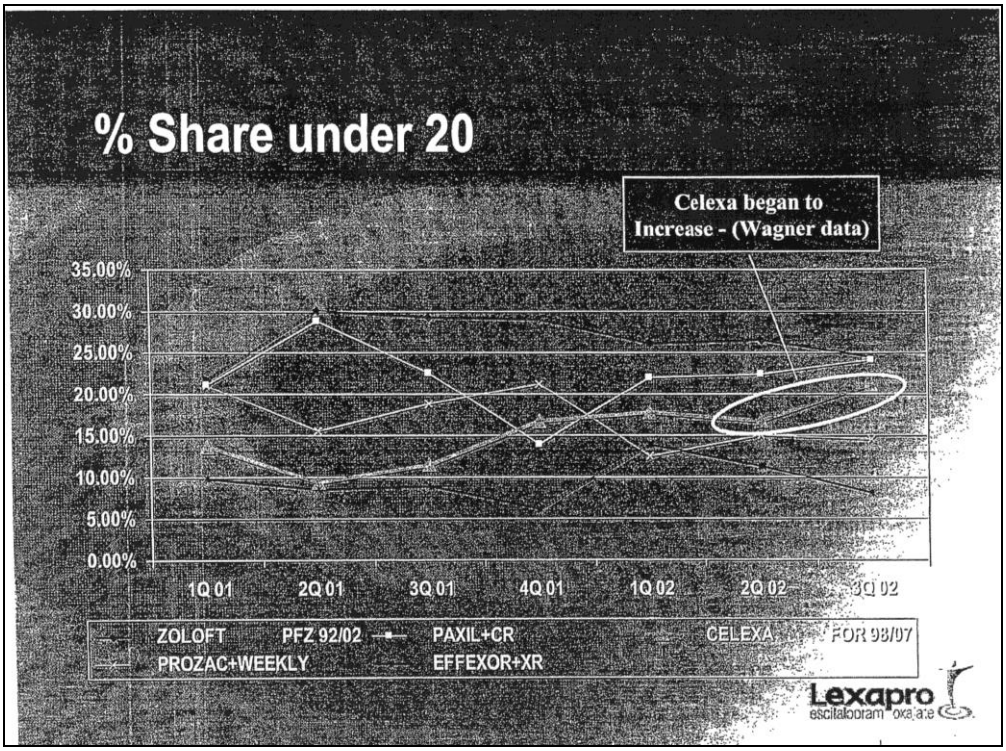
> Investigators in the Lundbeck sponsored study seem eager to submit a manuscript…. *I wanted to make sure that the positive data are in the public domain before their negative data get out* [emphasis added].

Apparently, the researchers who conducted the Lundbeck 94404 study wanted to published the results, but were held back until the misleading "positive" results of the Wagner Study 18 were publicized.

Pediatric Prescriptions for Celexa Increased after Forest Announced the Results of the Wagner Study

According to a December 3, 2002 internal Forest presentation regarding "Lexapro Strategic Operations," prescriptions for Celexa for younger patients began to increase in 2002 after the company announced the results of Wagner Study 18.[137] Figure 4 reproduces a graph from the internal Forest Power Point presentation.[138] As seen in Figure 4, Forest was tracking sales of antidepressants including Prozac, Zoloft, Paxil, Celexa, and Effexor for patients under the age of twenty, including children and adolescents. Forest's graph in Figure 4 tracks market share in this age group for each of the antidepressants. The graph specifically highlights that sales of Celexa for younger patients "began to increase" in 2002 due to the "Wagner data." Thus, Forest was tracking the effect of the company's announcement of its misleading "positive" results of the Wagner Study 18 on Celexa sales while suppressing the results of the Lundbeck 94404 study. Moreover, the graph was in a Forest presentation entitled "*Lexapro* Strategic Operation," linking the fate of Lexapro to its parent drug Celexa and the misleading Wagner data. Ultimately, Lexapro became a $2 billion a year blockbuster bestselling drug.[139]

Figure 4
Market Share: Patients Under 20 Years Old



In February 2004 the FDA Warned
Antidepressants May Make Pediatric Patients Suicidal

In February 2004, the FDA held a hearing and introduced a warning regarding antidepressants making pediatric patients suicide.[140] Later in the year, after analyzing all the pediatric data, the warning became a black box warning in the prescribing information for all antidepressants, including Celexa and Lexapro.

Forest Published the Wagner Study
in June 2004

In June 2004, Forest published the misleading Wagner results in the prominent *American Journal of Psychiatry*.[141] Wagner was the named, lead "author," but it has since come to light that Forest had the article ghostwritten by a "medical communications company."[142] Three additional co-authors were in-house Forest employees. Moreover, the published version failed to disclose Wagner's close ties to the pharmaceutical industry.[143]

According to Forest's published version of Wagner Study 18:[144]

> This randomized, placebo-controlled, double-blind trial provides evidence that Celexa produces a statistically and clinically significant reduction in depressive symptoms in children and adolescents. Specifically, Celexa was superior to placebo….

Forest made no mention of the suppressed Lundbeck 94404 study in its publication of the Wagner study. At her deposition, Dr. Wagner testified that at the time the published version was being written, she did not know the Lundbeck study existed; Forest had not informed her of its other, failed Celexa study in which the drug had an increased rate of suicidality.[145] Wagner testified she only learned of the Lundbeck study when the public did, from a *New York Times* exposé discussed below.

Regarding psychiatric side effects in particular, in the published version of Wagner Study 18, Forest said:[146]

> There were no serious adverse events observed in the Celexa group.…In this study, psychiatric events [including suicidality] were reported infrequently by patients randomly assigned to Celexa. For example, adverse events associated with behavioral activation (such as insomnia or agitation) [i.e., the precursor side effects to suicidality] were not prevalent in this trial [emphasis added].

Forest used publication of Wagner Study 18 to misleadingly reassure doctors, patients, and their families, while suppressing the suicidality results of the Lundbeck 94404 study. Given the close relationship between Celexa and Lexapro, Forest suggested Lexapro would produce similar results:[147]

> It is tempting to speculate that similar clinical results would be achieved in children and adolescents treated with the recently developed single isomer compound Lexapro….

Thus, Forest used publication of Wagner Study 18 to promote Lexapro for children and adolescents even though neither Celexa nor Lexapro was approved by the FDA for this patient population.

Letters to the Editor Criticized the Wagner Study

Following Forest's publication of the Wagner study, a number of academic psychiatrists wrote letters to the editor of *American Journal of Psychiatry* critical of Wagner and

Forest's claim that Celexa is effective for pediatric depression.[148] Said one of the letters to the editor written by eight psychiatrists:[149]

> This response rate, while in itself marginal compared to other studies of antidepressants, does not in itself show that Celexa is better than placebo….We would argue that the authors did not provide sufficient evidence to support their claim that Celexa produces a statistically and clinically significant reduction in depressive symptoms in children and adolescents. We are surprised that the most respected psychiatric journal in the world published a study that is misleading to its readers in the extreme [emphasis added].

The psychiatrists did not even know Forest's "positive" results in the Wagner publication relied on inappropriately counting unblinded patients.

The New York Times' June 2004 Exposé

On June 21, 2004, the *New York Times* published an exposé on Forest's suppression of Lundbeck Study 94404.[150] The *New York Times*' exposé, entitled "Medicine's Data Gap," coincided with Forest's publication of the Wagner study.[151] Said the *New York Times*:[152]

> The issue of *The American Journal of Psychiatry* that hit the desks of its 37,000 readers this month reported test results for the antidepressant drug Celexa, indicating that it could help children and teenagers….But neither the article nor the 27 scholarly footnotes that accompanied it mentioned another major drug-industry-sponsored trial [the Lundbeck study] completed in 2002, which found that Celexa did not help depressed adolescents any more than a placebo. Nor would the article's reviewers have been likely to find any clues of that trial's existence. The results of that trial were first noted last year on a single line of a chart that appeared on Page 96 of a textbook—one written in Danish.

Obviously, American doctors could not know of the Lundbeck study from a textbook written in Danish with a line referencing the study in a table. In fact, the Lundbeck study was completed in 2001, a year earlier than reported in the *New York Times.*[153] According to the *New York Times*:[154]

> In written responses to inquiries from *The New York Times*, Forest stated that the negative Celexa test, sponsored by a related company, was not

> mentioned in the recent article because "there was no citable public reference for the authors to examine."

Forest's claim that it could not mention the Lundbeck study in the Wagner publication because it was not published was spurious, as the *New York Times* recognized:[155]

> But drug makers often announce trials with positive results without waiting for the results to be published. Forest, for example, *issued a news release three years ago* that highlighted the outcome of the positive [Wagner] Celexa trial. That was shortly after the test's completion, when the findings were first presented at a medical conference, but before the study was even submitted to *The American Journal of Psychiatry* for consideration. Three of the authors of the Celexa drug article in this month's issue are Forest employees [emphasis added].

According to the *New York Times:*[156]

> Both companies [Forest and Lundbeck] also said that they did not promote the drug's use in children because regulators had not approved it for pediatric use.

This was not true. As discussed below, Forest has since pled guilty to civil and criminal charges brought against the company by the Department of Justice in relation to its off-label promotion of Celexa and Lexapro for children and adolescents.[157] Forest paid hundreds of millions of dollars to resolve a number of related charges.[158]

Forest's Misleading Testimony at a September 2004 Congressional Hearing

On September 9, 2004, the House of Representatives Committee on Energy and Commerce held a hearing on "Publication and Disclosure Issues in Pediatric Antidepressant Clinical Trials [Studies]."[159] Dr. Lawrence Olanoff, executive vice president of Forest Laboratories and head of the Forest Research Institute testified on behalf of the company.[160] Dr. Olanoff testified:[161]

> I am a medical doctor. My medical specialty is in clinical pharmacology, and I have devoted my entire career to the development of pharmaceuticals. The topic of today's hearing is the disclosure of clinical trial results. Forest routinely discloses the results of its sponsored clinical

> trials and believes its practices in this regard have been entirely appropriate and in full compliance with the law.

But, Forest had suppressed the results of Lundbeck Study 94404 and was continuing to be misleading about the suicidality results even after the *New York Times* exposé revealing the existence of the study. Moreover, Olanoff testified:[162]

> I want to emphasize that because the FDA has not approved pediatric labeling for our products, Forest has always been scrupulous about not promoting the pediatric use of our antidepressant drugs, Celexa and Lexapro. That is the law, and we follow it.

In fact, Forest was aggressively promoting Celexa and Lexapro off-label for pediatric patients, as discussed below.

Forest Published
Lexapro Study 15 in 2006

In March 2006, Forest published Lexapro Study 15, the failed Lexapro study the company had announced in the June 2004 press release discussed earlier following the *New York Times* exposé.[163] In Lexapro Study 15, the drug failed to be significantly more effective than placebo for children and adolescents.[164] Forest's report entitled, "A Double-Blind, Randomized, Placebo-Controlled Trial of Lexapro in the Treatment of Pediatric Depression" was published in the prominent *Journal of the American Academy of Child and Adolescent Psychiatry*.[165] Wagner was again the lead of five co-authors. Dr. Robert Findling of the Case Western Reserve Medical School in Cleveland, Ohio, was the second academic co-author. The other three co-authors were all in-house Forest employees, including Jeffrey Jonas, Forest's Vice President of Central Nervous System drugs.

By 2004, medical journals and the profession had become concerned about seemingly independent authors who, in fact, have extensive ties to the pharmaceutical industry. For this reason, medical journals began requiring disclosures. Wagner's disclosure read:[166]

> Disclaimer: Dr. Wagner has received research support from Abbott Laboratories, AstraZeneca, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Organon, Pfizer, and the National Institute of Mental Health, and serves as a consultant/advisory board member for Abbott Laboratories, Bristol-Myers Squibb, Cyberonics, Eli

> Lilly, Forest Laboratories, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Novartis, Ortho-McNeil, Otsuka, Pfizer, UCBV Pharma, Wyeth-Ayerst, and the NIMH Advisory Council.

In other words, Wagner had extensive ties to the pharmaceutical industry that were not disclosed two years earlier in Forest's publication of Study 18.[167] Findling's disclosure read:[168]

> Dr. Findling receives or has received research support and has acted as a consultant or served on a speaker's bureau for Abbott, AstraZeneca, Bristo-Myers Squibb, Celltech-Medeva, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Eli Lilly, New River, Novartis, Otsuka, Pfizer, Sanofi-Synthelabo, Shire, Solvay, and Wyeth-Ayerst.

In other words, Findling also had extensive ties to the pharmaceutical industry not disclosed two years earlier in Forest's publication of Study 18, of which he was a co-author.

Lexapro Study 15 included children and adolescents six to seventeen years old.[169] The primary efficacy measure was the Children's Depression Rating Scale-Revised (CDRS-R). In the publication, Forest acknowledged the study was a failed study:[170]

> Lexapro did not significantly improve CDRS-R scores compared to placebo at endpoint… [emphasis added].

When a study is a failed study, sometimes pharmaceutical companies perform after-the-fact analyses to statistically manipulate the results to claim the drug did better than placebo. The practice is known as "data dredging."[171] In the published version of Lexapro study 15, Forest manipulated the results to claim Lexapro was superior to placebo for a subset of adolescent patients.[172] According to Forest's abstract, or summary, of the study:[173]

> In a post hoc [i.e., after-the-fact] analysis of adolescent (ages 12-17 years) completers, Lexapro significantly improved CDRS-R scores compared with placebo….

Forest provided a p-value in the abstract, or summary, of 0.047, suggesting Lexapro was statistically significantly superior to placebo for the subset of adolescent patients. But, in the text of the article, Forest acknowledged the subset of adolescent patients was too small to be adequately powered to distinguish between the drug and placebo; that is,

there were too few adolescent patients. Thus, the manipulated results and p-value in the summary were scientifically of little value. Many busy doctors do not have enough time to read more than the summary of a published study. Doctors rely on pharmaceutical companies to provide fair, balanced, honest information in the summaries. Forest was using the manipulated, misleading results to promote Lexapro for adolescent patients, putting patients in this vulnerable age group at risk.

In 2006, the Lundbeck Study Is Published

In June 2006, the results of the Lundbeck 94404 study were published, almost two years after the FDA announced in 2004 the black box warning that antidepressants can make pediatric patients suicidal, five years after the study was completed in 2001, and five years after Forest began promoting the results of the Wagner Study 18 in 2001. In contrast to the Wagner Study 18 promoting Celexa's alleged safety published in the prominent *American Journal of Psychiatry* and the failed Lexapro Study 15 promoting Lexapro's alleged safety published in the prominent *Journal of the American Academy of Child and Adolescent Psychiatry*, the Lundbeck Study 94404 was published in the more obscure *Journal of Clinical Psychopharmacology*.[174] Anne-Liis von Knorring was the lead author of the published version, which was entitled "A Randomized, Double-Blind Placebo-Controlled Study of Celexa in Adolescents with Major Depressive Disorder." One of von Korring's co-authors was an in-house employee of Forest's Danish affiliate, the Lundbeck pharmaceutical company. The published version acknowledged the Lundbeck Study 94404 was a failed study:[175]

> The present trial [study] provides no evidence that Celexa results in a statistically significant reduction in depressive symptoms compared with placebo in this population of adolescent patients.

4. The FDA Approved Lexapro for Depressed Adolescents Using Data from the Wagner Study 18

By its own admission, the FDA has a relatively low minimal standard for approving antidepressants, whether for adults or children. The FDA generally requires two studies in which patients on the drugs do better than patients on placebo. The difference between the drug and placebo can be small, so long as it is statistically significant, even if it is so small that it is not clinically significant.

In 2009, the FDA approved Lexapro for depressed adolescents on the basis of Wagner Celexa Study 18 and Lexapro Study 32. The FDA allowed the company to ignore its other two failed studies (Lexapro Study 15 and Celexa Study 94404). Even without knowing that Celexa Study 18 was actually negative, the FDA's approval of Lexapro for adolescents was controversial. In my opinion, given the available evidence, the approval was not warranted.

The FDA's Standard for Approving Antidepressants

FDA officials and advisors have commented since the beginning of the modern antidepressant era that the agency's standards for approving antidepressants are minimal according to the law. For instance, during an FDA advisory committee meeting related to one of the SSRI antidepressants, Dr. Paul Leber, the Division Director of the FDA at the time explained:[176]

> I think you have to understand that when we face an application from a regulatory perspective, we are asked to face what the law requires us to do.

Dr. Leber stated:[177]

> We have to look at the application submitted to us and recognize, in a way, that we can exhort people [i.e., pharmaceutical companies] to do more. But the law did not set out a very Draconian or Procrustean set of standards that have to be met.

Because in antidepressant studies the differences between the drugs and placebos are so small, pharmaceutical companies often have to perform repeated, failed studies in order to obtain two studies in which the difference is statistically significant, even if it is not clinically significant. The FDA allows pharmaceutical companies to ignore these multiple failed studies; the agency does not require the companies to combine the efficacy results of the studies. Dr. Leber explained to the advisory committee:[178]

> The law, as far as I know, never discussed multiplicity [i.e., the law does not address drugs where multiple studies failed to show efficacy].

Commenting on the FDA only requiring two positive studies and allowing pharmaceutical companies to ignore multiple other failed studies, Dr. Leber pointed out that the FDA does "not have a systematic program" to analyze the combined results of all positive and negative studies, but admitted "Maybe there ought to be."[179]

Commenting on the FDA only requiring a statistically significant result, even if it is so small that it is clinically insignificant, Dr. Leber suggested the advisory committee members they could tell the FDA:[180]

> Look, we think the standards in this field are terrible. People have been getting away with non-substantive efficacy for years. We'd like you to change your standards [emphasis added].

But, Dr. Leber warned that, if the advisory committee were to make such a recommendation:[181]

> Where do we go from there? What about all the drugs that are out there? How many of them can meet that standard? Can we enforce it legally, and so on and so forth?

The chairman of the advisory committee, Daniel Casey, responded:[182]

> I do not think that we want to change the rules in the middle of the game or near the end of the game.

Dr. Leber commented:[183]

> I think over the past 27 years or so since people have been looking at that question, we have taken changes on the HAM-D [Hamilton depression rating scale], the Clinical Global Impression of severity, POMS [Profile of Mood States] factors and a variety of other things and taken those as testimony or indicators of efficacy. But that is tradition. That is not truth.

Indeed, Dr. Leber admitted:[184]

> I have no idea what constitutes proof of efficacy, except on the basis of what we, as a Committee, agree on an as *ad hoc* case as there needs to be. You can be guided by the past but the inference is an abstraction—what is an antidepressant?

In a later December 24, 1991 memo recommending approval of the antidepressant in question, Dr. Leber warned that the FDA's approval was likely to be criticized because the FDA is not "as demanding as it ought to be in regard to its standards for establishing the efficacy of antidepressant drug products."[185]

Dr. Leber stated, however, that approval does not mean a company is "entitled to every claim, every superlative ever made.…"[186] In other words, pharmaceutical companies should not make exaggerated claims as Forest has done exaggerating the efficacy of Celexa and Lexapro for pediatric patients while minimizing the serious risks.

In 2008, Forest Applied for a Pediatric Indication for Lexapro

On May 22, 2008, Forest submitted an application for approval of Lexapro for use in adolescent depression and asked for expedited consideration.[187] In support of its application, Forest submitted Celexa Study 18 and Lexapro Study 32. Two additional studies, Lexapro Study 15 and Celexa Study 94404 "contributed to the Lexapro adolescent safety database, but could not be used to support efficacy claims."[188]

In 2009, the FDA Approved Lexapro for Pediatric Patients

On March 20, 2009, the FDA approved Lexapro for the treatment of depressed adolescents. The FDA's approval was based on Lexapro Study 32 and the corrupted results of Celexa Study 18.[189] Forest issued a press release in which its CEO, Howard Solomon, stated:[190]

> We have long believed that Lexapro would be of benefit for the treatment of depression in adolescents and that is why we undertook the several studies described in the package insert. We are enormously gratified that Lexapro will be available for depressed adolescents who so much require the benefits which Lexapro has made available for depressed adults for the past seven years.

The FDA's Approval Has Been Controversial

Even though the medical profession and public are not aware Forest improperly included unblinded patients in its analyses of Celexa Study 18 to win approval of Lexapro for adolescents, the FDA's approval has been controversial. For instance, the website Psychcentral run by Dr. John M. Grohol pointed out:[191]

> Lexapro…has been approved by the U.S. Food and Drug Administration (FDA) to treat depression in children ages 12 to 17. This happened just weeks after the drug's maker, Forest Laboratories, was charged by

> prosecutors of illegally marketing this and another drug (Celexa) to children and paying kickbacks to doctors for prescribing them. Digging into the studies that resulted in the FDA's approval demonstrates a clearly mixed picture of Lexapro's effectiveness in children….

As Dr. Grohol pointed out:[192]

> So you have two studies that show effectiveness and two that do not, and you still approve because, according to Forest, "it's very difficult to do depression studies"?! That's the strangest rationale I've ever heard from a pharmaceutical company defending its product's less-than-stellar data.

Dr. Carlo Carandang at IWK Health Center in Halifax, Nova Scotia and three colleagues wrote an article in the November 2011 issue of the *Journal of the Canadian Academy of Child and Adolescent Psychiatry* entitled "A Review of Lexapro and Celexa in Child and Adolescent Depression."[193] The authors criticized the FDA's approval of Lexapro, pointing out: "there was controversy surrounding this approval."[194] They explained:[195]

> While only one RCT [randomized, controlled trial, i.e., study] for Lexapro was statistically superior to placebo on the primary outcome measure, according to Forest Laboratories, Inc…the FDA decision to approve Lexapro was based on two RCTs—the Lexapro RCT with positive results and an earlier trial with Celexa.

The authors pointed out the irony in the timing of the FDA's approval, stating:[196]

> The FDA approval decision for Lexapro came shortly after filing of a federal civil suit alleging Forest Laboratories, Inc. had illegally marketed Lexapro and Celexa for off-label use in children and adolescents from 1998 to 2005. The suit also alleged the company suppressed publication of a negative Celexa trial [i.e., Celexa study 94404, the Lundbeck study], and reports of increased suicidality in pediatric patients.

The authors reported that the lawsuit was "eventually settled in September 2010 for the sum of $149 million" as described in the next section of this report.[197] They went on to explain:[198]

> The [Celexa trial] that formed part of the basis for Lexapro FDA approval was alleged to have been written and submitted by a medical "ghost-writer" on behalf of Forest Laboratories, Inc. In April 2009, one month

> after the FDA approval for Lexapro in adolescents was granted, Forest Laboratories admitted that a medical communication company, Prescott Medical Communications Group was not acknowledged as a contributor to the article at the time of publication.

Carandang and his co-authors pointed out an important factor in evaluating the credibility of the studies forming the basis of the FDA's decision:[199]

> The research groups that have studied Celexa and Lexapro for pediatric depression in RCTs are not independent groups, with the exception of the von Knorring group from Sweden [i.e., Celexa study 94404]. However, the RCT by this group was a negative trial.

Carandang's skepticism was even without knowing Forest improperly included unblinded patients into its analysis of Celexa study 18, rendering the study negative.

I agree with the authors statement:[200]

> From these data, Lexapro and Celexa should not be considered for first-line treatment of adolescent depression, given the lack of replication of positive studies by independent groups.

I also agree with the authors' conclusion:[201]

> The US FDA approval of Lexapro was premature, given the available evidence.

5. In 2010, Forest Pled Guilty to Off-Label Marketing Its Antidepressants for Pediatric Patients

In September 2010, Forest pled guilty to both the criminal and civil charges brought by the United States Department of Justice that the company suppressed the Lundbeck study, while using the Wagner Study 18 to aggressively promote Celexa and Lexapro off-label for children and adolescents. According to a government press release issued on the day the guilty plea was announced "Forest used illegal kickbacks to induce physicians and others to prescribe Celexa and Lexapro" to children.[202] On related charges, in the guilty plea Forest acknowledged that it "acted knowingly and corruptly."[203]

Forest's guilty plea is a lengthy document with numerous attachments. According to the Information attached to the guilty plea:[204]

> In 1998, after the FDA approved Celexa for treatment of adult depression, Forest Pharmaceuticals began promoting, distributing and selling Celexa throughout the United States….From the outset, Forest Pharmaceuticals was well-aware that the FDA had not approved Celexa for treatment of any conditions other than adult depression. Moreover, in or about April 2002, Forest Labs, in an attempt to obtain, *inter alia*, a pediatric indication for Celexa, submitted data to the FDA from two double-blinded, placebo-controlled studies involving the use of Celexa in children. One of these studies (hereafter referred to as the "Forest study"), which had been sponsored by Forest Labs, had been conducted in the United Sates, [i.e., Celexa study 18, the Wagner study]. The Forest study had positive results, that is, the study indicated that Celexa was more effective than placebo in treating pediatric patients suffering from depression [i.e., the statistically significant but clinically insignificant finding, the corrupted result only achieved by counting the unblinded patients]. The other study (hereafter referred to as the "European study"), had been conducted in Europe and sponsored by the Danish company that developed and owned the rights to Celexa [i.e., Celexa study 94404, the Lundbeck study]. The European study had negative results, that is, the study did not show Celexa to be any more effective than placebo in treating pediatric depression. On or about September 23, 2002, the FDA denied Forest Labs' request for pediatric indication for Celexa, stating in part that the European study "is a clearly negative study that provides no support for the efficacy of Celexa in pediatric patients with [major depressive disorder].
>
> Forest Pharmaceuticals was equally well-aware that promoting a drug product for indications other than those explicitly approved by the FDA was illegal. For example, in or about August 2000, a Regulatory Affairs employee at Forest Labs circulated a document entitled "Promotion Guidelines for Sales Representatives" and strongly recommended that the document be incorporated into sales training at Forest Pharmaceuticals, along with a signature page for each representative to sign confirming that he or she had in fact been trained on permissible and impermissible sales promotion. This draft document made clear that off-label promotion was illegal: "Sales representatives should never initiate, or engage in, discussions about off-label uses or solicit these requests from physicians."

> The draft document explained that "Indications, dosing, or formulations that are not approved and are not part of the Package Insert have not met the regulatory testing requirements for safety and effectiveness and cannot be promoted as such by Forest." The draft document further affirmatively advised that Forest Pharmaceuticals could not hire speakers or provide off-label discussion….Forest Pharmaceuticals did not adopt this draft document, nor did it for several years thereafter require sales representatives to sign a document that discussed the prohibition against off-label marketing.
>
> Beginning in 1998 and continuing thereafter through at least September 2002, Forest Pharmaceuticals promoted Celexa for use in treating children and adolescents suffering from depression, even though Celexa was not FDA-approved for pediatric use. Forest Pharmaceuticals' off-label promotion consisted of various sales techniques including: (1) directing Forest Pharmaceuticals sales representatives who promoted Celexa to make sales calls to physicians who treated children and adolescents; (2) promoting Celexa by various Forest Pharmaceuticals sales representatives for use in children and adolescents; (3) hiring outside speakers to talk to pediatricians, child psychiatrists, and other medical practitioners who specialized in treating children and adolescents about the benefits of prescribing Celexa to that patient population; and (4) publicizing and circulating the positive results of the double-blind, placebo-controlled Forest study on the use of Celexa in adolescents while, at the same time, failing to discuss the negative results of the second double-blind, placebo-controlled European study on the use of Celexa in adolescents.

With regard to Forest's sales representatives promoting Celexa for children and adolescents, the Information attached to the guilty plea states:[205]

> Forest Pharmaceuticals assigned its sales representatives to specific geographic regions throughout the United States. The sales representatives were supervised by Division Managers, who in turn were supervised by Regional Directors.
>
> In order to identify the potential market for Celexa, Forest Pharmaceuticals obtained data identifying medical practitioners who prescribed SSRIs [selective serotonin re-uptake inhibitor-type antidepressants]. Using this data, Forest Pharmaceuticals created "call panels," which were lists of medical practitioners who prescribed SSRIs.

> Forest Pharmaceuticals directed its sales representatives to make sales calls promoting Celexa to the medical practitioners on the "call panels." These Celexa "call panels" included, among others, thousands of child psychiatrists and pediatricians who specialized in treating children and adolescents. Forest Pharmaceuticals also directed its Celexa sales representatives to call on physicians who worked in the pediatric wards of hospitals.
>
> During sales calls, various Forest Pharmaceuticals sales representatives, acting at times with the knowledge and encouragement of their Division Mangers and Regional Directors, promoted Celexa for use in treating not only adult patients suffering from depression, but also for use in treating children and adolescents who were suffering from depression. Forest Pharmaceuticals sales representatives often documented these details through "call notes," thousands of which reflected off-label promotional activity directed at the use of Celexa in children and adolescents….At various times…, certain Forest Pharmaceuticals Regional Directors and Division Managers provided their sales representatives with copies of posters and journal articles on studies of Celexa for use in children and adolescents and directed the sales representatives to read the studies, and use them as sales aids in their details to physicians. Various Forest Pharmaceuticals Division Managers also directed sales representatives to show off-label studies to physicians, but not leave copies of those studies with the physicians so as to avoid detection that would get the sales representative and Forest Pharmaceuticals in trouble.

Regarding Forest using outside speakers to promote Celexa for children and adolescents, the Information attached to the guilty plea states:[206]

> Forest Pharmaceuticals sales representatives and Division Managers identified speakers from lists maintained and approved by Forest Pharmaceuticals to organize promotional lunches and dinners as part of which speakers were paid to give a talk about Celexa. Certain of Forest Pharmaceuticals' approved speakers were medical practitioners who specialized in treating children and adolescents suffering from depression, and Forest Pharmaceuticals paid these practitioners to give promotional talks on the use of Celexa in children and adolescents. Various promotional programs for Celexa organized by Forest Pharmaceuticals sales representatives explicitly focused on off-label pediatric and adolescent use: the programs had titles such as "Adolescent Depression,"

> "Adolescent Treatment of Depression," "Assessment and Treatments of Suicidal Adolescents," "Treatment of Child/Adolescent Mood Disorders," "Treatments in Child Depression," "New Treatment Options in Depressive Disorders in Adolescents," "Use of Antidepressants in Adolescents," "New Topics in the Treatment of Children with Depression," "Benefits of SSRIs in Child Psychology," "Treating Depression and Related Illnesses in Children, Adolescents and Adults," "Celexa in CHP/Ped Practice," "Uses of Celexa in Children," "Treating Difficult Younger Patients," "Treating Pediatric Depression," and "Treating Adolescent Depression."
>
> To obtain funding support for these promotional programs, Forest Pharmaceuticals sales representatives were required to submit paperwork to their Division Managers describing the proposed program, identifying the medical practitioners who were to be invited to the program, and predicting the expected return on investment from the attendees—that is, the anticipated increase in the number of Celexa prescriptions resulting from the attendees' attendance at the program. Forest Pharmaceuticals Division Managers and others within Forest Pharmaceuticals consistently approved these requests for funding for promotional programs focusing on the use of Celexa in children and adolescents that were directed to child psychiatrists and other medical practitioners who specialized in treating children and adolescents.

The Information attached to the guilty plea explicitly states Forest suppressed the results of the Lundbeck study, while aggressively promoting Celexa for children and adolescents:[207]

> In or about mid-2001, Forest Labs learned of the positive results from the Forest study and the negative results from the European study, and Forest Labs shared these results with the FDA. Although both studies concerned the use of Celexa to treat children and adolescents suffering from depression, Forest Pharmaceuticals treated the studies differently: 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 result, doctors and psychiatrists received incomplete and misleading information concerning all available known data pertaining to the efficacy of using Celexa to treat depression n children and adolescents.

> Forest Pharmaceuticals communicated this incomplete and misleading information in, among others, the following ways: (1) via discussions that Forest Pharmaceuticals sales representatives had with medical practitioners about the use of Celexa in treating children; (2) via promotional speeches made by pediatric specialists [like Dr. Wagner] who were hired by Forest Pharmaceuticals to talk about the use of Celexa in treating children and adolescents; and (3) via letters sent by Forest Pharmaceuticals Professional Affairs Department to medical practitioners who had requested from Forest Pharmaceuticals all available information and data concerning the use of Celexa in treating children and adolescents.

In the plea Forest specifically plead guilty to the charges:[208]

> Forest expressly and unequivocally further admits that it committed the offenses charged in the Information and is in fact guilty of those offenses. Forest agrees that it will not make any statements inconsistent with its explicit admission of guilt to these offenses.

Elsewhere in the guilty plea on related charges, Forest acknowledged that it "acted knowingly and corruptly."[209]

The guilty plea was signed by Forest's general counsel, Herschel Weinstein on September 15, 2010. According to his acknowledgment:[210]

> The Board of Directors of Forest Laboratories, Inc., has authorized me to execute this Side Letter Agreement and the Civil Settlement Agreement on behalf of Forest Laboratories, Inc. The Board of Directors has been advised of the contents of this Side Letter Agreement, the Civil Settlement Agreement, the Plea Agreement with Forest Pharmaceuticals, Inc., the criminal Information charging Forest Pharmaceuticals, Inc., and the Corporate Integrity Agreement, and has discussed them fully with its counsel.

In other words, Forest's senior management authorized the company's guilty plea.

On the same day, September 15, 2010, the Department of Justice issued a press release entitled, "Drug Maker Forest Pleads Guilty: To Pay More Than $313 Million to Resolve Criminal Charges and False Claims Act Allegations."[211] According to the Justice Department's press release:[212]

Forest Pharmaceuticals, Inc., a subsidiary of New York-City-based Forest Laboratories, Inc., has agreed to plead guilty to charges relating to obstruction of justice….and the illegal promotion of Celexa for use in treating children and adolescents suffering from depression, the Justice Department announced today. The companies also agreed to settle pending False Claims Act allegation that Forest caused false claims to be submitted to federal health care program for the drugs…Celexa, and Lexapro. Forest has agreed to pay more than $313 million to resolve criminal and civil liability arising from these matters….

After the FDA approves the product is safe and effective for a specified use, any promotion by the manufacturer on other uses—known as "off label" uses—renders the product misbranded….Celexa and Lexapro are antidepressant drugs that, at the time period at issue, were approved only for use in treatment of adult depression….

Despite a limited approval only for adult depression, Forest Pharmaceuticals promoted Celexa for use in treating children and adolescents suffering from depression. The government alleges that Forest Pharmaceuticals publicized and circulated the positive results of a double-blind, placebo-controlled Forest study on the use of Celexa in adolescents [the Wagner study] while, at the same time, Forest Pharmaceuticals failed to discuss the negative results of a contemporaneous double-blind, placebo-controlled European study on the use of Celexa in adolescents [the Lundbeck study].

The government alleges that Forest Pharmaceuticals' off-label promotion consisted of various sales techniques, including directing its sales representatives to promote pediatric use of Celexa in sales calls to physicians who treated children and adolescents, and hiring outside speakers to talk to pediatric specialists about the benefits of prescribing Celexa to children and teens.

The False Claims Act complaint also alleges that Forest engaged in such marketing conduct in connection with Lexapro, which, at that time, also lacked any approvals for pediatric use. The civil complaint further alleges that Forest used illegal kickbacks to induce physicians and others to prescribe Celexa and Lexapro. Kickbacks allegedly included cash

> payments disguised as grants or consulting fees, expensive meals and lavish entertainment….
>
> "We will not tolerate any company that obstructs justice and illegally promotes drugs that were not approved to treat children," said Tony West, Assistant Attorney General for the Civil Division of the Department of Justice. "Forest Pharmaceuticals has pled guilty to breaking the law. The Justice Department will continue to ensure that taxpayers do not foot the bill when such unlawful and improper conduct occurs."

On March 2, 2011, a U.S. District judge sentenced Forest to pay criminal fines.[213] The same day, the Department of Justice issued a press release entitled "Forest Pharmaceuticals Sentenced to Pay $164 Million for Criminal Violations."[214] According to the press release:[215]

> Regarding Celexa, court documents state that Forest promoted the drug for use in treating children and adolescents suffering from depression despite the fact that the FDA had only approved the drug to treat adult depression. Prosecutors stated that Forest's off-label promotion consisted of various sales techniques, including directing its representatives to promote pediatric use of Celexa in sales calls to doctors who treated children and adolescents, and hiring outside speakers to talk to pediatric specialists about the benefits of prescribing Celexa to children and teens. Prosecutors stated that in conjunction with this off-label promotion, Forest aggressively publicized the positive results of a double-blind, placebo-controlled Forest study on the use of Celexa in adolescents while, at the same time, Forest Pharmaceuticals suppressed the negative results of a contemporaneous double-blind, placebo-controlled European study on the use of Celexa in adolescents…."Both the criminal and civil cases were predicated upon the fact that Forest Pharmaceuticals made a calculated decision to place a higher priority on increasing corporate sales than on complying with the basic, legal requirements that Congress and the FDA created to protect the American public," said Carmen Ortiz, U.S. Attorney for the District of Massachusetts.

The same day, Forest issued a press release entitled "Forest Laboratories, Inc. Finalizes Previously Disclosed Settlement of U.S. Government Investigations and Related Civil *Qui Tam* [i.e., whistleblower] Litigation Relating to Past Sales and Marketing Activities."[216] According to Forest's press release:[217]

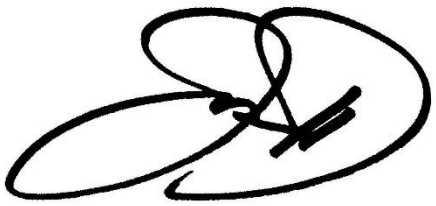
> Forest has agreed to resolve civil claims asserted by DOJ [Department of Justice] under the False Claims Act and in qui tam [whistleblower] lawsuits relating to allegations concerning the…off-label promotion of Celexa…and Lexapro for pediatric use….

Thus, Forest's repeated claims that the company was not marketing Celexa and Lexapro off-label for children and adolescents—for example Forest's press release responding to the *New York Times* exposé and its testimony at the Congressional hearing on pediatric antidepressant studies—were not true.

In addition to the opinions set forth in this report, I incorporate by reference the declarations I have submitted in the course of this litigation.

This completes my opinion at this time. Of course, my opinion is subject to revision based on additional discovery. Please keep me informed of the progress in this case.

Sincerely yours,



Joseph Glenmullen, MD

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For example, Celexa is referred to as citalopram. When journal articles or company documents are quoted in the text, for readability the well-recognized commercial names of the drugs have been substituted for their chemical names. In addition, abbreviations and shorthand commonly used in medical or pharmaceutical records have also been spelled out, and typographical errors have been corrected, again, for readability.

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[3] Side Letter Agreement (Plea Agreement) entered between the United States and Forest Pharmaceuticals, Inc. on September 15, 2010 in *United States of America v. Forest Pharmaceuticals, Inc*., Criminal Action No. 10-10294-NG, in the United States District Court for the District of Massachusetts.

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[6] Ibid.

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[10] Study Report for Celexa Study 94404

[11] Study Report for Celexa Study CIT-MD-18

[12] Study Reports for Celexa Study 94404 and CIT-MD-18

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[26] Study Report for Lexapro Study SCT-MD-32, pp. 1828-1914

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[33] Ibid.
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[35] Study Report for Celexa Study 94404, p. 31
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[48] MDL-FOREM0018197
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[52] Kupfer, D.J., Kraemer, H.C., Katona, C., Bostic, J.Q., Lenze, E.J. "Navigating the Maze: Understanding Methods, Results and Risk in Psychiatric Research," presentation at APA Annual Meeting, May 20, 2006, Toronto. Supported by an educational grant from Forest Pharmaceuticals.
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[60] Ibid.
[61] Ibid.
[62] Study Report for CIT-MD-18, p. 54
[63] Ibid., pp. 100-105; Closter Dep., 142:6-11
[64] April 5, 2016 Hudson Decl., ¶ 13

[65] Celexa Study 18 Protocol, p. 328 ("Any patient for whom the blind has been broken will immediately be discontinued from the study and no further efficacy evaluations will be performed."); 2nd Dep. of William Heydorn, p. 107
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[68] Study Report for CIT-MD-18, pp. 63, 70
[69] Study Report for CIT-MD-18, p. 244; 2nd Dep. of William Heydorn, pp. 87-88
[70] Study Protocol for CIT-MD-18, p. 334; Charles Flicker Dep. pp. 118, 121-122; Steven Closter Dep., p. 168
[71] Ibid.
[72] Ibid.
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[77] Ibid.
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[80] Flicker Dep. pp. 278-279; 2nd Heydorn Dep., pp. 156-157
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[114] Forest email from Karoline Als to Ivan Gergel, forwarded to Paul Tiseo, Julie Kilbane, Charles Flicker, and Lawrence Olanoff, July 16, 2001, with attachment MDL-FORP0017926, MDL-FORP0010491
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[124] Ibid., Deposition of Dr. William Meury, April 3, 2012, p. 132.
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[126] MDL-FOREM0000904; MDL-FOREM0001515; Mitchner Dep, pp. 47-49; MDL-FORPM0000906; MDL-FOREM0000977.
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JOSEPH GLENMULLEN, M.D.

Curriculum Vitae

Academic Appointments

1988 to present: Lecturer in Psychiatry, Harvard Medical School, in the Department of Psychiatry, Cambridge Hospital, Cambridge, MA
1988-89: Associate Director, Medical Student Education, Cambridge Hospital/Harvard Medical School, Cambridge, MA
1987-89: Instructor, Psychiatry 700 Course, Harvard Medical School

Clinical Practice

Clinical Practice
1986 to present: Private practice in Harvard Square, Cambridge, MA
1988 to 2008: Psychiatrist, Harvard Law School Health Services, Cambridge, MA

Forensic Practice
2001 to present: Expert witness and forensic consulting
2002-2014: Member, Program in Psychiatry and the Law, Harvard Medical School

Teaching and Awards

Teaching
1988-present: Supervision of psychiatry residents, psychology fells, and social work interns at the Cambridge Hospital/Harvard Medical School.

Awards:
May, 2001: Annual Achievement Award in Medicine, American College for Advancement in Medicine (ACAM), and delivered the keynote address, the Linus Pauling Lecture, at ACAM's annual convention.

Education and Training

Education
1984: MD, Harvard Medical School, Boston, MA
1972: BA, magna cum laude, Brown University, Providence, RI

Postdoctoral Training
1987-88: Psychiatry Fellow, Harvard University Health Services, Cambridge, MA
1987-88: Chief Resident, Outpatient Department, Department of Psychiatry, Cambridge Hospital/Harvard Medical School, Cambridge, MA
1986-88: Residency, Department of Psychiatry, Cambridge Hospital/Harvard Medical School, Cambridge, MA
1984-85: Internship, Department of Medicine, Cambridge Hospital/Harvard Medical School, Cambridge, MA

Board Certification
1990: Board certified in psychiatry by the American Board of Psychiatry and Neurology

Licensure
1985 to present: Medical License, Massachusetts Board of Registration in Medicine

Board Membership/Professional Organizations

2008-present: Member, Board of Directors, New England Division of the American Foundation for Suicide Prevention
2008-present: Member, American Association of Suicidology

Bibliography

T.J. Moore, J. Glenmullen, "Varenicline study confirms psychiatric risks but reveals design flaws," rapid response to: Molero et al, "Varenicline and risk of psychiatric conditions, suicidal behavior, criminal offending, and transport accidents and offenses: population based study," BMJ 2015;350:h2388

T.J. Moore, J. Glenmullen, D.R. Mattison, "Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated with Dopamine Receptor Agonist Drugs," *JAMA Intern Med*. 2014 Oct 20. doi: 10.1001/jamainternmed.2014.5262. [Epub ahead of print]

T.J. Moore, C.D. Furberg, J. Glenmullen, J.T. Maltsberger, and S. Singh, "Suicidal Behavior and Depression in Smoking Cessation," *PLoS ONE* Nov 2011;6(11)

T.J. Moore, J. Glenmullen, and C.D. Furberg, "Prescription Drugs Associated with Reports of Violence Towards Others," *PLoS ONE* Dec 2010;5(12): e15337

Moore TJ, Glenmullen J, Furberg CD, Thoughts and Acts of Aggression/Violence Toward Others Reported in Association with Varenicline, *Annals of Pharmacotherapy*, 2010 Sep;44(9):1389-94

Wanzer, Sidney and Glenmullen, Joseph. *To Die Well: Your Right to Comfort, Calm, and Choice in the Last Days of Life.* New York: Perseus Books Group, 2007.

Glenmullen, Joseph. *The Antidepressant Solution: A Step-by-Step Guide to Overcoming Antidepressant Withdrawal, Dependence, and "Addiction."* New York: Free Press (division of Simon & Schuster), 2005

Glenmullen, Joseph. *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil and Other Antidepressants with Safe, Effective Alternatives.* New York: Simon & Schuster, 2000

Glenmullen, Joseph. *Sexual Mysteries: Tales of Psychotherapy* with a Foreword by Robert Coles. Cambridge, MA: Orbit Publishing, 2000. Originally published by Harper Collins in 1993.

Reliance Material

1. Documents identified in endnotes to report dated April 28, 2017
2. eCTD FDA Lexapro submission for adolescent use
3. Celexa and Lexapro labels
4. Final Report for Celexa Study CIT-MD-18
5. Final Report for Celexa Study 94404 (Lundbeck Study)
6. Final Report for Lexapro Study SCT-MD-15
7. Final Report for Lexapro Study SCT-MD-32
8. Protocol for Celexa Study CIT-MD-18
9. Protocol for Celexa Study 94404 (Lundbeck Study)
10. Protocol for Lexapro Study SCT-MD-15
11. Protocol for Lexapro Study SCT-MD-32
12. Arraignment on Information dated November 19, 2010 in *United States v. Forest Pharmaceuticals, Inc.,* 10-CR-10294-NG (D. Mass).
13. Criminal plea agreement and Information dated September 15, 2010 in *United States v. Forest Pharmaceuticals, Inc.,* 10-CR-10294-NG (D. Mass).
14. Civil Settlement Agreement and Release.
15. Deposition of Thomas Laughren, M.D., taken on January 27, 2017, and exhibits.
16. Deposition of Thomas Laughren, M.D., taken on July 9, 2013, in *Brown v. Demuth,* 09-CV-900734 (Ala. Cir. Ct.) and exhibits.
17. Deposition of William Heydorn, Ph.D., taken on October 14, 2016, and exhibits.
18. Deposition of Olchaskey pursuant to 30(b)(6) taken on February 14, 2017 and exhibits.
19. Deposition of Camardo, taken on November 22, 2011 taken in *Brown v. Demuth,* 09-CV-900734 (Ala. Cir. Ct.) and exhibits.
20. Deposition of William Meury, taken on April 3, 2012 in *Brown v. Demuth,* 09-CV-900734 (Ala. Cir. Ct.) and exhibits.
21. Deposition of Karen Wagner, taken on July 16, 2013 and exhibits.
22. Deposition of Ivan Gergel taken on December 20, 2016 and exhibits.
23. Deposition of William E. Heydorn, Ph. D., taken on August 29, 2007, in *In re Forest Laboratories, Inc. Securities Litigation*, 05-CV-2827 (S.D. N.Y.) and exhibits.
24. Deposition of Charles Flicker, Ph. D., taken on November 4, 2016, and exhibits.
25. Deposition of James Jin, Ph. D., taken on October 21, 2016, and exhibits.
26. Deposition of Lawrence S. Olanoff, M.D., Ph. D., taken on October 24, 2016 and exhibits.

27. Email from Amy Rubin editing letter to FDA regarding results of the CIT-18, dated March 15, 2000.
28. Draft letter by Paul Tiseo to investigators regarding unblinding, dated March 8, 2000.
29. CIT-MD-18 Deviation Report, dated March 7, 2000.
30. Facsimile sent by Paul Tiseo to investigators of MD-18, dated March 2, 2000.
31. Excerpts of the deposition of Steven L. Closter, taken on October 6, 2016.
32. Declaration of James I. Hudson, M.D., SC.D. in this litigation, dated April 5, 2016.
33. Forest's Statement of Undisputed Facts, dated October 25, 2013, in *Wilcox v. Forest Laboratories, Inc.*, 10–CV–10154 (D. Mass.).
34. Email to Andrew Korotzer regarding Lundbeck's comments on the MD-15 manuscript dated November 5, 2004.
35. Letter from the U.S. Food and Drug Administration to Forest denying pediatric indication.
36. Defendant's Responses and Objections to Plaintiffs' First Set of Requests for Admission (Revised), dated September 27, 2016.
37. Email from Joan Barton, Bates numbered MDL-FORP0168046-0168047, listing investigational sites where patients were unblinded in the CIT-MD-18 study.
38. PharmaNet conference notes, dated October 4, 2001.
39. Email from biostatistician Jane Wu regarding results of the CIT-18, dated August 10, 2001.
40. Email from Julie Kilbane regarding results of the CIT-18, dated April 28, 2002.
41. Letter from Tracy Varner to the FDA regarding a packaging error, dated March 20, 2000.
42. Thomas Laughren memorandum regarding recommendation for Non-Approval Action for Pediatric Supplement for Celexa (Citalopram); negative results for Celexa in the treatment of Major Depressive Disorder (MDD) in pediatric patients, dated September 16, 2002.
43. Email correspondence between Natasha Mitchner, and Christina Goetjen containing the Karen Wagner abstract with the latest edition of the Pediatric Data as it was submitted to the American College of Neuropsychopharmacology (ACNP).
44. Email correspondence between Natasha Mitchner, and William Heydorn containing the Karen Wagner posters.
45. Forest's press release dated December 13, 2001.
46. Forest Pharmaceuticals, Inc., *A Closer Look at Identifying Depression in Children and Adolescents*, dated March 11, 2002.
47. Forest's Lexapro FYo4 marketing plan.
48. Letter from the U.S. Food and Drug Administration to Andrew Friedman regarding pediatric study proposal.

49. Transcripts of The FDA's Psychopharmacological Drugs Advisory Committee meetings held on February 2, 2004, September 13 and 14, 2004.
50. Email correspondence between Natasha Mitchner, and Jeffrey Lawrence regarding outline of the Karen Wagner manuscript.
51. Forest internal emails regarding reviewer comments on manuscript, dated November 18, 2008.
52. Excerpts from Kenneth J. Rothman's, *Epidemiology: An Introduction* (2002).
53. Newman, A Black-Box Warning for Antidepressants in Children? *New England Journal of Medicine*, Vol. 351:1595-1598, October 14, 2004.
54. Graham J. Emslie, et al., *Escitalopram in the Treatment of Adolescent Depression: A Randomized Placebo-Controlled Multisite Trial*, 48 J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY. 721-729, (2009).
55. Richard S.E. Keefe, et al., *Defining a Clinically Meaningful Effect for the Design and Interpretation of Randomized Controlled Trials*, 10 Innov Clin Neurosci. 4S-19S, (2013).
56. Forest's *Navigating the Maze* presentation sponsored by the American Psychiatric Association, dated May 20, 2006.
57. Forest's press release dated June 24, 2004.
58. Portions of *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials before House Subcomm. on Oversight and Investigations of the Comm. on Energy and Commerce*, 108 Cong., Serial No. 108-121 (Sept. 9, 2004).
59. Letters to the editor in response to Wagner publication.
60. Editor's Note, Am. J. Psychiatry 166:8, August 2009.
61. The Lancet, "Depressing Research."
62. March 20, 2009 Press Release announcing approval of Lexapro for adolescents.
63. November 19, 1990 Psychopharmacological Drugs Advisory Committee ("PDAC") meeting transcript.
64. December 24, 1991 FDA memo recommending approval of Zoloft.
65. May 4, 1998 FDA memo related to the approval of Celexa for adult depression.
66. January 5, 2004 FDA memo re antidepressants and pediatric suicide.