UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

CHARLES SEIFE, Plaintiff, *v.* FOOD AND DRUG ADMINISTRATION and DEPARTMENT OF HEALTH AND HUMAN SERVICES, Defendants, and SAREPTA THERAPEUTICS, Intervenor-Defendant.	Case No. 1:17-cv-3960 **DECLARATION OF CHARLES SEIFE** May 29, 2018

I, CHARLES SEIFE, declare as follows:

1. I am a Professor of Journalism at New York University, an active freelance journalist, and the plaintiff in this Freedom of Information Act (FOIA) lawsuit against defendants the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS). My FOIA requests at issue sought records concerning the FDA's approval of eteplirsen (Exondys 51), a drug manufactured by intervenor-defendant Sarepta Therapeutics, Inc. (Sarepta) for the treatment of Duchenne Muscular Dystrophy (Duchenne). I submit this declaration in opposition to the motions for summary judgment filed by the government and Sarepta (collectively, defendants) and in support of my cross-motion for summary judgment. The facts set forth in this declaration are true and correct, and based on my personal knowledge.

2. The pending cross-motions are limited to the issue of whether information in the Clinical Study Reports (CSRs), including Appendices, that Sarepta submitted to the FDA to gain

approval for Exondys 51 may be withheld under FOIA Exemption 4, which governs confidential commercial information provided to government agencies. As described below and in the accompanying declarations and memorandum of law submitted on my behalf, there is no factual basis for defendants' claim that disclosing the withheld CSR information would cause substantial competitive harm to Sarepta, and there is an overwhelming public interest in its disclosure, both to illuminate how the FDA is carrying out its statutory duties and to inform doctors, patients, and the public at large about the potential risks and benefits of taking Exondys 51, a drug with a list price that can amount to more than $1,000,000 per patient per year.

3. This declaration sets forth below:

a) My scientific and journalistic qualifications;

b) The background to the FDA's controversial approval of Exondys 51 that led to my FOIA requests;

c) Questions raised by the Sarepta CSRs and other documents disclosed by the government in response to this lawsuit;

d) The present litigation and facts surrounding the *Vaughn* Index and requested information;

e) Facts demonstrating that much of the information withheld from the CSRs is already public, so that any incremental disclosures here could not inflict any substantial competitive harm on Sarepta;

f) The overwhelming public interest in disclosure of the information withheld from the CSRs, both to shed light on "what the government is up to" and to assess whether Exondys 51 is actually effective enough to justify its enormous cost and the risks attendant to its administration; and

g) Facts refuting many claims by defendants about how the release of these materials could cause competitive harm to Sarepta.

A. QUALIFICATIONS

4. I have been an investigative reporter with a focus on science, data, and mathematics for over two decades. I hold a Master's degree in journalism from Columbia University, a Master's degree in mathematics from Yale University, and a Bachelor's degree in mathematics from Princeton University.

5. Before joining the faculty at NYU in 2005, I was a writer for eleven years, including eight years as a writer for *New Scientist* and *Science Magazine*, where I specialized in physics and mathematics reporting. My work has appeared in *The Economist*, *Scientific American*, *The Philadelphia Inquirer*, *The Washington Post*, *The New York Times*, and other publications. I am a member of the National Association of Science Writers, the Society for Professional Journalists, the Association of Health Care Journalists, and PEN. I have written six books, including a work on mathematical and statistical deception, and won the PEN/Martha Albrand Award for First Nonfiction.

6. I regularly use FOIA and data analysis to investigate cases of potential scientific misconduct and to understand the actions of federal agencies and the quality of the scientific research they oversee. For example, in an article for *ProPublica*,[1] I detailed the FDA's decision to allow drugs that had been fraudulently tested at a bioequivalence lab to remain on the market. My reporting explored how the FDA had found the lab's violations so "egregious" that the studies conducted there over four years might have been worthless, yet the FDA did not warn patients or doctors about the potentially affected drugs. Through FOIA requests, I was able to discover that about 100 drugs had been approved by the FDA, at least in part, on the strength of tainted tests and to identify a number of the drugs that were still being sold in the United States. I am the plaintiff in an ongoing FOIA suit about the revelations stemming from these drugs. *Seife v. FDA*, No. 1:15-cv-5487 (S.D.N.Y. July 14, 2015).

7. I have similarly used FOIA as a key component of my science reporting on a number of other occasions, including in connection with a report for *Scientific American*.[2] In the article, I

[1] Rob Garver & Charles Seife, *FDA Lets Drugs Approved on Fraudulent Research Stay on the Market*, ProPublica, Apr. 15, 2013, https://www.propublica.org/article/fdalet-drugs-approved-on-fraudulentresearch-stay-on-the-market.

[2] Charles Seife, *How Drug Company Money Is Undermining Science*, Scientific American, Dec. 2012, https://www.scientificamerican.com/article/how-drug-company-money-undermining-science/.

detailed the shortcomings and conflicts of interest in the systems by which government funding is provided to prominent scientists who conduct research affecting the pharmaceutical industry. I also used FOIA in connection with a peer-reviewed article on research misconduct that was published in the top medical journal *JAMA Internal Medicine*.[3] My *JAMA* paper demonstrated that FDA findings of significant departures from good clinical practice in the conduct of research studies are rarely disclosed in the peer-reviewed reports on the results of those studies, even when the FDA has found evidence of data fabrication or other forms of research misconduct. To reach this conclusion, I conducted a cross-sectional analysis on fifteen years of published reports describing FDA inspections where significant evidence of objectionable conditions or practices was found. Then, with information gleaned from FOIA requests, I was able to identify seventy-eight published reports on trials in which significant violations had been found. Only three (4%) mentioned the objectionable practices the FDA had identified.

B. FDA ACTIONS AND THE RESULTING FOIA REQUESTS

8. I became interested in the validity of the approval process for Exondys 51 in September 2016, after the FDA granted "accelerated approval" for the drug in a highly controversial and abnormal approval process. According to news reports published at that time, this approval set off a "civil war" within the FDA. Kenney Decl., Ex. GG, 8.

9. Exondys 51 is a drug manufactured by Sarepta for the treatment of Duchenne, a genetic muscle-wasting disease that primarily occurs in young boys and adolescents and that eventually leads to death from cardiac or respiratory failure. The disease causes the body to produce extremely low levels of the protein dystrophin. Exondys 51 was developed to target the gene responsible for

[3] Seife C. Research Misconduct Identified by the US Food and Drug Administration: Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature. *JAMA Intern Medicine.* 2015;175(4):567–577, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2109855.

dystrophin production through a mechanism known as "exon-skipping" that causes the cell to skip the particular portion of the gene with the mutation when transcribing protein.

10. In 2013, prior to FDA approval of Exondys 51, the *Annals of Neurology* published an article by a Sarepta collaborator, Dr. Jerry Mendell, who reported along with his co-authors the results of two clinical trials that the FDA ultimately relied upon for approval—Study 201 and Study 202. Kenney Decl., Ex. N. Study 201 was a single-center, double-blinded, randomized-controlled trial conducted with just twelve patients with Duchenne, four of whom received a placebo. In Study 201, researchers used the change in the percentage of dystrophin-positive fibers over time as a surrogate marker, or proxy, for neuromuscular health. Researchers also conducted a number of clinical outcome measures, including the 6-minute-walk test (6MWT), recording the distance patients could travel in six minutes. After twenty-four weeks, the four patients initially given the placebo were switched to treatment with Exondys 51. After forty-eight weeks, the study was extended to an "open-label phase," meaning that all test-givers and all patients were aware that all patients were receiving the study drug. The open label phase was Study 202.

11. In the 2013 *Annals of Neurology* article, Dr. Mendell stated that Exondys 51 increased the percentage of dystrophin-expressing muscle fibers to 47% of normal after 48 weeks of treatment, and Sarepta repeated this claim in a later press release. *Id.* at 6; *see also id.*, Ex. O, 3. Because patients with Duchenne typically have less than 1% of normal dystrophin levels, *see id.*, Exs. E, 3-4 & D, 20, these results caused the neurologists and the Duchenne community to label the drug as a miracle cure, *see id.*, Ex. F, 16. But the results of this article were soon called into question by FDA reviewers tasked with evaluating the drug's efficacy. The FDA's then Chief Acting Scientist, Dr. Luciana Borio, would later say that "Sarepta's misleading communications led to unrealistic expectations and hope for [Duchenne] patients and their families." *Id.*, Ex. G, 27.

12. As a result of these published findings and Sarepta's press releases, the FDA was inundated with calls to approve Exondys 51 promptly, and the Director of the Office of Drug Evaluation-I (ODE I), Dr. Ellis Unger, reported receiving thousands of emails directed to him personally urging approval. *Id.*, Ex. F, 24.

13. The FDA convened the Peripheral and Central Nervous System Drugs Advisory Committee, a group of outside experts advising the FDA on whether to approve the drug. On April 25, 2016, it held an eleven-hour public meeting. Of the fifty-two presenters who spoke at the public hearing portion of the meeting, fifty-one urged approval for Exondys 51. According to media accounts, when the Advisory Committee voted 7-6 that Exondys 51 failed to demonstrate the effectiveness of the drug to the degree required for accelerated approval, audience members broke into angry shouts. *Id.*, Ex. GG, 21.

14. The FDA subsequently required Sarepta to submit interim results from an ongoing confirmatory trial, Study 301, which Sarepta submitted on June 27, 2016. *Id.*, Exs. S, 46 & G, 14. However, even with these additional results, FDA reviewers in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs all uniformly recommended against approval of Exondys 51. *Id.*, Ex. D, 4. Dr. Ronald Farkas, then the clinical team leader, expressed "strong doubts" about the accuracy of Sarepta's clinical trials. *Id.*, Ex. GG, 9.

15. In an extraordinary move, Dr. Woodcock, head of the Center for Drug Evaluation and Research (CDER), overrode the conclusion of the review team and unilaterally approved the drug on July 14, 2016. *Id.*, Ex. E. According to the FDA's then-Acting Chief Scientist, Dr. Luciana Borio, this may be the first time in FDA history that a Center Director had overruled a review team (and an Advisory Committee) that had found insufficient evidence of a drug's efficacy. *Id.*, Ex. G, 15.

16. Rumors abounded that Dr. Woodcock had succumbed to external influence when she overruled the review team. Indeed, Dr. Woodcock shared her concern in a public presentation that Sarepta "needed to be capitalized" and "noted that the sponsor's stock went down after the [Advisory Committee] meeting," *id.* at 17, though she later denied this concern had influenced her decision to approve the drug, *id.*, Ex. H, 20, n.23. At least two members of the review team left the FDA in the wake of her decision. *Id.*, Ex. G, 11.

17. In an effort to overturn Dr. Woodcock's approval, Dr. Unger filed an Agency Scientific Dispute Appeal with the FDA's Office of Scientific Integrity on July 18, 2016. *Id.*, Ex. F. Dr. Unger's appeal called attention to procedural flaws in the approval process, including that Dr. Woodcock had made clear to the review team in May 2016 that she intended to approve Exondys 51 even before she had read the final review memoranda and seen Sarepta's new Study 301 images. *Id.* at 27.

18. Dr. Unger's appeal also challenged Dr. Woodcock's scientific analysis of the Exondys 51 study results and pointed to problems with the Western blot tests that Sarepta used to measure patients' dystrophin levels. *Id.* at 5-7. Dr. Unger conducted statistical analyses to show that the measured level of dystrophin increase produced by Exondys 51 showed no correlation at all with the clinical outcome measures of patient muscle health, in particular the results of the 6-Minute Walk Test (6MWT) and another outcome measure known as the North Star Ambulatory Assessment (NSAA). *Id.* at 17-20.

19. Finally, Dr. Unger expressed concern about the "certain" risk of side effects from using Exondys 51, including possible death from infections that could easily result from the drug's intravenous administration. In his view, Duchenne patients would be taking an "elegant placebo" and given "false hope in exchange for hardship and risk." *Id.* at 22.

20. On August 8, 2016, Dr. Borio submitted a report from the appeals committee to the FDA Commissioner, then Dr. Robert Califf, finding that Dr. Unger's appeal warranted a further scientific review of Exondys 51. *Id.*, Ex. G. Dr. Borio also provided a brief statement on her own behalf supporting Dr. Unger's scientific conclusions, including that the increase in dystrophin levels shown in Sarepta's studies was not "reasonably likely to predict a clinical benefit," the standard required for accelerated approval of a drug based on surrogate measures. *Id.* at 26-28.

21. On September 16, 2016, Commissioner Califf upheld Dr. Woodcock's accelerated approval of Exondys 51. *Id.*, Ex. H. In doing so, however, he also stated that flaws in Sarepta's clinical trials "made it impossible to use much of the resulting data as reliable evidence in regulatory decision-making," and specifically called for the correction or retraction of Dr. Mendell's article in the *Annals of Neurology*. *Id.* at 5 & 12, n.28.

22. The approval of Exondys 51 provoked an outcry in the scientific community and generated intense media coverage. It was covered by *Forbes*, *The Washington Post*, *The New York Times*, *NPR*, *STAT News* (a news site run by the Boston Globe), as well as in at least one major medical journal, and generated literally thousands of hits on Lexis Nexis. Because I frequently write about the FDA, this highly unusual approval immediately caught my attention. I began an investigation and sources provided me with information about the Exondys 51 approval process on a confidential basis. These sources described serious issues concerning both Dr. Woodcock's role in the approval process and the scientific studies on which the accelerated approval was based.

23. My sources expressed concern that Dr. Woodcock or her Deputy Director, Dr. Richard Moscicki, may have behaved improperly during the approval process. They noted in particular Dr. Moscicki's professional ties with Dr. Edward Kaye, then CEO at Sarepta and formerly its Chief Medical Officer. They also described Dr. Woodcock's stated concern about the ability of

Sarepta to survive financially if the drug were not approved and questioned whether Dr. Woodcock had improperly had undisclosed contacts with Sarepta employees during the drug approval process.

24. Raising further red flags, these sources indicated that the scientific studies submitted by Sarepta to win approval were seriously flawed. An abstract from a different Sarepta clinical trial published in October 2016 confirmed that the 6MWT endpoint used in the studies was open to manipulation (consciously and subconsciously) by both parent coaching and staff sympathy.[4]

25. To investigate these concerns, I submitted my FOIA request in December 2016. Given the urgency of the matter, I asked for expedited processing under 5 U.S.C. § 552(a)(6)(E)(i). The FDA denied that request on December 21, 2016, and I appealed the denial administratively. The FDA denied my appeal on April 25, 2017.

26. I filed suit in this Court on May 25, 2017, challenging both the denial of expedited processing and the constructive denial of my FOIA request. *See* Complaint, ECF No. 1.

27. I then moved for partial summary judgment on expedited processing on June 21, 2017. Mot. for Partial Summary Judgment, ECF No. 16. On July 11, 2017, the Court: (a) ordered production of the "Jenkins memo," an internal document I requested; and (b) referred the parties to Magistrate Judge Ellis for settlement talks. *See* ECF No. 29.

28. After settlement talks, the FDA granted my request for expedited processing in the exercise of its discretion and agreed to an aggressive production schedule for the remaining information in the FOIA request that this Court ordered on July 27, 2017. Stipulation and Order, ECF No. 39.

[4] *See* Servais L, Grelet M, Seferian A, et al. Movement monitoring at home and during study visits identifies sources of variability in 6MWT performance in Duchenne muscular dystrophy. *Neuromuscular Disord* 2016;26:S152-S153 (Kenney Decl. Ex. V, 2-3).

C. QUESTIONS RAISED BY THE DISCLOSED RECORDS

29. Pursuant to the Stipulation and Order, the FDA has produced over 45,000 pages of documents, including "smoking gun" internal emails and memos from high-ranking FDA officials, Sarepta employees, and the public. I have reviewed these documents carefully. They reveal important information on both the controversial Exondys 51 approval process and on the scientific validity of claims made about the effects of the drug in Dr. Mendell's article in *Annals of Neurology*. Specifically, documents disclosed by defendants bear out concerns over possible improprieties in the drug approval process and provide support for accusations that have been leveled concerning the violation of the FDA's approval standards and potential "scientific misconduct" by Sarepta.

30. First, the "Jenkins memo" that the Court ordered to be disclosed at the outset describes potential misconduct on the part of Dr. Woodcock and potential violation of the statutory standards for accelerated drug approval. *Id.*, Ex. I. The memo was authored by the Director of the Office for New Drugs (OND), Dr. John Jenkins, and was addressed to Commissioner Califf in response to his decision to uphold Dr. Woodcock's approval of Exondys 51. OND is the component within the Center for Drug Evaluation and Research (CDER) tasked with reviewing applications to ensure that proposed drugs are safe and effective. In this memo, Dr. Jenkins expressed many concerns with the procedural irregularities surrounding the approval of Exondys 51, underscoring that he did not support Commissioner Califf's decision and did not want his name associated with the statement that "reasonable people can disagree" about the outcome. *Id.* at 2.

31. Dr. Jenkins objected strongly to the behavior of Dr. Woodcock during the approval process, noting that she had circumvented the normal review process and had said her mind was made up to approve the drug before she had even seen the evaluations of the team charged with reviewing its safety and efficacy. *Id.* at 2-3. Dr. Jenkins also asserted that Dr. Woodcock "had frequent private conversations" with Sarepta employees and patients with Duchenne and their families without, to his

knowledge, "document[ing] the substance of those conversations to the record, as is required by FDA regulations." *Id.* at 4.

32. Dr. Jenkins further questioned Dr. Woodcock's scientific analysis and expressed his doubt that Sarepta's studies could possibly have met the statutory standard for accelerated approval, which requires "substantial evidence" that a surrogate measure is "reasonably likely to predict clinical benefit." According to Dr. Jenkins, Dr. Woodcock provided "no rational basis" for identifying what level of dystrophin produced by Exondys 51 would meet this statutory standard. He objected that Dr. Woodcock's analysis "defies any sense of scientific reason." He also noted that Commissioner Califf based his initial decision to uphold Dr. Woodcock on an ill-defined "totality of the evidence" standard, instead of the "substantial evidence" required by law. *Id.* at 3.

33. Finally, Dr. Jenkins stated that the approval of Exondys 51 undermined the FDA's ability to "reach science-based conclusions on future applications" and worried that the decision to grant accelerated approval without more evidence of efficacy had eroded the "substantial evidence" standard and "lowered the bar" for "future drug approvals." *Id.* at 4. Dr. Jenkins concluded by noting that he was so concerned about the adverse impact of Dr. Woodcock's actions that he had delayed his retirement from the FDA. *Id.* at 5.

34. Other correspondence disclosed by defendants calls into question the integrity of the Advisory Committee convened to review the safety and efficacy of Exondys 51. The Advisory Committee's voting members typically consist of independent experts and a consumer (patient) representative. Dr. Unger repeatedly voiced objections to the temporary appointment of Benjamin Dupree as a voting patient representative on the Exondys 51 Advisory Committee because his parents owned stock in Sarepta, creating a "blatant conflict of interest." *Id.*, Ex. K, 4.

35. Although the Advisory Committee ultimately voted against approval, Dr. Unger refused to sign the Committee's vote memo because of Dupree's continuing role despite his conflict

of interest. *Id.* Within the FDA, Dr. Unger protested that he had been "stonewalled" by the Center for Drug Evaluation and Research and "blocked by CDER management" when he requested that the FDA appoint a different patient representative on the Committee. *Id.* at 6. Dr. Woodcock is the head of the CDER, further calling into question her actions and motives.

36. Documents disclosed by defendants turned up evidence of apparent improprieties in the Exondys 51 approval process by other FDA employees as well, including Dr. Moscicki. Dr. Moscicki recused himself from the approval process because he had previously worked with Dr. Edward Kaye, then CEO of Sarepta. But despite his recusal, the documents produced by defendants reveal ongoing involvement by Dr. Moscicki in the Exondys 51 approval process.

37. Multiple FDA officials questioned Dr. Moscicki's involvement, and his emails disclosed by defendants corroborate their concerns. For example, Dr. Mosckicki wrote that Dr. Woodcock asked him to "join her for a discussion with [REDACTED] patient advocate" about Exondys 51, *id.*, Ex. J, 3, and another indicates that Dr. Moscicki received communications from Sarepta about Exondys 51 while approval was pending, *id.* at 18, 21-22. After the drug was approved, Dr. Moscicki also sent an email to Dr. Billy Dunn, Director of the Neurology Products Division, conveying concerns raised by Christine McSherry, Executive Director of the Jett Foundation (a patient organization that lobbied vigorously for the approval of Exondys 51 and that is an "industry partner" of Sarepta) that post-approval trials were "designed to fail" because they measured the wrong clinical endpoints to determine efficacy and urged the use of other "non-ambulatory" measures. *Id.* at 25.

38. In other email, Dr. Unger noted that Dr. Moscicki "seem[ed] to have some involvement" despite his recusal. *Id.* at 2. Dr. Jenkins agreed that Dr. Moscicki's ongoing involvement was an "awkward" issue that the team would "need to address." *Id.* Despite these observations, Dr. Moscicki continued his involvement throughout the approval process. *Id.* at 2-3, 15, 17-18.

39. Emails disclosed by defendants also reveal FDA concerns that Sarepta and its collaborators may have committed "scientific misconduct." Kenney Decl., Ex. L, 10. Dr. Ronald Farkas, a clinical team leader, reviewed Western blots images. Dr. Farkas wrote to Dr. Jenkins and several others to express concerns about "misrepresentation of the data, even beyond that fact that it isn't clear what band [in the Western blot] represents dystrophin in the patient samples." *Id.* at 2. Dr. Farkas warned:

> To my eyes . . . the immunohistochemistry and western data recently sent by Sarepta is looking far less impressive than portrayed in their regulatory submissions and the Mendell paper [in the *Annals of Neurology*] – my initial impression is that we need to be concerned that the Mendell paper, at least, represents scientific misconduct through the omission and misrepresentation of results such that findings are not accurately portrayed.

Id. at 10. Dr. Farkas stated that one of the Western blot images submitted to the FDA "seems like it must also have been heavily manipulated photographically" and thought that Sarepta had "delete[d] edges of the band that were darker than the central part." *Id.* at 8. He also noted that the images did not match those Dr. Kaye (CEO of Sarepta) had presented in an earlier presentation to the FDA. *Id.*

40. Additional concerns about the article were raised in exchanges between Commissioner Califf and Dr. Unger and the editors of the *Annals of Neurology*. Commissioner Califf and Dr. Unger initially called for the retraction or correction of the Mendell article based on their conclusion that it was inaccurate. *Id.*, Ex M, 8. The editor then asked if Dr. Mendell had committed "scientific misconduct," defined as "deliberate intent to deceive," or rather if the paper represented "sloppy science." *Id.* at 5. Dr. Unger replied that, to his mind, the paper was "sloppy science – not scientific misconduct." *Id.* at 4. Eventually, Commissioner Califf and Dr. Unger ultimately published a letter in the *Annals of Neurology* detailing their numerous concerns. They stated that they believed "that the

reported findings for the 48-week study are based on unreliable data and that the conclusions, based on these erroneous findings, are misleading."[5]

41. Finally, defendants disclosed highly redacted copies of the Clinical Study Reports (CSRs) for Study 201 and Study 202, the studies relied upon by Dr. Woodcock in her decisional memo granting approval and the studies reported by Dr. Mendell in the *Annals of Neurology*. CSRs are documents created by drug sponsors that the FDA requires to be submitted to obtain drug approval. They contain crucial data for evaluating drug safety and efficacy.

42. The information withheld from the CSRs for Study 201 and Study 202 is the subject of the pending cross-motions. These documents were redacted in outrageous ways, including the removal of portions of the table of contents that had been disclosed earlier, the deletion of the names of tables, figures and listings referenced in the text, and, most importantly, the removal of portions of the narrative descriptions and underlying summary results, including individual patient-level results, for the safety and efficacy tests conducted on Exondys 51. These redactions, purportedly to prevent competitive harm to Sarepta, go far beyond the redactions in CSRs that are being proactively released by the FDA and by the European Medicines Agency (EMA).

43. The redactions from the CSRs for Exondys 51 are far more than the redactions to the first CSR released under a new FDA pilot program to proactively release CSRs on the FDA website after drug approval, with consent of the manufacturer. *See* Aragon Pharmaceuticals, Inc., Clinical Study Report (body), *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer Selective Prostate AR Targeting*

[5] Unger EF, Califf RM. Regarding "Eteplirsen for the treatment of Duchenne muscular dystrophy." Annals of Neurology 2017;81(1):162-164 (Kenney Ded., Ex. M, 12-14).

with ARN-509 (SPARTAN) (Sept. 25, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/rev_210951_arn-509-003_CSR_Redacted.pdf.

44. In the 113-page Erleada protocol, only a signature, an ingredient, less than one sentence about the rationale for a protocol amendment involving statistical analysis regarding an exploratory biomarker, four lines of text regarding an exploratory biomarker, and the text of two copyright questionnaires were redacted. In the 891-page CSR, the sole redactions involve names of employees, contract agencies and foreign study sponsors, drug formulation information, quality control information, and information that would identify the trial participants: subject identification number; study site identification number; and specific dates. In the 68-page statistical analysis plan, the only redactions are the names of contract agencies, and a copyright questionnaire, and scoring guide. The Sarepta CSRs are also far more redacted than the CSRs released by the European Medicines Agency (EMA) under its proactive release policy. The EMA proactively releases the clinical overview, clinical summary, CSRs, protocol amendments, and statistical analysis plans. According to the EMA, for the first two drugs subject to the proactive release policy, it released 260,000 pages of documents, of which only two pages were redacted as confidential commercial information.[6]

D. THE PRESENT LITIGATION

45. In the lead up to the present summary judgment motions, I annotated a copy of the *Vaughn* Index provided to me by Sarepta. I indicated that I objected to the redaction of the safety and efficacy information contained in the CSRs. However, the *Vaughn* Index provided by defendants is ambiguous regarding the classification of certain types of information and what categories they fall

[6] Michael Mehzer, *EMA Transparency: New Clinical Reports Go Live*, Regulatory Focus, Oct. 20, 2016, https://www.raps.org/news-articles/news-articles/2016/10/ema-transparency-new-clinical-reports-go-live?feed=Regulatory-Focus (Kenney Decl., Ex. AA, 107-110).

into (for example, whether the information is safety or efficacy data or whether it pertains to a clinical protocol).

46. I thus challenged a document numbered Bates FDACDER_SAR 21629, which is identified in defendants' *Vaughn* Index as part of the protocol for Study 202 that contains a "description of study results." *See* Ittig Decl., Ex. A, 29, ECF No. 73. The redactions to this page are identified as containing a description of "Sarepta's study at a granular level, providing the results of a particular test Sarepta performed," information directly relevant to assessing the drug's efficacy. *Id.* I also objected to the withholding of information from Bates FDACDER_SAR 21635, described as "individual patient results descriptions," and to the withholding of "exploratory endpoints" from Bates FDACDER_SAR 21636, 21643, 21644, 21645, and 2291. All of this material is directly relevant to understanding the extent to which Sarepta's studies established the efficacy of Exondys 51, as the FDA concluded. *Id.* at 31, 33.

47. I also identified the type of safety data that could not properly be withheld. For example, I identified Bates FDACDER_SAR 21652 as containing redactions to which I objected, because it is identified as containing descriptions of Adverse Events occurring to study participants. *Id.* at 32.

48. Similarly, I objected to the redactions made to documents numbered Bates FDACDER_SAR 21624, 21634, and 21643-21647 because they are described as containing "Appendix name"—i.e., the name of scientific documents, which is another category of information I contend defendants may not properly withhold. *Id.*

49. I am willing to forgo challenges to Bates FDACDER_SAR 21640 (a sentence titled "dose modification, reduction, or delay") and Bates FDACDER_SAR 21650 (a paragraph that describes the "adverse event reporting procedure").

50. In its motion, Sarepta gives specific examples from selected pages of the material produced, annexed as Exhibit B, ECF No. 73-2. The Bates page numbers at the bottom of the pages of Exhibit B do not exactly match the Bates page numbers given to me by the FDA. The FDA provided a February 2018 production that contained a less-redacted version of some previously released information. The pages in the February 2018 production had an -A added to the original Bates numbers. Many of the pages in Exhibit B are alternate versions of the pages provided in the February 2018 production, with the redactions identical to those in the February 2018 production but without the -A at the end of the Bates numbers. However, the redactions on one of the pages, Bates number FDACDER_SAR_000417 (page 25 of Exhibit B), match neither the redactions on the original page FDACDER_SAR_000417, provided to me, nor on the page FDACDER_SAR_000417-A provided to me in the February 2018 production. I have referred to the pages provided to me by the FDA, rather than those annexed by Sarepta.

51. Attached to the Kenney Declaration is a true and correct copy of the spreadsheet explaining when certain pages in Exhibit B are not pages I am seeking, and why the pages that I am seeking should be released because the information I am seeking is in the public domain. In addition, attached to the Kenney Declaration is Exhibit A, an index of the entire two CSRs and Appendices, color-coded by the redactions I am challenging.

52. I am not contesting the majority of the redactions in the study protocols for Studies 201 and 202 and the interim analysis plan, which my attorneys made clear to opposing counsel. I am not conceding that clinical study protocols are generally exempt from disclosure under Exemption 4, but I do not seek the complete clinical study protocols in this case. I am also not challenging the vast majority of statistical plans or asking for researcher names.

53. Similarly, I am not seeking any demographic information, nor patient's age, height, and weight information.

E. INFORMATION ALREADY PUBLIC ABOUT EXONDYS 51

54. As part of my investigation, I have reviewed sources of public information regarding Exondys 51, including Sarepta press releases, peer-reviewed articles in scientific journals, and abstracts of scientific material presented at conferences. I also reviewed materials available on the FDA website, including the FDA "Action Package" for approval of Exondys 51, and materials provided by Sarepta, the FDA, and others for use at meetings of the FDA Peripheral and Central Nervous System Drugs Advisory Committee scheduled for January 22, 2016 and April 25, 2016, and for a May 18, 2017 meeting of the Pediatric Advisory Committee and Pediatric Ethics Subcommittee. I reviewed the transcripts of the April 25, 2016 and May 18, 2017 committee meetings as well.

55. I have also reviewed sources of public information regarding Duchenne and its treatment, including the most recent expert recommendations for care of Duchenne patients, as well as guidance documents on the development of new treatments for Duchenne published by the FDA and the EMA. Among the materials I reviewed were comments submitted by Sarepta on the FDA's draft guidance on development of treatments for Duchenne.

56. My investigation included a review of the public clinical trial listings reported by Sarepta or its investigators to the ClinicalTrials.gov website maintained by the National Institutes of Health. The responsible party for any "applicable clinical trial"[7] that began after September 27, 2007 is required by statute to register the study on ClinicalTrials.gov. *See* 42 U.S.C. § 282. This public disclosure must include a description of the study, the method of recruiting human participants, the location of the study, and contact information for those who wish to join the trial. § 282(j)(2)(A)(ii). The public disclosure must also set forth the primary purpose of the study, the study design, study

[7] An "applicable drug clinical trial" is defined by statute to mean: "The term 'applicable drug clinical trial' means a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 355 of title 21 or to section 262 of this title. § 282(j)(1)(A)(iii). Studies 201 and 202 are "applicable clinical trials."

phase, study type, primary disease or condition being studied, intervention name and type, study start date, expected completion date, target number of subjects, primary outcome measures, and secondary outcome measures. *Id.*

57. Sponsors must also report the "basic results" of their study to ClinicalTrials.gov at the end of the study or within thirty days of drug approval. § 282(j)(3)(iv). This information includes participant participation information, demographic and baseline characteristics of participants, primary and secondary outcomes and statistical analyses, adverse event information, and other administrative information. § 282(j)(3)(C).

58. Sarepta has registered eight trials for Exondys 51 on ClinicalTrials.gov. *See* Kenney Decl., Ex. S (collecting the most important listings). It has reported all required information for Study 201, *id.* at 2-32, and all required information except the test results for Study 202, *see id.* at 44. The completion date for Study 202 was April 2016, according to its ClinicalTrials.gov listing, but Sarepta did not report study results by the statutory deadline. *Id.*; *id.* at 32. To date, no results have been posted.

59. The EMA also has a publicly searchable registry of clinical trials called the EU Clinical Trials Register. It is similar to ClinicalTrials.gov and presents information provided by drug manufacturers. Sarepta registered Studies 201 and 201 on the EU Clinical Trials Register. *See id.*, Ex. T.

1. Public Disclosure of Sarepta's Clinical Endpoints

60. Sarepta sought to measure clinical trial efficacy of Exondys 51 using various clinical metrics, or endpoints, the results and descriptions of many of which were redacted from the CSRs. In the Study 201 CSR, the narrative descriptions of the following endpoints were completely redacted: Change from Baseline in the Timed 4-Step Test; Change from Baseline on the Maximum Voluntary Isometric Contraction Test; Change from Baseline on the Timed 10-Meter Run; Change from Baseline on the 9-Hole Peg Test; Change from Baseline on Pulmonary Function Test Measurements; Change

from Baseline on the Pediatric Quality of Life Inventory. The following tables were completely redacted from the Study 201 CSR: Summary of Drug Exposure Through Week 24 (Safety Population); Summary of Exon Skipping (Full Analysis Population); Summary and Change from Baseline in 10-Meter Run Scores (Full Analysis and *m*ITT [modified Intent to Treat] Populations); Summary and Change from Baseline in 9-Hole Peg Test Scores (Full Analysis Population); Summary and Change from Baseline in Select PFT Parameters (Full Analysis Population); Plasma Pharmacokinetic Parameters for Eteplirsen At Week 12 (PK Population); and Week 24-28: Summary of Treatment Emergent Adverse Events (Safety Population). Additional tables withheld, with redacted names, pertain to the: Maximum Voluntary Isometric Contraction Test; and the Timed 4-Step Test. All the listings containing patient-level results were completely redacted, and the names of some of the listings were redacted as well. The western blot and immunofluorescence images were withheld that shed light on the amount of dystrophin.

61. Redactions in the Study 202 CSR were even more extensive. The narrative descriptions of the following endpoints were completely redacted: Efficacy, Safety and Pharmacokinetic Variables. In Efficacy Assessments, subsection Muscle/Motor Function and Strength, the following narrative descriptions are completely redacted: Timed 4-Step Test; Maximum Voluntary Isometric Contraction Test; Timed 10-Meter Run; 9-Hole Peg Test; and Pediatric Quality of Life Inventory. Also completely redacted were all but one case study narrative in the Serious Adverse Events subsection of Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events. The following tables were completely redacted: Baseline Disease Characteristics (Safety Population); Analysis of Change from Baseline to Week 48 in Percent; Dystrophin- Positive Fibers Detected by IHC, ITT (Intent to Treat) Population; Analysis of Change from Baseline for 6MWT, *m*ITT Population; Summary Results for Select Pulmonary Function Tests, ITT Population; Eteplirsen Plasma Concentrations (5 Minutes Post-Infusion); Summary of Eteplirsen

Exposure; Summary of Most Common (2:10% Overall) Treatment-Emergent Adverse Events through Week 168, Safety Population; Summary of Severe Treatment-Emergent Adverse Events, Safety Population; Summary of Treatment-Related Treatment-Emergent Adverse Events, Safety Population; Serum Chemistry Laboratory Mean (SD) Test Results of Special Interest Parameters Over Time, Safety Population; Coagulation Laboratory Mean (SD) Test Results of Special Interest Parameters Over Time, Safety Population; and Protein in Urine. The following figures were completely redacted: Spaghetti Plot: 6 Minute Walk Test by Week of Assessment, ITT Population; Spaghetti Plot: 6 Minute Walk Test by Week of Assessment, *m*ITT Population; Spaghetti Plot: Percent Predicted FVC, ITT Population; Spaghetti Plot: Percent Predicted MEP, ITT Population; and Spaghetti Plot: Percent Predicted MIP, ITT Population. All of the listings containing patient-level results were completely redacted, and the names of many listings were withheld as well. The western blot and immunofluorescence images were withheld in full. The FDA also withheld the schedule of events detailing when tests were administered, although it was made public in the FDA Medical Review. *See* Bates FDACDER_SAR_[redacted]21643; Bates FDACDER_SAR [redacted]6503; Kenney Decl., Ex. R, 54.

62. But Sarepta itself has disclosed all of these endpoints to the U.S. and European clinical trial registries, even disclosing endpoints described as "exploratory" in Sarepta's Corrected Motion for Summary Judgment. The publicly disclosed clinical endpoints for Sarepta's study of Exondys 51 on the clinical trial registries include physical measures and patient- and parent-reported outcomes.

63. The disclosed clinical endpoints include the change from baseline in the 6-Minute Walk Test (6MWT); the North Star Ambulatory Assessment (NSAA) Total Score; ability to independently rise from supine; rise time; timed 10-meter walk/run; Timed 4-Step Test; and 9-Hole Peg Test. The change from baseline in Maximum Voluntary Isometric Contraction Test (MVICT) to measure: elbow flexion and extension; knee flexion and extension; and hand grip strength was also an

endpoint. Pulmonary Function Tests (PFTs) included: forced vital capacity (FVC); percent predicted FVC (FVC%p); maximum expiratory pressure (MEP); percent predicted MEP (MEP%p); maximum inspiratory pressure (MIP); percent predicted MIP (MIP%p); forced expiratory volume in 1 second (FEV1); percent predicted FEV1(%FEV1); and FEV1/FVC ratio. In addition, Sarepta has included on the clinical trial registry listings patient and parent reports on portions of the Pediatric Quality of Life Inventory™ (PedsQL): Child report (total score and domain scores); Parent report (total score and domain scores); Child neuromuscular report total score; and Parent neuromuscular report total score.

64. Many of the clinical measures used by Sarepta as clinical endpoints are commonly administered in Duchenne clinical trials,[8] and according to a report from the International DMD Clinical Outcomes Working Group, were recognized clinical outcome measures used in other clinical trials as early as 2010.[9] The EMA guidelines refer by name to the majority of these tests, and many are discussed in the FDA guidance for industry as well.[10] None of the physical measures and parent- and patient-reported outcomes were developed by Sarepta—some studies of their use for Duchenne

[8]Mah JK. An Overview of Recent Therapeutics Advances for Duchenne Muscular Dystrophy. *Methods Mol Biol* 2018;1687:3-17 (Kenney Decl., Ex. V, 128-142).

[9]Bushby K, Connor E. Clinical Outcome Measures for Trials in Duchenne Muscular Dystrophy: Report from International Working Group Meetings. *Clin Investig* (London) 2011;1(19):1217-35 (Kenney Decl., Ex. V, 91-127); Bushby K, et al., Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care, *The Lancet Neurology*, 2010;9(2):177-189 (Kenney Decl., Ex. V. 74-90).

[10]U.S. Department of Health & Human Services, Food & Drug Administration, Center for Drug Evaluation and Research, *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment, Guidance for Industry* (2018) (Kenney Decl., Ex. U, 2-17); European Medicines Agency Committee for Medicinal Products for Human Use, *Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy* (2015) (Kenney Decl., Ex. U, 18-37).

were actually funded by competitors to Sarepta, including the pulmonary function tests[11] and the 6MWT.[12]

65. The 6MWT is a commonly used test used to evaluate patients with Duchenne. The test is used to measure how far patients can walk in six minutes (measured in meters).[13] This is a relevant measure because individuals with Duchenne lose ambulatory function over time. The detailed, de-identified patient-level results regarding the 6MWT are particularly of interest because, as noted above, a recent publication concerning another Sarepta clinical trial concedes that the 6MWT results can be manipulated by both parent coaching and staff sympathy.[14]

66. Results from the 6MWT in Exondys 51 clinical trials have been reported and commented upon extensively in the scientific literature. Methods for conducting the test, detailed results including tables and figures, and statistical analysis of those results have all been published, with the most detail included in an article by Dr. Mendell and others focused on longitudinal effects of the drug on walking.[15] Since the 6MWT was one of the main outcomes assessed by the FDA, Sarepta's briefing materials prepared in advance of the April 2016 FDA advisory committee meeting and released on the FDA website contain detailed information for the 6MWT. The material includes

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[11]Schoser B, Fong E, Geberhiwot T, et al. Maximum inspiratory pressure as a clinically meaningful trial endpoint for neuromuscular diseases: A comprehensive review of the literature. *Orphanet Journal of Rare Diseases* 2017;12:52 (Kenney Decl., Ex. V, 62-73).

[12]McDonald CM, Henricson EK, Han JJ, et al. The 6-Minute Walk Test as a New Outcome Measure in Duchenne Muscular Dystrophy. *Muscle Nerve* 2010;41(4):500-20 (Kenney Decl., Ex. V, 12-21).

[13]ATS Statement. *American Journal of Respiratory and Critical Care Medicine.* 2002;166(1):111–117 (Kenney Decl., Ex. V, 4-10).

[14]Servais L, Grelet M, Seferian A, et al. Movement monitoring at home and during study visits identifies sources of variability in 6MWT performance in Duchenne muscular dystrophy. *Neuromuscular Disord* 2016;26:S152-S153 (Kenney Decl., Ex. V, 2-3.)

[15]Mendell JR, et al. Eteplirsen for the Treatment of Duchenne Muscular Dystrophy. *Annals of Neurology* 2013;74(5):637-47 (Kenney Decl., Ex. N); Mendell JR, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology* 2016;79(2):257-71 (Kenney Decl., Ex. X, 118-133).

description of the testing procedure, statistical analyses, justification for excluding the two patients who lost the ability to walk from the modified intent to treat (*m*ITT) analyses, statistical methods, statistical correction analyses, results, including a table of individual patient-level results by study participant ID, tables and figures depicting change over time for four years, comparing 6MWT results to North Star Ambulatory Assessment results, and comparing 6MWT results to ability to rise. Kenney Decl., Ex. Q, 74, 76, 148. The briefing document also contained a spaghetti plot, graphically depicting each patient's 6MWT results over the course of four years, as compared to the individual historical control patients. *Id.* at 106. The FDA reviews of Exondys 51, available on its website contain detailed evaluation of Sarepta's 6MWT results, and also the methods and results of re-analyses of the 6MWT data by FDA scientists.

67. The reasoning, if any, justifying the redactions to the 6MWT information is incomprehensible. Although the methods as well as results have been made public in multiple forums, the FDA made extensive redactions to the narrative description of methods and results in the CSRs and appendices. For Study 201, I was provided with unredacted narrative description of methods and results in the CSR, as well as with results tables in the Study 201 CSR and Appendix. Only the individual patient-level results from the Appendix for the Study 201 CSR were withheld. However, for Study 202, not only were the narrative description of methods and results redacted, but also many of the results tables and figures in the Study 201 CSR and Appendix were withheld. *See* Bates FDACDER_SAR_000545 to FDACDER_SAR_000550. The individual patient-level results from the Appendix for the Study 202 CSR also were withheld.

68. One striking example of the illogic of the redactions made to the CSRs is the redaction of the spaghetti plots depicting individual 6MWT results over the course of four years for study participants as compared to historical control patients. This figure was withheld from me in the Study

202 CSR Appendix. However, an apparently identical figure was made publicly available as part of Sarepta's briefing document in advance of the April 25, 2016 FDA Advisory Committee Meeting.

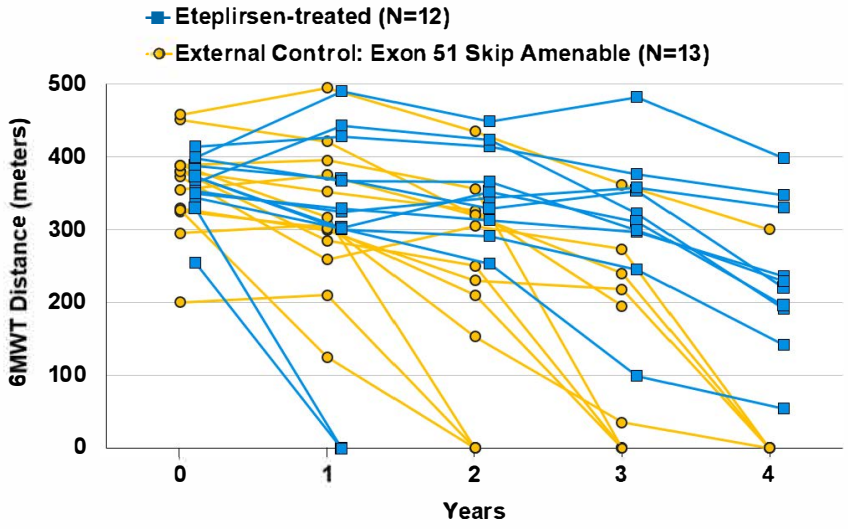
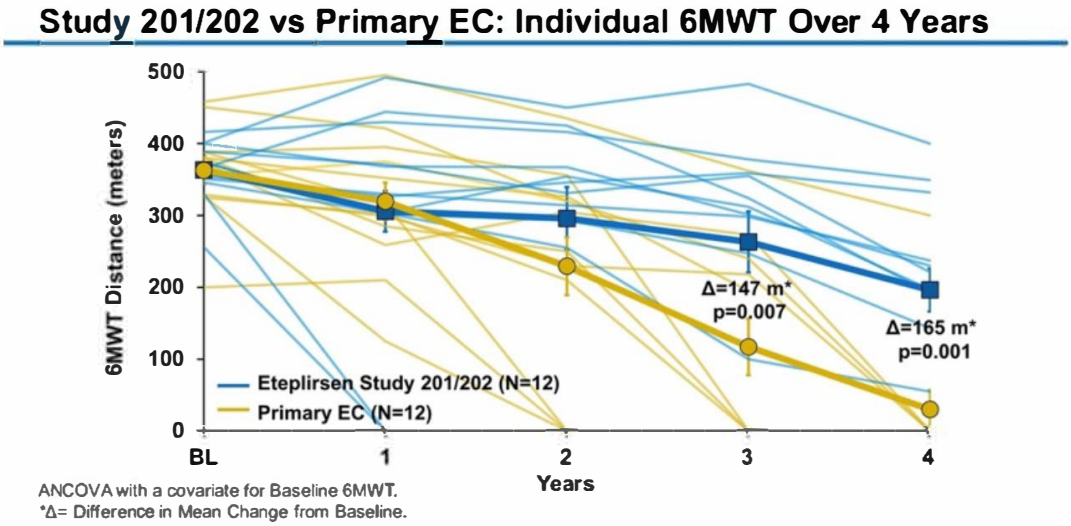


Figure 19: Individual 6MWT Values Over Time in Eteplirsen-Treated Patients (Studies 201/202) vs. External Control (N = 13)

Kenney Decl., Ex. ●, 66.

69. Sarepta even disclosed this withheld 6MWT table in a publicly available May 3, 2018 Securities and Exchange Commission (SEC) Form 8-K filing, which contained the presentation slides from Sarepta's April 24, 2018 presentation to the EMA.



Kenney Decl., Ex. P, 38.

70. In addition to the 6MWT, Sarepta used another clinical endpoint that is widely accepted. The NSAA is used to evaluate ambulatory function in muscular dystrophy patients. It has been "validated" and is "widely used internationally, in clinical settings and as a secondary outcome measure[] in clinical trials."[16] Patients' capabilities are assessed as they perform a variety of tasks, including rising from supine, running, jumping, hopping on one foot, and stepping up and down on a box. Patients are given a score of 0, 1, or 2 for each task.[17] NSAA methods and results were also extensively discussed in Sarepta's briefing documents, and results were displayed graphically, including individual patient-level results for the NSAA, *id.*, Ex. Q, 74, 150, and for components of the NSAA including the ability to rise without external support and rise time, *id.* at 76, 148, 150. The FDA Medical Review, available on the FDA website, contains individual patient-level results and analysis on the 10-meter run, another NSAA component. *See id.*, Ex. R, 62. Yet narrative portions of the CSRs and patient level results of the NSAA were redacted. Another measure for ambulatory functioning, the 4-Step Test, was also used. The FDA Medical Review contains a detailed description, tables and figures depicting the Timed 4-Step Test results, including change from baseline, individual patient-level results over time, as well as a spaghetti plot of individual patient-level results over time, and individual plots of each patient's results over time. *Id.* at 53, 63-65. The FDA redacted the description of the 4-Step Test and all of the results from the Study 202 CSR and Appendix. *Id.*, Ex. C, 24-28.

71. Results from upper limb function testing by Sarepta have specifically been reported, including results of the 9-Hole Peg Test and MVICT with a quantitative movement assessment system.

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[16]Ricotti V, Ridout DA, Pane M, et al. The North Star Ambulatory Assessment in Duchenne Muscular Dystrophy: Considerations for the Design of Clinical Trials. *J Neurol Neurosurg Psychiatry*. 2016;87(2):149-155 (Kenney Decl., Ex. V, 25-32).

[17]North Star Clinical Network, *The North Star Ambulatory Assessment*, http://www.musculardystrophyuk.org/assets/0000/6388/NorthStar.pdf (last accessed May 29, 2018) (Kenney Decl., Ex. V, 22-24).

In the 9-Hole Peg test, the patient is given nine pegs and a pegboard with nine holes and then timed to see how long it takes them to place all pegs in the board. According to the scientific literature, this test is used to assess the function of patients' upper extremities.[18] The MVICT is a common test for assessing muscular strength in patients with a variety of neuromuscular diseases. According to the literature, the MVICT measures the force exerted by certain muscle groups, in this case elbow flexion and extension and hand grip.[19] Sarepta reported its intention to use some measures for upper limb function outcomes prospectively.[20] The results of the 9-Hole Peg Test and the MVICT from Studies 201 and 202 were presented at a scientific conference in 2017.[21] *See* Bates FDACDER_SAR_00095-A to FDACDER_SAR_00096-A. 9-Hole Peg Test); Bates FDACDER_SAR_00092-A to FDACDER_SAR_000 93-A (MVICT).

72. Pulmonary function tests were also an important outcome measure. As muscle function declines, patients with Duchenne become unable to breathe on their own, and many require a ventilator. A paper regarding longitudinal pulmonary function results in Studies 201 and 202 was published earlier this year, and contains descriptions of methods, statistical analyses, and detailed results including forced vital capacity (FVC), percent predicted FVC, maximal inspiratory pressure (MIP), percent predicted MIP, maximal expiratory pressure (MEP) and percent predicted MIP.

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[18] *9-Hole Peg Test (9-HPT)*, National Multiple Sclerosis Society, https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/9-Hole-Peg-Test-(9-HPT) (Kenney Decl., Ex. V, 45-46).

[19] See Meldrum D, Cahalane E, Conroy R, Fitzgerald D, O. H. Maximum voluntary isometric contraction: reference values and clinical application. *Amyotroph Lateral Scler*. 2007 Feb;8(1):47-55, 47 (Kenney Decl., Ex. V, 33-44); Alfano L, Berry K, Mendell J, et al. Effects of long-term eteplirsen treatment on upper limb function in patients with Duchenne muscular dystrophy: findings of two phase 2 clinical trials. *Neuromuscular Disorders*. 2017;27:S216-S216 (Kenney Decl., Ex. X, 2).

[20] Muntoni F, et al., A Phase I/IIa Clinical Trial in Duchenne Muscular Dystrophy Using Systemically Delivered Morpholino Antisense Oligomer to Skip Exon 53 (SKIP-NMD). *Hum Gene Ther Cl Dev* 2015;26(2):92-95 (Kenney Decl., Ex. X, 143-46).

[21] Alfano L, Berry K, Mendell J, et al. Effects of Long-term Eteplirsen Treatment on Upper Limb Function in Patients with Duchenne Muscular Dystrophy: Findings of Two Phase 2 Clinical Trials. *Neuromuscular Disorders* 2017;27:S216-S216 (Kenney Decl., Ex. X, 2).

Detailed result tables and figures are included in the paper.[22] Two conference abstracts specifically on respiratory function in Exondys 51 trial participants have also been published.[23] The methods for the pulmonary function tests were disclosed in Sarepta's briefing document, as were individual patient-level results. Kenney Decl., Ex. Q, 25, 76-77.

73. The redactions with regard to pulmonary function testing are illogical and contradictory. The CSRs contain descriptions of the methods, and high-level summaries of the results. Due to extensive redactions, I was provided with only one paragraph of text regarding pulmonary function testing procedures from the CSR for Study 201, and no results information. However, I was provided with all of the more detailed pulmonary function test results contained in the Study 201 Appendix, other than the individual patient-level results. *See* Bates FDACDER_SAR_0001372 to FDACDER_SAR_0001406. The CSR for Study 202 pulmonary function testing section was heavily redacted, *see* Bates FDACDER_SAR_0006552 to FDACDER_SAR_0006559, yet I was provided with all of the pulmonary function test results in the Study 202 Appendix, other than individual patient-level results.

74. There can be no reasonable justification for the redaction of summary information and release of detailed information regarding pulmonary function, particularly since the pulmonary function results and procedures from Studies 201 and 202 have been published and presented at scientific conferences.

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[22] Kinane TB, Mayer OH, Duda PW, Lowes LP, Moody SL, Mendell JR. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *Journal of Neuromuscular Diseases.* 2018;5:47-58 (Kenney Decl., Ex. X, 92-103).

[23] Kinane TB, Mayer O, Lowes L, et al. Respiratory Function in Eteplirsen-Treated Duchenne Muscular Dystrophy (DMD) Patients Compared to Natural History. *American Journal of Respiratory and Critical Care Medicine* 2017;195:A2649 (Kenney Decl., Ex. X, 104). Kinane B, Mayer O, Lowes L, et al. P.219 - Respiratory function in eteplirsen-treated Duchenne muscular dystrophy (DMD) patients compared to natural history. *Neuromuscular Disord* 2016;26(Supplement 2):S154 (Kenney Decl., Ex. X, 105).

75. The Pediatric Quality of Life Inventory (PedsQL) was also used by Sarepta. According to the scientific literature, this is a standardized survey created for pediatric patients with acute and chronic health conditions to evaluate their quality of life.[24] The neuromuscular module is a specific module of the PedsQL and is often used to assess quality of life for patients with Duchenne.[25] Results from the PedsQL are of interest to me, because of the importance in assessing children's subjective perceived quality of life, in addition to quantifiable objective measures. Yet these results were completely redacted in the Study 201 CSR (Bates FDACDER_SAR_00098-A to FDACDER_SAR_00099-A), as well as in the Study 202 CSR (Bates FDACDER_SAR_0006513 to FDACDER_SAR_0006514).

2. Public Disclosure of Sarepta's Surrogate Measures

76. Patients with Duchenne have a mutation on a gene responsible for the production of a protein called dystrophin and are extremely dystrophin deficient. According to both the CSRs and the listings on ClinicalTrials.gov, in Study 201 and Study 202 patients' dystrophin protein levels were used as a "surrogate measure" of the efficacy of Exondys 51, that is a measure that is "reasonably likely" to predict a clinical benefit from the drug.

77. Researchers thus looked at the change in dystrophin production in patients over time as an indicator that Exondys 51 was likely to produce a clinical benefit. To measure this change, muscle biopsies were conducted at baseline, and at 12, 24, 48 and 180 weeks during the clinical trials. Kenney Decl., Ex. N; *id.*, Ex. Q, 80. Tissue from the muscle biopsies were used for a number of tests, including the difference from untreated controls in: percentage of dystrophin positive fibers as

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[24] James W. Varni, *The PedsQL Measurement Model for the Pediatric Quality of Life Inventory*, PedsQL, http://www.pedsql.org/about_pedsql.html (last accessed May 29, 2018) (Kenney Decl., Ex. V, 47-48).

[25] Davis SE, Hynan LS, Limbers CA, et al. The PedsQL™ in Pediatric Patients with Duchenne Muscular Dystrophy: Feasibility, Reliability, and Validity of the Pediatric Quality of Life Inventory Neuromuscular Module and Generic Core Scales. *Journal of Clinical Neuromuscular Disease.* 2010;11(3):97-109, at 97 (Kenney Decl., Ex. V, 49-61).

measured in the muscle biopsy tissue using IHC; and muscle biopsy levels of dystrophin intensity per fiber (determined by BIOQUANT® software). Disclosed surrogate measures also included the change from baseline in: Exon skipping (assessed by reverse transcription polymerase chain reaction [RT-PCR]); Total dystrophin protein levels in muscle biopsy tissue as determined by Western blot analysis; dystrophin percent of normal protein as determined by Western blot analysis; percentage of dystrophin positive fibers as measured in the muscle biopsy tissue using immunohistochemistry (IHC); percentage of dystrophin positive fibers as measured by immunohistochemistry (IHC) using anti-dystrophin antibody MANDYS106; dystrophin intensity levels as measured by immunohistochemistry (IHC); dystrophin intensity per fiber in muscle biopsy tissue as determined by immunohistochemistry (IHC); muscle biopsy levels of dystrophin intensity per fiber (determined by BIOQUANT® software); CD3, CD4, and CD8 lymphocyte counts as measured in the muscle biopsy tissue; and finally, CD3, CD4, and CD8 lymphocyte counts as measured in the muscle biopsy tissue by immunohistochemistry (IHC). *Id.*, Ex. T.

78. IHC is a technique that utilizes the properties of specific antibodies to bind to a stain, to allow visual identification of a target protein, in this case dystrophin.[26] Sarepta conducted IHC analyses using several antibodies, including MANDYS106. IHC methods, summary results, and individual patient-level results and images were publicly released in Sarepta's briefing document in advance of the April 25, 2016 FDA Advisory Committee Meeting. *Id.*, Ex. Q, 158-159.

79. Sarepta obtained CD3, CD4 and CD8 lymphocyte (white blood cells called T-cells) counts from analyses of muscle biopsy tissue. When a person's immune system is threatened by a foreign agent, their bone marrow typically produces white blood cells to counter it as part of the

[26] *Overview of Immunohistochemistry (IHC)*, ThermoFisher Scientific, https://www.thermofisher.com/us/en/home/life-science/protein-biology/protein-biology-learning-center/protein-biology-resource-library/pierce-protein-methods/overview-immunohistochemistry.html (last visited May 29, 2018) (Kenney Decl., Ex. W, 2-10).

normal inflammatory immune response. The briefing document in advance of the April 25, 2016 FDA Advisory Committee Meeting contains discussion of the results. *Id.* at 158-159, 120-87.

80. Dystrophin protein levels were measured using Western blot tests. Western blotting is a common technique used to separate mixtures of proteins and can be used to identify visually the existence of a specific protein within the mixture.[27] Western blot images were prepared using the tissue from the muscle biopsies. Individual patient-level Western blot images and results, tables and figures, along with narrative description of methods and results were publicly released in Sarepta's briefing document in advance of the April 25, 2016 FDA Advisory Committee Meeting. *Id.* at 158-59.

81. RT-PCR analysis of dystrophin production using mRNA extracted from muscle biopsy tissue was used to assess whether Exondys 51 successfully caused cells to skip over mutated exons and produce dystrophin. Sarepta's briefing document in advance of the April 25, 2016 FDA Advisory Committee Meeting describes the theory and methodology used for RT-PCR analysis. *Id.* at 79-80.

82. Information related to dystrophin as a clinical endpoint has been published in multiple scientific forums, and the metric was not invented by Sarepta. Early studies describe the basic science involved, the creation of antisense oligomers (the class of drugs), and the chemical structure of

[27] Mahmood T, Yang P-C. Western blot: Technique, Theory, and Trouble Shooting. *North American Journal of Medical Sciences*. 2012;4(9):429-434 (Kenney Decl., Ex. W, 32-37).

Exondys 51.[28] Results from in vitro testing[29] as well as pharmacokinetics and toxicology results from animal studies have been published.[30]

83. The specific methodology adopted by Sarepta in its Western blot analysis and RT-PCR analysis, and in conducting biopsies, tissue preparation, and exon-skipping assay development have been reported in the scientific literature in great detail.[31] Information regarding the dystrophin measures and results, lymphocyte counts, and exon-skipping from Sarepta's studies have also been published.[32] Individual patient-level results for multiple dystrophin measures were contained in Sarepta's briefing document. *Id.* at 74, 76-77, 148, 156-157, 160. Although Sarepta contends in its papers that its IHC method is confidential commercial information, Sarepta has publicly conceded, in

[28]Kinali M, Arechavala-Gomeza V, Feng L, et al. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. *Lancet Neurol* 2009;8(10):918-28 (Kenney Decl., Ex. X, 73-90); Cirak S, Feng L, Anthony K, et al. Restoration of the dystrophin-associated glycoprotein complex after exon skipping therapy in Duchenne muscular dystrophy. *Mol Ther* 2012;20(2):462-7 (Kenney Decl., Ex. X, 65-70); Arechavala-Gomeza V, Graham IR, Popplewell LJ, et al. Comparative analysis of antisense oligonucleotide sequences for targeted skipping of exon 51 during dystrophin pre-mRNA splicing in human muscle. *Hum Gene Ther* 2007;18(9):798-810 (Kenney Decl., Ex. X, 13-25).

[29]Sazani P, Magee T, Charleston JS, et al. In Vitro Pharmacokinetic Evaluation of Eteplirsen, SRP-4045, and SRP-4053; Three Phosphorodiamidate Morpholino Oligomers (PMO) for the Treatment of Patients with Duchenne Muscular Dystrophy (DMD) *Neurology* 2015;84(14 Supplement):P5.061 (Kenney Decl., Ex. X, 182-85).

[30]Sazani P, Van Ness KP, Weller DL, et al. Chemical and Mechanistic Toxicology Evaluation of Exon Skipping Phosphorodiamidate Morpholino Oligomers in mdx Mice. *International Journal of Toxicology* 2011;30(3):322-33 (Kenney Decl., Ex. X, 161-172); Sazani P, Van Ness KP, Weller DL, et al. Repeat-Dose Toxicology Evaluation in Cynomolgus Monkeys of AVI-4658, a Phosphorodiamidate Morpholino Oligomer (PMO) Drug for the Treatment of Duchenne Muscular Dystrophy. *International Journal of Toxicology* 2011;30(3):313-21 (Kenney Decl., Ex. X, 173-81); Kole R, Leppert BJ. Targeting mRNA Splicing as a Potential Treatment for Duchenne Muscular Dystrophy. *Discovery Medicine* 2012;14(74):59-69 (Kenney Decl., Ex. X, 106-14).

[31]Schnell F, Donoghue C, Dworzak J, et al. Development of a validated western blot method for quantification of human dystrophin protein. *Neuromuscular Disord* 2016;26:S160-S160 (Kenney Decl., Ex. X, 187); Anthony K, Feng L, Arechavala-Gomeza V, et al. Exon skipping quantification by quantitative reverse-transcription polymerase chain reaction in Duchenne muscular dystrophy patients treated with the antisense oligomer eteplirsen. *Hum Gene Ther Methods* 2012;23(5):336-45 (Kenney Decl., Ex. X, 3-12).

[32] Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the Treatment of Duchenne Muscular Dystrophy. *Annals of Neurology* 2013;74(5):637-47 (Kenney Decl., Ex. N); Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology* 2016;79(2):257-71 (Kenney Decl., Ex. E, 118-133).

encouraging the FDA to adopt IHC as a standard for measuring dystrophin, that IHC is "a well-established method, having been used for over 20 years in the diagnosis of [Duchenne] and has been validated in [Duchenne] clinical trials." *Id.*, Ex. W, 18.

84. Similar to the redactions to physical outcome measures, the redactions to the biological measures appear to follow no rhyme or reason. As discussed *supra,* the Western blot, IHC methods, analyses, and results have been made publicly available not only through journal articles, but also through the Sarepta briefing document and the FDA's review documents. Yet with regard to the key outcome measure of dystrophin production, more than a dozen summary results tables, listings of results by individual patients, as well as the key figure regarding change in dystrophin production from baseline as a percent of normal were withheld from me in their entirety. The FDA also withheld the timing of muscle biopsies, although that information has been made public as discussed *supra.*

85. In my experience as a science journalist, I would have expected to see much of the information related to these additional outcome measures readily disclosed if those measures supported the conclusion that the drug was effective. It is noteworthy that Sarepta has failed to disclose these outcome measures, especially given the intense controversy over the effectiveness of its drug.

3. Public Disclosure of Sarepta's Safety Results and Adverse Events

86. In developing its protocols for Study 201 and Study 202, Sarepta included specific tests to address safety concerns, with special emphasis on "inflammatory events, coagulopathies, and hepatic and renal toxicity."[33] In other words, they were testing for acute flare-ups of the immune system, blood-clotting problems, and attacks on the liver and kidney. This was due to well-known

[33]Mendell JR, Sahenk Z, Rodino-Klapac LR. Clinical trials of exon skipping in Duchenne muscular dystrophy. *Expert Opin Orphan* D 2017;5(9):683-90. (Kenney Decl., Ex. X, 134-42).

risks posed by related compounds.[34] A similar drug, drisapersen (Kyndrisa), developed by BioMarin Pharmaceuticals, was rejected by the FDA in 2016, due in part to kidney and liver toxicity, thrombocytopenia (a loss of platelets reducing the blood's ability to clot), and adverse reactions at the drug's injection site.[35]

87. Some of the laboratory testing in the clinical trials was conducted because it focused on laboratory anomalies typically seen in patients with Duchenne. Duchenne can be diagnosed in infants after laboratory tests reveal abnormally high creatine kinase (CK) levels.[36] The CD3, CD4, and CD8 inflammation markers are also elevated in patients with Duchenne. Exondys 51 trials included these measures in part under the theory that if the treatment worked, these abnormal laboratory values would shift closer to the normal range.[37]

88. The clinical trials also included assessment of cardiac function. Information collected included vital signs, physical examination findings, 12-lead electrocardiogram results, echocardiography results, coagulation laboratory results, and Holter monitoring results. This information regarding the safety of the drug was largely removed from both the text of the CSRs and the Appendices provided to me. Detailed results of creatine kinase (CK) levels and CD3, CD4 and CD8 inflammation markers were all withheld. So too were cardiac measures, vital signs, physical examination findings, 12-lead electrocardiogram results, echocardiography results, coagulation

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[34]Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology* 2016;79(2):257-71 (Kenney Decl., Ex., 118-133).

[35]Mendell JR, Sahenk Z, Rodino-Klapac LR. Clinical trials of exon skipping in Duchenne muscular dystrophy. *Expert Opin Orphan D* 2017;5(9):683-90 (Kenney Decl., Ex. X, 134-42).

[36]Mendell JR, Shilling C, Leslie ND, et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. *Annals of Neurology* 2012;71(3):304-13 (Kenney Decl., Ex. W, 22-31).

[37]Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet* 2011;378(9791):595-605 (Kenney Decl., Ex. X, 26-64).

laboratory results, and Holter monitoring results. *See* Bates FDACDER_SAR_0001794 to FDACDER_SAR_0002371 (Study 201 Appendix); Bates FDACDER_SAR0006590 to FDACDER_SAR_0006592 (Study 202 CSR); Bates FDACDER_SAR00014874 to FDACDER_SAR_00017455 (Study 202 Appendix).

89. The withheld information includes laboratory measures by patient of serum chemistry results, blood coagulation results, urinalysis of protein in the urine, pharmacokinetic results, and lymphocyte counts. Tables detailing abnormal laboratory values were entirely withheld. The withheld tables include numerous shift tables, which list how the study participants' laboratory values and other measures changed over time. *See* Bates FDACDER_SAR0001523 to FDACDER_SAR_0001753 (Study 201 Appendix); Bates FDACDER_SAR_0006583 to FDACDER_SAR_0006590 (Study 202 CSR); Bates FDACDER_SAR00013499 to FDACDER_SAR_00014700 (Study 202 CSR Appendix).

90. Many of these key laboratory results, including serum chemistry, urinalysis, coagulation, and pharmacokinetics, are included in the scientific literature published about Exondys 51. An article regarding an earlier Phase 1b/2 study of Exondys 51 included findings of reduction in CD3, CD4 and CD8 inflammatory markers.[38] The published literature also includes cardiac results.[39]

91. Adverse events from Studies 201 and 202, and from earlier trials of Exondys 51, have been reported in the scientific literature.[40] In addition, Sarepta included detailed information regarding

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[38]Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet* 2011;378(9791):595-605 (Kenney Decl., Ex. X, 26-64).

[39]Cripe L, Colan S, Eliopoulos H, et al. Effects of long-term treatment with eteplirsen on cardiac function. *Neuromuscular Disord* 2017;27:S114-S114 (Kenney Decl., Ex. X, 72); Colan S, Cripe L, Eliopoulos H, et al. Effects of Long-Term Treatment with Eteplirsen on Cardiac Function: Left Ventricular Ejection Fraction in Eteplirsen-Treated Patients. *Annals of Neurology* 2017;82:S325-S325 (Kenney Decl., Ex. X, 71); Mendell J, Powers J, Duda P, et al. Clinical safety of eteplirsen, a phosphorodiamidate morpholino oligomer (PMO), in Duchenne muscular dystrophy (DMD) patients amenable to skipping exon 51 of the DMD gene. *Neuromuscular Disord*2016;26:S153-S154 (Kenney Decl., Ex. X, 115-17).

[40]Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the Treatment of Duchenne Muscular Dystrophy. *Annals of Neurology* 2013;74(5):637-47 (Kenney Decl., Ex. N); Mendell JR, Goemans N, Lowes LP,

adverse events in its briefing document prepared for the FDA Advisory Committee, including narrative descriptions of adverse events, a discussion of adverse event categories of particular interest, case reports by individual participant number for particular adverse events, a table of all adverse events in the 24 weeks of Study 201, and a table of all adverse events from all Exondys 51 trials, by dosing and number of patients exposed. Kenney Decl., Ex. Q, 93-127, 163-177. The FDA's Medical Review also contains a discussion of adverse events, and tables of adverse events. *Id.*, Ex. R, 49, 66-71. A summary of all adverse events experienced by patients in each treatment group in Study 201 and another study involving Exondys 51 are also available on ClinicalTrials.gov. *Id.*, Ex. S, 80-89.

92. However, despite the extensive public disclosure of adverse event information, the information that I am seeking regarding adverse events in the CSRs and Appendices was partially redacted, with one column completely redacted in many of the summary-level tables that I am seeking, as well as redactions in the CSR narrative descriptions regarding adverse events. The FDA's haphazard manner of redaction is also apparent here: although as described *supra*, extensive information regarding adverse events in Studies 201 and 202 is already public, the description of adverse events in the CSRs is redacted, the case narratives of particular adverse events are redacted, some of the adverse event tables are completely redacted—even though they appear to be identical to those in the Briefing document—and the more detailed summary-level tables in the Appendices are redacted.

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et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology* 2016;79(2):257-71 (Kenney Decl., Ex., 118-33); Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet* 2011;378(9791):595-605 (Kenney Decl., Ex. X, 26-64); Kinali M, Arechavala-Gomeza V, Feng L, et al. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. *Lancet Neurol* 2009;8(10):918-28 (Kenney Decl., Ex. X, 73-90).

F. PUBLIC INTEREST IN THE WITHHELD INFORMATION

93. As these examples demonstrate, defendants have removed from the CSRs that were provided to me a great deal of entirely public information concerning the safety and efficacy of Exondys 51 based upon Sarepta's unfounded claims that disclosure would cause substantial competitive harm. The redaction of this information impedes my ability to assess and report on matters of great public concern, including whether the FDA followed its statutory mandates and applied proper scientific methods in approving Exondys 51, and whether the risks and benefits of this drug justify its use, particularly given the extraordinarily cost of Exondys 51.

1. FDA Transparency

94. Although much of the redacted information is public, the withheld details are vital to the public interest. Disclosure of Sarepta's CSRs for Studies 201 and 202 would shed light on the FDA's performance of its statutory duties, including the effectiveness of its approval processes and compliance with its duty to inform the public about the efficacy and safety of new drugs.

95. The Food Drug and Cosmetic Act (FDCA) requires the FDA to "promote the public health by promptly and efficiently reviewing clinical research" and to maximize "the availability and clarity of information about the process for review of applications and submissions . . . [and] the availability and clarity of information for consumers and patients concerning new products." 21 U.S.C. § 393.

96. The FDA's mandate to "efficiently review" clinical research while simultaneously maximizing "the availability and clarity" of public information about its review imposes a directive of transparency on the agency that is widely recognized by scholars and by the FDA itself. In 2009, the FDA launched a "Transparency Initiative" described by the agency as "[a]n agency-wide effort to open the doors of the agency and promote innovation." Kenney Decl., Ex. Z, 2.

97. The FDA acknowledges the public interest in CSR disclosure specifically, and the relationship between CSR disclosure and its transparency mandate. On January 16, 2018, at the Johns Hopkins Forum on Transparency at the U.S. Food and Drug Administration, current FDA Commissioner Scott Gottlieb announced the commencement of a CSR Disclosure Pilot Program that will proactively disclose the CSRs of approved drugs, beginning with nine drugs whose sponsors have agreed to participate.

98. In his speech, Commissioner Gottlieb underscored the importance of CSR disclosure because CSRs provide a key "window into the basis for [the FDA's] approval decisions." *Id* at 7. As he explained, the CSR is "a scientific document addressing efficacy and safety," and therefore CSR disclosure provides "insight into the data and decision-making process behind the FDA's approval of new drugs." *Id.* at 6-7.

99. Commissioner Gottlieb's remarks responded directly to a detailed blueprint for greater transparency at the FDA prepared by independent researchers at Johns Hopkins, Harvard and Yale. The "Blueprint for Transparency at the FDA" calls for maximum disclosure of CSRs, noting that CSR disclosure will enhance public understanding of medical products in a manner consistent with the FDA's statutory mandate. *Id.*, Ex. BB, 2-51. The Blueprint also calls for the FDA to harmonize its CSR disclosure program with that of the EMA, which approved a policy on proactive CSR disclosure for all products in 2014. *Id.* at 20.

100. In an accompanying press release, Commissioner Gottlieb acknowledged that information currently disclosed by the FDA upon approval of a New Drug Application (NDA) does not provide an adequate level of transparency for medical professionals or the public at large. Without disclosure of CSRs, it is "difficult for external audiences to extract all of the detailed clinical evidence that supported the FDA's approval decisions." *Id.*, Ex Z, 7.

101. Dr. Woodcock has stated that publication of CSRs will:

- Enhance the accuracy of information used in scientific publications;
- Increase stakeholders' understanding of the basis for FDA's approval decisions; and
- Inform physicians and other healthcare providers about the detailed results upon which regulatory decisions were based.

Id. at 14.

102. In addition, the EMA proactively releases anonymized clinical information, including CSRs, after a final decision is reached on an application for "marketing authorisation" in the European Union. After the EMA reaches a final decision, the EMA will prepare to proactively release portions of the application, clinical study report, and some appendices. The EMA has a broad policy requiring proactive disclosure of applications submitted for marketing authorization. *Id.*, Ex AA, 2-106. For all approved, withdrawn, or refused applications, the EMA discloses: the clinical overview and clinical summary from the Electronic Common Technical Document (application); and the anonymized CSRs. Three areas of the CSR Appendices are disclosed: the protocol and protocol amendments; the sample case report forms; and the documentation of statistical methods. Non-commercial users can register to review clinical study information on the website. Notably, I am seeking less information about Exondys 51 than the EMA proactively releases for all drugs. I am not seeking release of redacted information from the vast majority of the protocol and protocol amendments, the sample case report forms, and the vast majority of documentation of statistical methods, which are released by the EMA.

103. Current scholarship supports the FDA and EMA's recognition of the importance of CSR disclosure in other respects. Without CSR disclosure, "selective publication of favorable results, gag orders on corporate-funded research, and misleading presentations of data" allow drug manufacturers to manipulate the medical community and the public at large by presenting drugs as

more effective or less risky than they actually are.[41] Publication bias occurs at a number of levels, including "not publishing data at all, selectively reporting data, or framing data."[42]

104. Drs. Aaron Kesselheim and Michelle Mello highlight the potential of "call[ing] into question manufacturers' claims or the FDA's decisions." *Id.*, Ex. BB, 82. While noting the importance of protecting genuine confidential commercial information (CCI), Drs. Kesselheim and Mello assert that "safety data from clinical trials will rarely fit" the definition of CCI. *Id.* at 86. Safety and efficacy data are never enough on their own to support product approval for a competitor, yet the "public health significance [of such data] is particularly high." *Id.*

105. CSR disclosure is important to assessing the FDA's actions because the limited clinical trial data otherwise available to the medical community are often plagued by errors and misrepresentations. Rising and colleagues found a 9% discordance between the conclusions that drug manufacturer's report to the FDA and the conclusion published in scientific reports on the same studies.[43] Turner and colleagues conducted a study of published articles regarding approved antidepressant drug trials and found that although FDA analyses reported that only 51% of the trials were positive, the scientific articles indicated that 94% of the trials conducted were positive.[44]

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[41] Lurie P, Zieve A. *Sometimes the Silence Can Be like the Thunder: Access to Pharmaceutical Data at the FDA.* Law and Contemporary Problems. Summer 2006;69:85-98. (Kenney Decl., Ex. BB, 52.)

[42] Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: Review of publication and presentation. *PLoS Med.* 2008;5(11):e217 (Kenney Decl., Ex. BB, 71); Rising K, Bacchetti P, Bero L (2009) Correction: Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation. *PLoS Med* 6(1): e1000017 (Kenney Decl., Ex. BB, 75).

[43] Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: Review of publication and presentation. *PLoS Med.* 2008;5(11):e217 (Kenney Decl., Ex. BB, 71-72).

[44] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med.* 2008;358(3):252-260 (Kenney Decl., Ex. BB, 85).

106. By redacting unfavorable clinical trial data at scientific sessions and in medical journals, drug manufacturers are able to present their products more favorably to the medical community than they do to the FDA. *Id.* When the FDA withholds unfavorable clinical trial data at the request of manufacturers like Sarepta, it allows them to manipulate the public.

107. Concerns about data accuracy and misrepresentation extend to ClinicalTrials.gov, the most extensive source of clinical trial data currently available to the public. A recent study of the disparities between data on ClinicalTrials.gov and data in matching publications found that study investigators "inconsistently reported the primary outcome result" for 20% of trials.[45] Adverse events, or undesirable patient experiences associated with use of a drug, "were reported inconsistently in more than one-third of trials." CSR disclosure would allow the medical community to determine the source of these discrepancies and evaluate whether FDA approval of a drug adequately evaluated the safety and efficacy of a drug.

2. Knowing If The FDA Is Properly Carrying Out Its Statutory Mission

108. Defendants produced thousands of pages of internal documents in response to this lawsuit, including Exhibits I-M to the Kenney Declaration. These Exhibits reveal an intense internal conflict among FDA officials over the validity of Studies 201 and 202, the integrity of Exondys 51's approval process, and the conduct of certain FDA officials.

109. Four examples highlight the ways in which disclosure of the CSRs will illuminate these controversies and shed light on what the FDA did in this case: (a) the controversy over the Western blots reviewed in the Exondys 51 approval process; (b) the conflicting analyses of dystrophin production and its claimed correlation to a clinical benefit from the drug; (c) the validity of endpoint

[45] Hartung DM, Zarin DA, Guise J-M, McDonagh M, Paynter R, Helfand M. Reporting Discrepancies Between the ClinicalTrials.gov Results Database and Peer-Reviewed Publications. *Ann Intern Med.* 2014;160(7):477-483 (Kenney Decl., Ex. BB, 98).

measures that critically impact the interpretation of study results; and (d) the dispute over the weight to be given to safety concerns in light of the minimal evidence of efficacy provided by Sarepta. CSR disclosure will shed critical light on whether a group of FDA officials inaccurately characterized the Exondys 51 study results or a senior FDA official approved the drug despite scientifically sound resistance from her colleagues. The answer to these questions will also inform the issue of whether Dr. Woodcock improperly based her unprecedented reversal of FDA's staff and advisory committee recommendations on extra-statutory factors such as Sarepta's financial solvency or intense patient lobbying.

a. Questions about Sarepta's Western Blot Images.

110. Disclosing the Western blots images redacted and withheld from the CSRs will shed light on whether the FDA approved a drug based on potentially falsified clinical trial data. According to Dr. Farkas, the FDA clinical team reviewer, the results of certain Western blot images were "to [his] eyes . . . far less impressive than portrayed in [Sarepta's] regulatory submissions and the Mendell paper" published in the *Annals of Neurology*. *Id.*, Ex. L, 10. Dr. Farkas warned that there "seem[ed] to be reason for concern of misrepresentation of the data, even beyond that fact that it isn't clear what band represents dystrophin in the patient samples." *Id.* at 2.

111. CDER scientists were also concerned that the procedures used to perform the IHC analyses were unreliable, and the FDA requested that Sarepta allow three independent pathologists, blinded to patient group, to re-read the stored images. The independent analyses were not as favorable to Sarepta. *Id.*, Exs. G, 3-4 & F, 7-9. The FDA then required Sarepta to submit additional Western blot results from Study 301, *id.*, Ex. G at 3-4, and Dr. Unger and Commissioner Califf later called for the retraction or correction of the *Annals* study, *id.*, Ex. M.

112. It is unclear which Western blot results Dr. Woodcock used in her decision to approve Exondys 51. But members of the review team claimed that Dr. Woodcock had indicated she had

already made up her mind to approve the drug as early as 2014, or at the latest in May 2016, before the new data from Study 301 were requested by the FDA. *Id.*, Ex. G, 11, 23. Disclosure of the Western blots from the final CSRs for Study 201 and 202—likely on Dr. Woodcock's desk when she wrote her decisional memo—will help independent scientists to evaluate her claim that these data "clearly show[ed], using adequate controls, that the drug increases dystrophin protein production in some of the patients." *Id.*, Ex. E, 4. Disclosing the withheld CSR information would allow the public to fully evaluate the competing claims made by Dr. Woodcock and her colleagues.

b. Questions about the FDA's statistical analyses.

113. Dr. Unger and Dr. Woodcock present contradictory analyses to evaluate the alleged correlation between dystrophin production and clinical benefit. These analyses bear directly on the question of whether, in the words of Dr. Unger, approval was "on the basis of a surrogate endpoint with a trivial treatment effect," *id.*, Ex. F, 28, and relied on a "scientifically invalid" analysis, *id.*, Ex. I. 3-4, or whether these results showed a correlation between dystrophin and clinical outcomes, *id.*, Ex. F, 17-20 (containing graph created by Dr. Woodcock). Their graphs are based on data from two endpoints: The 6MWT and the NSAA, but the underlying data on both of these endpoints has been withheld as confidential to Sarepta. In addition, all of the detailed NSAA summary result tables in the CSR appendices for Studies 201 and 202 have been withheld. *See id.,* Ex. C, 16. Thus, the FDA is failing to disclose information that is at the crux of one of the key internal disagreements about whether or not Exondys 51 should have been approved. Without disclosure of the redacted dystrophin tables and the redacted results from the 6MWT and NSAA tests, independent scientists have no access to crucial context surrounding the graphs created by Drs. Woodcock and Unger that have been disclosed. *Id.*, Ex. F, 17-20. Disclosure of the CSRs could therefore help independent scientists evaluate whether a small increase in dystrophin was linked to improvement in these measures of muscle health or not.

c. Questions about Sarepta's endpoint switching.

114. Dr. Unger raised concerns about approving Exondys 51 "without substantial evidence of effectiveness." *Id.* at 24, 28. Crucial to evaluating efficacy are the study "endpoints" or metrics. Primary endpoints are those measures deemed most indicative of a drug's efficacy. Typically, primary endpoints are pre-specified to ensure experimental validity. Otherwise, researchers could label a different endpoint "primary" mid-study based on unpromising preliminary results. Modifying a primary endpoint generally requires FDA approval because such a modification can significantly impact the soundness of the trial design.

115. Changes in a study's design protocol can be tracked on ClinicalTrials.gov. Sarepta repeatedly changed its primary endpoints throughout the clinical investigation. This suggests a risk of endpoint switching: choosing the most favorable endpoints after part of the experiment is conducted to best promote a drug rather than tracking the most indicative endpoints for clinical efficacy from the beginning of the scientific investigation.

116. Endpoint switching is considered to be poor scientific practice and "can lead to false positive results and lack of reproducibility."[46] The FDA warns against such biased analyses:

> In the past, it was not uncommon, after the study was unblinded and analyzed, to see a variety of post hoc adjustments of design features (e.g., endpoints, analyses), usually plausible on their face, to attempt to elicit a positive study result from a failed study —a practice sometimes referred to as data-dredging. Although post hoc analyses of trials that fail on their prospectively specified endpoints may be useful for generating hypotheses for future testing, they do not yield definitive results. The results of such analyses can be biased because the choice of analyses can be influenced by a desire for success.[47]

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[46] Alberto Falk Delgado & Anna Falk Delgado, Outcome switching in randomized controlled oncology trials reporting on surrogate endpoints: a cross-sectional analysis. *Scientific Reports*, 7:9206 (2017) (Kenney Decl., Ex. CC, 2-8).

[47] U.S. Department of Health & Human Services, Food & Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), *Multiple Endpoints in Clinical Trials, Guidance for Industry, Draft Guidance* (2017); https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf (Kenney Decl., Ex. CC, 19-20).

117. Sarepta identified two main endpoints for the FDA: "percent of dystrophin positive fibers change from Baseline" and the 6MWT. *See* Bates FDACDER_SAR_0006474. Sarepta also reported on eight other endpoints that it labeled "exploratory" and which it claims are therefore less clinically relevant than the primary or secondary endpoints. Bates FDACDER_SAR_0006474. However, one of these exploratory endpoints—CD3, CD4 and CD8 lymphocyte (white blood cell) count in muscle biopsy tissues—was initially a key secondary endpoint, and only later labeled "exploratory," according to available data on ClinicalTrials.gov. As discussed *supra*, much of the information that I am seeking regarding methods and results regarding listed endpoints has been redacted.

118. Disclosing the withheld information will establish whether the results for the main endpoints identified by Sarepta, the 6MWT and dystrophin production, were the only favorable results among Sarepta's test data. Such a situation would undermine claims of Exondys 51's efficacy, since it would suggest that Sarepta cherry-picked the promising data and suppressed negative results, confirming Dr. Unger's concerns.

d. Questions about the drug's safety and efficacy.

119. Knowing the CSR data is essential to understanding how the FDA is performing its duties and whether it violated a statutory mandate by approving Exondys 51 without "substantial evidence" of the drug's effectiveness. The CSR data is also needed to inform physicians, patients and the general public about the safety and efficacy of Exondys 51.

120. CSR disclosure is particularly important given Dr. Unger's concerns over a lack of data demonstrating the drug's effectiveness and the inevitable safety risks associated with taking the drug, especially the risk of infection. In Dr. Woodcock's view, "the therapy has been relatively safe in the clinic, although intravenous administration always carries risk." Kenney Decl., Ex. E, 13. By contrast, Dr. Unger objects that Exondys 51's "safety profile is not well characterized" given that only twelve

patients were exposed to the drug for an extended period, and the need to administer Exondys 51 through an injection port surgically attached to a patient's vein will "definitely" lead to "serious infections and possibly deaths." *Id.*, Ex. F, 22,

121. Dr. Unger was especially concerned about the safety risks given that he found evidence of Exondys 51's efficacy to be "lacking." In his view, patients may be risking serious side-effects to take a drug for which no benefit has been established. The public has a compelling interest in evaluating these competing claims, an evaluation that can only meaningfully take place with disclosure of the withheld CSR information.

1. Informing the ongoing debate over the drug's efficacy.

122. Disclosing the CSRs would enable researchers, doctors, and patients to more effectively evaluate Exondys 51's efficacy. Specifically, further information on selected clinical endpoints and raw blot images would provide a more complete picture of the drug's utility. Without this information, patients and their doctors cannot effectively evaluate whether Sarepta's disclosed results are accurate or representative of the entire data pool. Information that calls into question the efficacy of the drug will undoubtedly influence the decisions of doctors and patients on whether to use Exondys 51 in light of its known risks and side-effects, discussed *infra*, and its extraordinary price. Since Sarepta was criticized for misrepresenting data, both in the public sphere through the *Annals of Neurology* and in internal FDA emails, this issue is particularly pressing. In the absence of CSR disclosure, the public is left guessing about the accuracy of the available clinical trial information.

123. In addition, because the drug was approved on an accelerated basis, it requires confirmatory results, which Sarepta is attempting to collect in Study 301. Disclosing the CSRs for Studies 201 and 202 will provide valuable assistance to public understanding of Study 301's results when they are released. For example, if Study 301 were to show indications of worsening

cardiomyopathy, the public could more effectively evaluate cardiomyopathy prevalence only with access to the underlying data for all three studies.

124. The FDA has fully redacted more than a dozen tables from the Study 201 CSR Appendix which contain summary results and individual patient level results for Sarepta's 6MWT analysis, including the 12-patient ITT (intent to treat) population, and the 10-patient *m*ITT (modified intent to treat) population from which Sarepta controversially excluded data from two patients who lost ambulation during the study. The patient-level results and figures are withheld from the Study 202 CSR Appendix. Disclosure would allow doctors to evaluate Sarepta's justification for excluding two patients with unpromising data from an already modest study size of twelve patients, and further inform about the effectiveness of Exondys 51.

125. As also discussed, Sarepta's Western blot analyses were the subject of an extensive controversy in the *Annals of Neurology* and in FDA email correspondences. The FDA released certain Western blot images attached to an FDA email after I repeatedly requested their release, but the FDA has refused to provide the Western blot images and IHC images included in the CSR Appendices. *See* Bates FDACDER_SAR_000133. Disclosure of any additional images or interpretations of released images would shed light on the drug's ability to improve dystrophin levels.

2. Informing the ongoing debate over the risks of taking Exondys 51

126. Fully disclosing the contested portions of Sarepta's CSRs would shed important light on seven possible safety concerns surrounding Exondys 51: infection/sepsis; cardiomyopathy; blood clots; autoimmune responses; kidney damage; balance disorder; and hypokalemia. Further information on each of these safety risks would allow patients and their doctors to more effectively evaluate if Exondys 51's possible benefits are worth its potentially deadly drawbacks. Doctors treating patients with existing conditions such as cardiac issues or compromised immune systems may decide against prescribing Exondys 51 to their patients if currently redacted sections of the CSRs show that

the drug's risks outweigh its benefits. Disclosure could prevent early deaths associated with these safety signals and improve patient quality of life. These safety concerns qualify as "adverse events." Relevant data on adverse events will therefore be referenced in the following sections.

127. **Infection/sepsis.** As noted above, there is a significant public interest in obtaining access to data about infections and sepsis. Difficulty in accessing veins is a common condition among patients with Duchenne who receive repeated injections of drugs. Exondys 51 is therefore often administered through an indwelling central venous access device surgically attached to a patient's vein. Because patients with Duchenne take steroid hormones, their immune systems are particularly vulnerable to infection through these catheters.

128. Incidences of infection and sepsis during the use of Exondys 51 have been recorded in the FDA's Adverse Event Reporting System (FAERS). FAERS is a public database of post-market adverse event reports, medication error reports and product quality complaints that resulted in adverse events. The FDA may take regulatory action to improve a product's safety based on FAERS data by, for example, "updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market." Kenney Decl., Ex. DD, 2.

129. As of March 12, 2018, the FAERS database for Exondys 51 includes a patient who died with septic shock, two cases of bacteremia (bacteria in the blood), and two patients with a "device-related infection" after the drug was introduced onto the market. *Id.* at 7-41. In Study 201, according to Sarepta's briefing document for the April 2016 Advisory Committee Meeting, one patient in the placebo group experienced a soft tissue infection. *Id.*, Ex. Q, 163.

130. Disclosing the CSRs would provide further information on currently redacted "adverse events," including cases of infection. As discussed *supra*, the FDA has extensively redacted adverse events information that I sought, including narrative information. Narrative sections

regarding adverse events are especially important for Sarepta's studies because the studies only included twelve patients. Detailed discussions of individual adverse events are of particular importance where due to the small number of subjects in the studies, even adverse events that may be frequent in a larger population may not reach statistical significance in Studies 201 and 202.

131. Since the body produces additional white blood cells to counter infections, the tables providing hematology information in the Appendices for Studies 201 and 202 would also shed light on this safety risk. However, all of the hematology tables are completely redacted. *See* Bates FDACDER_SAR_000123 and Bates FDACDER_SAR_0006600 (listing hematology tables). For example, Sarepta has contended that there were no "clinically meaningful treatment related changes detected for any safety laboratory parameters." *See* Bates FDACDER_SAR_0006578. Because the sample sizes were so small, asserting a lack of "clinically meaningful" changes is not informative, since particularly high or low readings can easily cancel each other out. Dr. Unger alluded to this limitation in his memo noting that "only a few dozen patients have been exposed to the drug" and that its safety profile is therefore "not well characterized." *Id.*, Ex. F, 22. Narrative sections from the CSRs will establish whether particularly high or low readings did, in fact, cover up meaningful changes.

132. As noted, the FDA repeatedly redacted shift tables that show the number of patients who were initially rated low, normal, or high for a particular condition, and then show how their condition shifted post-dose. For example, a shift table might indicate that a patient started with a low white blood cell count, but then shifted to an abnormally high count after receiving treatment. This shift, possibly indicating that Exondys 51 causes infection, would not be detectable based on Sarepta's broader statistics regarding the entire study sample. Again, access to shift tables is especially important because of Sarepta's small study sizes. Average measures have little meaning when they describe twelve to thirteen patients, since outliers can easily cancel each other out.

133. **Cardiomyopathy.** A second safety signal possibly associated with Exondys 51 is cardiomyopathy, or disease of the heart muscle. It is a common cause of death for patients with Duchenne. In Study 28, an earlier study of Exondys 51, one patient with a pre-existing case of cardiomyopathy discontinued Exondys 51 treatment after experiencing a "decrease in left ventricular ejection fraction" of his heart—in lay terms a reduction in the heart's ability to pump blood—to the body after receiving seven once-weekly doses of Exondys 51 4 mg/kg. *Id.*, Ex. R, 72. According to the publicly available briefing document that Sarepta presented to the FDA Advisory Committee, this instance of cardiomyopathy was reported by the investigator as possibly related to eteplirsen. *Id.*; *Id.*, Ex. Q, 106.

134. As of March 12, 2018, the FAERS database contains twelve reports of cardiac disorders, including four deaths and one cardiomyopathy diagnosis. *Id.*, Ex. DD, 7-41.

135. Knowing whether and the extent to which Exondys 51 exacerbates this deadly condition is of vital interest to patients. Information related to cardiac side effects should be included in Sarepta's redacted narratives of adverse events. *See* Bates FDACDER_SAR_0006578 to Bates FDACDER_SAR_0006582 (Study 202 CSR). As in the case of infection, the combination of statistical and narrative data would provide patients and their doctors with a more complete picture of the drug's clinical impact. Without these statistical and narrative data, it is impossible for patients and doctors to know whether the small size and faulty design of Studies 201 and 202 cover up an important risk of cardiomyopathy.

136. In addition, disclosing the redacted data related to electrocardiogram (ECG) results and vital signs would shed light on whether Exondys 51 causes cardiac issues, because cardiomyopathy can be linked to heart rhythm disorders. ECG data track the progress of electrical signals through the heart muscle and can show how much a drug interferes with a patient's heart conduction. The redacted ECG tables would provide doctors with more information on potential signals of cardiac

disease. Vital signs like blood pressure, pulse rate, oxygenation, and respiration rate would shed light on how patients' circulatory and pulmonary systems reacted to the drug. Yet in the Study 202 CSR, the text describing ECG results is partially redacted, and the vital signs table and the ECG table are fully redacted. *See* Bates FDACDER_SAR_00073 to FDACDER_SAR_00074 (Study 201 CSR). The detailed tables containing summary and individual patient-level vital sign and ECG measurements contained in the Appendices to Studies 201 and 202 are completely redacted. *See* Bates FDACDER_SAR_0001794 to FDACDER_SAR_0002371 (Study 201 CSR Appendix); Bates FDACDER_SAR_00014874 to FDACDER_SAR_00017456 (Study 202 CSR Appendix).[48]

137. **Blood clots.** Patients with DMD can have inadequate veins due to both disease progression and the side effects of corticosteroid treatment, and an indwelling central venous access device, such as a port-a-cath, is often implanted surgically to allow for treatment with Exondys 51. Yet implantation of a port-a-cath exposes patients to risks of blood clots and infections.

138. One patient's mother wrote, in an email produced in response to my FOIA request, that her child's veins had "blown every time" individuals had tried to access them. The patient's veins were "worn out" after he endured eighty-four infusions of Exondys 51 in addition to two years of blood draws for another Duchenne drug. *Id.*, Ex. DD, 42.

139. Due to the difficulty in administering intravenous drugs to children with Duchenne, even children in the placebo arm of a trial may have port-a-caths implanted. In an August 2016 email disclosed pursuant to my FOIA request, Dr. Robert Nelson, Deputy Director of the Office of Pediatric Therapeutics and Senior Pediatric Ethicist, expressed concern about possible use of indwelling catheters for the administration of placebos in Sarepta's ESSENCE trial testing experimental drugs for Exons 43 and 45. *Id.* at 44. Dr. Nelson was concerned that the study might

[48] Note: These page ranges are approximate as table of contents entries are also redacted.

not satisfy ethical standards because patients taking placebos could risk experiencing harmful side-effects like infection or thrombosis without the potential for treatment. *See* Bates FDACDER000759 to FDACDER000761. The FDA Institutional Review Board subsequently approved the placement of port-a-caths.

140. Blood clotting is a known safety issue with Exondys 51. Following a redacted passage, the CSR for Study 202 reports on four adverse events of moderate severity, "3 episodes of thrombosis in device in 2 patients taking eteplirsen 30 mg/kg, one of whom also reported device occlusion." Bates FDACDER_SAR_0006477. Thrombosis refers to blood clotting, and device occlusion signals blockage in the indwelling central venous access device. Sarepta considered these episodes of thrombosis and device occlusion to be related to the port-a-cath. *See* Bates FDACDER_SAR_0006478.

141. Patients who are considering taking Exondys 51 would benefit immensely from further information on blood clot risks. Disclosure would allow parents to make the best medical decision possible for their children, whose veins may already be affected by corticosteroids and disease progression. Further information on the risk of blood clots for patients with Duchenne with a port-a-cath could therefore tip the scale for patients deciding whether to take Exondys 51 to improve their quality of life.

142. Disclosing the information sought in the CSRs and appendices would allow the public to evaluate thrombosis risks for patients taking placebos as compared to patients who were given Exondys 51, shedding light on Dr. Nelson's ethical concerns. Coagulation data, which provide information on the ability of a patient's blood to clot, are currently redacted. Detailed hematology data, which provide information on blood physiology, are also redacted. Disclosing the detailed, de-identified summary level tables and the patient-level listings contained in the Appendices to Studies 201 and 202, would therefore help the public evaluate risks of systemic clotting. As in the case of

white blood cell counts, redacted shift tables would further inform how clotting arose in individual patients based on their initial health status. Currently, all of the hematology and coagulation data in the Appendices has been redacted. *See* Bates FDACDER_SAR_0001617 to FDACDER_SAR_0001753 (Study 201 CSR Appendix); Bates FDACDER_SAR_00018191 to FDACDER_SAR_00018773 (Study 202 CSR Appendix).[49]

143. **Immune responses.** Another safety concern surrounding Exondys 51 is the potential for patients' immune systems to damage their muscle tissue. This is a well-known disease process in Duchenne, and as discussed *supra*, some related compounds to Exondys 51 cause immune system reactivity. Sarepta measured lymphocyte levels to address these concerns. When a person's immune system is threatened by a foreign agent, their bone marrow typically produces white blood cells to counter it as part of the normal inflammatory immune response. Sarepta recorded CD3, CD4 and CD8 lymphocyte (white blood cells, called T-cells) levels in patients' muscle tissue in its tests. A muscular auto-immune response could be dire for patients with Duchenne, who already suffer from inflammation-related muscle breakdown.

144. Although Sarepta disclosed that there are no statistically significant differences in immune response between the treatment and placebo groups in the groups at large, patients and their doctors have no information on individual immune responses. As previously noted, Sarepta's small sample size makes it imperative that de-identified individual patient-level results are closely examined. It is possible that individual patients experienced adverse immune responses not adequately captured by summary-level data. Examining individual-patient results for anomalies that could result from auto-immune responses, such as abnormal white blood cell values from muscle biopsies, is important, yet both summary-level and patient-level information is completely redacted from the Study 202 CSR

[49] Note: These page ranges are approximate as table of contents entries are also redacted. It is not possible to give page numbers for the listings because the names of most listings are redacted.

Appendix. *See* Bates FDACDER_SAR-0006832 to FDACDER_SAR-0006897. Disclosure would therefore shed light on this pressing concern.

145. **Kidney function.** Sarepta "followed and analyzed" adverse treatment events associated with kidney function "in detail," yet the FDA redacted information on adverse kidney events in the CSR for Study 202. *See* Bates FDACDER_SAR_0006569 (Study 202 CSR). Six patients who took Exondys 51, or 58% of the treatment group, experienced "proteinuria" (the presence of abnormal quantities of protein in urine), an adverse event associated with kidney damage. *See* Bates FDACDER_ SAR_0006569. Although summary-level information regarding urinalysis results in the Appendices to Studies 201 and 202 were provided to me, all of the patient-level results contained in the listings were redacted.

146. The CSR for Study 201 refers to creatinine and blood urea nitrogen (biomarkers of kidney function) in its summary, but relevant tables are redacted. Disclosing the CSRs would therefore provide further information on possible side-effects related to kidney function.

147. **Balance disorder.** Balance disorder is one of the drug's most common adverse reactions and can easily lead to fractures. Although balance disorder is on the drug's label among the other known side effects, the public has no other way to evaluate the disorder's possible severity. Redacted adverse events and narrative sections could provide information such as whether balance disorder affects younger children more than older children, whether it emerges early on during treatment or more gradually, and how severe the disorder may become.

148. For now, patients are left guessing about whether the drug causes occasional dizziness, leads to debilitating loss of balance, or something in between. Furthermore, doctors are not provided with a complete picture of this side-effect when prescribing the drug, and thus cannot include this consideration in their evaluation of whether the drug would improve their patients' quality of life. As

in the case of muscle deterioration, patients with Duchenne already suffer from risk of falls. Exondys 51's potential association with balance disorders would therefore actively harm patients' quality of life.

149. **Hypokalemia.** Six patients in Study 201 experienced hypokalemia, or potassium deficiency in the bloodstream. *See* Bates FDACDER_SAR_000107. Of these cases, two were in the placebo group and four were in Exondys 51 groups. Disclosing the Study 201 Appendix serum chemistry laboratory parameters tables—shift tables and abnormal results tables—as well as the de-identified patient-level listings would help the public evaluate whether the drug may have induced hypokalemia in patients. *See* Bates FDACDER_SAR_0001617 to Bates FDACDER_SAR_0001753 (Study 201 CSR Appendix); Bates FDACDER_SAR_00014147 to Bates FDACDER_SAR_00014700 (Study 202 CSR Appendix)[50] As in the case of white blood cell counts and blood clotting, shift tables would provide more information by demonstrating how particular patients' hypokalemia changed over the course of treatment or placebo administration.

G. LACK OF COMPETITIVE HARM

1. Data Sharing and Cooperation with Competitors

150. Sarepta argues that disclosure of study measures and endpoints, information about test methods and measures, and patient-level data would harm it financially. Yet Sarepta is involved in a number of collaborative efforts with academic researchers from multiple institutions, as well as with its direct competitors. Science is not practiced in a vacuum, but involves joint efforts, particularly in the context of a rare disease like Duchenne.

151. Although Sarepta contends that it has proprietary control over the two natural history datasets that it used as historical controls in Study 201, the public record suggests to the contrary. According to public documents, these natural history registries were obtained from the University

[50] Note: These page ranges are approximate as table of contents entries are also redacted. It is not possible to give page numbers for the listings because the names of most listings are redacted.

Hospitals Leuven, Leuven Neuromuscular Reference Center (LNMRC) in Belgium and the Fondazione Telethon Registry in Italy.[51] Both registries share their data with researchers and pharmaceutical companies through the Collaborative Trajectory Analysis Project (cTAP), a public-private partnership focused on clinical trial data sharing and scientific analysis regarding Duchenne.[52] The Leuven Neuromuscular Reference Center also shares data with other researchers who contact it directly.[53]

152. Sarepta has joined with other competitor companies and researchers in cTAP. As of 2015, cTAP had shared longitudinal natural history data on over 1250 patients that included more than 5000 patient-years.[54] The first two scientific publications on which cTAP collaborated were analyses of the 6MWT data from the Leuven Neuromuscular Reference Center and the Fondazione Telethon Registry[55] Sarepta co-funded this research with competitor companies, and multiple

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[51] Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology*. 2016;79(2):257-271 (Kenney Decl., Ex., 117-33); Collaborative Trajectory Analysis Project, *cTAP Announces Two Research Publications Categorizing and Predicting Disease Progression in Duchenne Muscular Dystrophy* (Oct. 31, 2016), http://www.ctap-duchenne.org/assets/files/cTAP-Publications-Press-Release-103016.pdf (Kenney Decl., Ex. EE, 2-4).

[52] Collaborative Trajectory Analysis Project, *Enabling the right trial design, the first time: Supporting new therapies to patients sooner*, http://ctap-duchenne.org/assets/files/cTAP-Overview_2016.pdf (last accessed May 29, 2018) (Kenney Decl., Ex. EE, 5-24).

[53] Goemans N, vanden Hauwe M, Signorovitch J, Swallow E, Collaborative Trajectory Analysis Project (cTAP). Individualized Prediction of Changes in the 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. *PLoS One*. 2016;11(10):e0164684 (Kenney Decl., Ex. EE, 25-39).

[54] Hoffman EP. Facilitating orphan drug development: Proceedings of the TREAT-NMD International Conference, December 2015, Washington, DC, USA. *Neuromuscular Disorders*.2017;27(7):693-701, 695.k (Kenney Decl., Ex. EE, 40-48).

[55] Goemans N, vanden Hauwe M, Signorovitch J, Swallow E, Collaborative Trajectory Analysis Project (cTAP). Individualized Prediction of Changes in the 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. *PLoS One*. 2016;11(10):e0164684 (Kenney Decl., Ex. EE, 25-39); Mercuri E, Signorovitch JE, Swallow E, et al. Categorizing Natural History Trajectories of Ambulatory Function Measured by the 6-minute Walk Distance in Patients with Duchenne Muscular Dystrophy. *Neuromuscular Disorders*. 2016;26(9):576-583 (Kenney Decl., Ex. EE, 40-56); Mercuri E, Signorovitch JE, Swallow E, et al. Corrigendum to "Categorizing Natural History Trajectories of Ambulatory Function Measured by the 6-minute Walk Distance in Patients with Duchenne Muscular Dystrophy" [Neuromuscul Disorders 26/9 (2016) 576-583] *Neuromuscular Disorders*. 2017;27:e1 (Kenney, Ex. EE, 57).

companies, including Sarepta, were involved in providing editorial assistance and guidance to the authors of the papers.[56] At the time of publication, Sarepta's CEO was quoted in the cTAP press release:

> Without this understanding of the natural clinical progression of the various genetic causes for DMD, it would be extremely difficult to design the clinical trials or choose the appropriate endpoints necessary to develop novel drugs to use for [Duchenne]. . . . cTAP is one of the best examples of international academic collaboration that has advanced the clinical understanding of [Duchenne].[57]

153. In addition to cTAP, Sarepta is a member and provides financial support to the Duchenne Regulatory Science Consortium (D-RSC), a project of the Critical Path Institute and Parent Project Muscular Dystrophy, which includes members from academia and seven pharmaceutical companies, along with FDA and NIH observers. The D-RSC's mission is to accelerate drug development for Duchenne. Sarepta and other pharmaceutical companies participated in an April 2016 D-RSC meeting to discuss development of a clinical disease progression model for Duchenne, and clinically meaningful endpoints. At the meeting, the evidence supporting use of the 6MWT, the NSAA, and respiratory measures such as forced vital capacity (FVC) and other outcome measures were discussed by the group.[58]

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[56] Goemans N, vanden Hauwe M, Signorovitch J, Swallow E, Collaborative Trajectory Analysis Project (cTAP). Individualized Prediction of Changes in the 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. *PLoS One*. 2016;11(10):e0164684 (Kenney Decl., Ex. EE, 25-39); Mercuri E, Signorovitch JE, Swallow E, et al. Categorizing Natural History Trajectories of Ambulatory Function Measured by the 6-minute Walk Distance in Patients with Duchenne Muscular Dystrophy. *Neuromuscular Disorders*. 2016;26(9):576-583 (Kenney Decl., Ex. EE, 40-56); Mercuri E, Signorovitch JE, Swallow E, et al. Corrigendum to "Categorizing Natural History Trajectories of Ambulatory Function Measured by the 6-minute Walk Distance in Patients with Duchenne Muscular Dystrophy" [Neuromuscul Disorders 26/9 (2016) 576-583] *Neuromuscular Disorders*. 2017;27:e1 (Kenney, Ex. EE, 57).

[57] Collaborative Trajectory Analysis Project, *cTAP Announces Two Research Publications Categorizing and Predicting Disease Progression in Duchenne Muscular Dystrophy* (Oct. 31, 2016), http://www.ctap-duchenne.org/assets/files/cTAP-Publications-Press-Release-103016.pdf (Kenney Decl., Ex. EE, 2-4).

[58] Larkindale J, Abresch R, Aviles E, et al. Duchenne Regulatory Science Consortium Meeting on Disease Progression Modeling for Duchenne Muscular Dystrophy. *PLoS Currents*. 2017; Jan 12:9 (Kenney Decl., Ex. FF, 2-12).

154. As part of the D-RSC, Sarepta, along with other pharmaceutical companies, co-funds efforts to share Duchenne patient-level data. D-RSC has "created an integrated database of patient-level natural history data collected in DMD clinical trials."[59] Currently, nine separate datasets from Duchenne clinical trials are shared.[60] D-RSC has also submitted a biomarker for liver damage to the EMA for approval.[61]

155. The D-RSC has collaborated in the development of a standardized Therapeutic User Guide to be used by pharmaceutical companies in submitting applications to the FDA for approval of Duchenne drugs. The guide includes detailed information about suggested trial endpoints, including pulmonary function tests such as maximal inspiratory pressure, maximal expiratory pressure, peak cough flow, and forced vital capacity, the 6MWT, rise from floor, 10-meter walk/run, Ascend/Descend 4 stairs, NSAA, Performance of Upper Limb Scale, and the Pediatric Quality of Life Neuromuscular Module, all of which were outcome measures in the Exondys 51 trials.[62]

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[59] Larkindale J, Romero K, Berg A, CINRG investigators, Duchenne Regulatory Science Consortium (D-RSC). Accelerating Drug Development: Data Sharing and Developing Quantitative Tools Through the Duchenne Regulatory Science Consortium (D-RSC). Poster presented at 2018 MDA Clinical Conference; March 13, 2018; Arlington, VA (Kenney Decl., Ex. FF, 13); Larkindale J, Duchenne Regulatory Science Consortium. Duchenne Regulatory Science Consortium—Developing Tools to Accelerate Drug Development for Duchenne. Poster presented at MDA Scientific Conference; March 19-22, 2017 (Kenney Decl., Ex. FF, 15); Arlington, VA; Larkindale J, Duchenne Regulatory Science Consortium. Duchenne Regulatory Science Consortium—Developing Tools to Accelerate Drug Development for Duchenne. Poster presented at Parent Project Muscular Dystrophy Conference; June 29-July 10, 2017; Chicago, Il (Kenney Decl., Ex. FF, 16).

[60] Larkindale J, Romero K, Berg A, CINRG investigators, Duchenne Regulatory Science Consortium (D-RSC). Accelerating Drug Development: Data Sharing and Developing Quantitative Tools Through the Duchenne Regulatory Science Consortium (D-RSC). Poster presented at 2018 MDA Clinical Conference; March 13, 2018; Arlington, VA. (Kenney Decl., Ex. FF, 13).

[61] Larkindale J, Sauer J-M, Aubrecht J, Duchenne Regulatory Science Consortium (D-RSC), (PSTC). PSTC. Biomarkers for Muscle Diseases—Data Supporting Glutamate Dehydrogenase as a Specific Biomarker of Liver Damage. Poster presented at MDA Clinical Conference; March 13, 2018; Arlington, VA (Kenney Decl., Ex. FF, 14).

[62] Clinical Data Interchange Standards Consortium (CDISC), Coalition for Accelerating Standards and Therapies (CFAST) Duchenne Muscular Dystrophy Team. CDISC Therapeutic Area User Guide for Duchenne Muscular Dystrophy Duchenne Regulatory Science Consortium (D-RSC);2017 (Kenney Decl., Ex. FF, 17-46); Critical Path Institute, C-Path and CDISC Announce Therapeutic Area User Guide for Duchenne Muscular Dystrophy, October 18 2017, https://c-path.org/c-path-and-cdisc-announce-therapeutic-area-user-guide-for-duchenne-muscular-dystrophy/ (Kenney Decl., Ex. FF, 47-49).

156. Sarepta has participated in multiple Duchenne international workshops along with academic researchers, non-profit organizations, and industry. This includes a March 2007 workshop, "Planning Phase I/II Clinical trials using Systematically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy," a September 25, 2009 workshop on "The Development of Antisense Oligonucleotide Therapies for Duchenne Muscular Dystrophy," a January 2014 "International Workshop on Biomarkers in Duchenne Muscular Dystrophy" a December 2015 TREAT_NMD International Conference workshop on "Facilitating Orphan Drug Development" and the January 2017 European Neuromuscular Centre workshop on developing "validated and qualified biomarkers for therapy development for Duchenne muscular dystrophy."[63] Discussions at these meetings by Sarepta representatives have included the planned trial design for an early Exondys 51 trial,[64] and Sarepta's entire antisense oligonucleotide research program, including Exondys 51

[63] Muntoni F, Bushby KD, van Ommen GJ. 149th ENMC International Workshop and 1st TREAT_NMD Workshop on: "Planning Phase I/II Clinical Trials using Systematically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophies. *Neuromuscular Disorders*. 2008;18:268-275 (Kenney Decl., Ex. Y, 36-43); Muntoni F. The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy: Report on a TREAT-NMD workshop hosted by the European Medicines Agency (EMA), on September 25th 2009. *Neuromuscular Disorders*. 2010; 20(5):255-362 (Kenney Decl., Ex. Y, 44-51); Ferlini A, Flanigan KM, Lochmuller H, Muntoni F, 't Hoen PAC, McNally E. 204th ENMC International Workshop on Biomarkers in Duchenne Muscular Dystrophy 24–26 January 2014, Naarden, The Netherlands. *Neuromuscular Disorders*. 2015;25(2):184-198 (Kenney Decl., Ex. Y, 12-26); Hoffman EP. Facilitating orphan drug development: Proceedings of the TREAT-NMD International Conference, December 2015, Washington, DC, USA. *Neuromuscular Disorders*. 2017;27(7):693-701 (Kenney Decl., Ex. Y, 27-35); Aartsma-rus A, Ferlini A, McNally EM, Spitali P, Sweeney HL. 226th ENMC International Workshop: Towards Validated and Qualified Biomarkers for Therapy Development for Duchenne Muscular Dystrophy 20-22 January 2017, Heemskerk, the Netherlands. *Neuromuscul Disord*. 2018;28:77-86 (Kenney Decl., Ex. Y, 2-11).

[64] Muntoni F, Bushby KD, van Ommen GJ. 149th ENMC International Workshop and 1st TREAT_NMD Workshop on: "Planning Phase I/II Clinical Trials using Systematically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophies. *Neuromuscular Disorders*. 2008;18:268-275 (Kenney Decl., Ex. Y, 36-43).

trials.[65] Sarepta has also co-sponsored at least one additional conference along with other pharmaceutical companies.[66]

2. Dosing Information Disclosed by Sarepta

157. Contrary to Sarepta's assertions, earlier trials—not Studies 201 and 202—explored the optimal dosing schedule and method of administration for Exondys 51. The results of those trials have already been published and are not the subject of my FOIA request.[67] The dosing schedules for Study 201 and Study 202 have already been disclosed on the clinical trials registries, and in publications in scientific journals.[68] As detailed in the journal articles, dosing was a once per week infusion at 30 mg/kg, 50 mg/kg or placebo in Study 201.[69] In Study 202, those participants who had been in the Study 201 placebo group were randomly assigned to either weekly 30mg/kg or 50mg/kg eteplirsen dosing, and the other participants maintained their original dosage. This dosage and dosing schedule was steady throughout Study 202.[70] The publicly available label for Exondys 51 gives dosing

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[65] Muntoni F. The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy: Report on a TREAT-NMD workshop hosted by the European Medicines Agency (EMA), on September 25th 2009. *Neuromuscular Disorders*. 2010; 20(5):255-362 (Kenney Decl., Ex. Y, 44-51).

[66] Hoffman EP. Facilitating orphan drug development: Proceedings of the TREAT-NMD International Conference, December 2015, Washington, DC, USA. *Neuromuscular Disorders*. 2017;27(7):693-701 (Kenney Decl., Ex. Y, 27-35).

[67] Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet*. 2011;378(9791):595-605 (Kenney Decl., Ex. X, 26-64); Kinali M, Arechavala-Gomeza V, Feng L, et al. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. *Lancet Neurology* 2009;8(10):918-928 (Kenney Decl., Ex. X, 73-90).

[68] Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Annals of Neurology*. 2013;74(5):637-647 (Kenney Decl., Ex. N); Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology*. 2016;79(2):257-271 (Kenney Decl., Ex. X, 118-33).

[69] Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Annals of Neurology*. 2013;74(5):637-647 (Kenney Decl., Ex. N.)

[70] Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of Neurology*. 2016;79(2):257-271 (Kenney Decl., Ex. X, 118-33).

instructions for its prescribed use: "[t]he recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion."[71]

3. Information Disclosed by Sarepta to the EMA

158. Sarepta has submitted an application for "marketing authorisation" to the EMA for Exondys 51. The application is pending. According to Sarepta's May 3rd 8-K filing, after Exondys 51 received a negative trend vote at the EMA Committee for Medicinal Products for Human Use (CHMP) of the EMA, Sarepta plans to seek re-examination of their application and appointment of a scientific advisory committee. Kenney Decl., Ex. P, 3.

159. The information that I am seeking within the CSRs for Studies 201 and 202 will eventually be released by the EMA to the public once a decision is made on Sarepta's marketing authorization application. The EMA policy applies to drugs that are rejected, withdrawn, given marketing authorization, and given conditional marketing authorization, so regardless of the EMA decision regarding Exondys 51, the proactive release policy will still apply once a final decision is reached.

[71] *Exondys 51 (eteplirsen) Injection Label*, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf (last accessed May 29, 2018) (Kenney Decl., Ex. R, 37-46).

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Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed this 29th day of May 2018, in Cape Charles, Virginia.

Charles Seife

Charles Seife

[redacted](voice/work)
web: www.charlesseife.com e-mail:

Published Work:

Books

Zero: *The Biography of a Dangerous Idea* (Viking, 2000)

An account of the strangest number in the universe. (Winner, 2001 PEN/Martha Albrand award for first nonfiction; one of five best non-fiction books of the year, *Esquire* magazine.)

Alpha & Omega: The Search for the Beginning and End of the Universe (Viking, 2003)

The story of a cosmological revolution that is revealing the origin and ultimate fate of the universe. (One of the top 20 science books of the year, *Discover* magazine.)

Decoding the Universe: How the New Science of Information Is Explaining Everything in the Cosmos, from Our Brains to Black Holes. (Viking, 2006)

A tale of the third great scientific revolution of the 20th century -- information theory -- and how it is giving scientists the power to understand the mysteries of quantum mechanics, relativity, and even of life itself. (Among top science titles of 2006, *Library Journal*.)

Sun in a Bottle: The Strange History of Fusion and the Science of Wishful Thinking (Viking, 2008)

A history of the quest for fusion energy -- and how it has produced a trail of broken promises and shattered careers. (*New York Times* Editor's Choice, December 2008, Winner, History of Science Society's Davis Prize for a book in the history of science directed to a wide public.)

Proofiness: The Dark Arts of Mathematical Deception (Viking, 2010)

A book that describes how the misuse of mathematics and statistics has become a powerful form of propaganda. (*Booklist* starred review.)

Virtual Unreality (Viking, 2014)

An exploration of how digital technology is changing the way we lie to each other and to ourselves. (*Kirkus* starred review; top 20 reads of the year, *Nature* magazine.)

Book chapters / Anthology contributions

"Randomness." In *The Best Writing on Mathematics 2013*. (Princeton University Press, 2014.)

A description of three "laws" of randomness, and how those laws, paradoxically, yield the most absolute and certain physical principles known to humanity.

"Malthusian Information Famine." In *This Will Change Everything: Ideas That Will Shape the Future*. (Harper Perennial, 2009.)

A discussion of how, paradoxically, easy access to digital data will leave us starved for information.

"Science and Democracy." In *What Have You Changed Your Mind About?: Today's Leading Minds Rethink Everything.* (Harper Perennial, 2009.)

An argument that science and Democracy are fundamentally at odds.

"The True and the Absurd." In *My Einstein*. (Pantheon, 2006)

An essay about Einstein as master of the gedankenexperiment.

Articles

Published in such outlets as:

- *Discover*
- *The Economist*
- *The New York Times*
- *Nature*
- *New Scientist*
- *ProPublica*
- *Science*
- *Scientific American*
- *Slate*
- *Smithsonian*
- *The Washington Post*
- *Wired*

Selected Awards:

- 2001 PEN/Martha Albrand Award for First Nonfiction (for *Zero*)
- 2008 History of Science Society/Davis Prize for a book in the history of science directed to a wide public (for *Sun in a Bottle*)
- 2014 NASW/Science in Society Award (for "23 and Me is Terrifying....")
- 2016 Kantar/Information is Beautiful Awards (both "Gold/Data Journalism" and "Most Beautiful" for "Spies in the Skies")

Work Experience:

New York University, Arthur L. Carter Journalism Institute, Professor (2012-present), Associate Professor (2005-2012).

· Classes taught: Programming for Journalists; the Beat; Journalism by the Numbers; Science Literacy and Numeracy; Science, Policy, and the Media; Investigative Reporting; Investigative and Data Journalism; Opinion Writing; Sophomore Honors Seminar; Freshman Honors Seminar.

· Director of Graduate Studies, Journalism (2011-2017); Director of Undergraduate Studies, Journalism (2008-2011); Director of Graduate Financial Aid, Journalism (2008-2011); Director of Honors, Journalism (2006-2011).

· Serving on various departmental committees including search and tenure committees; CAS Student Discipline Committee (2010-2013, 2015-present, chair 2011-2013); CAS Nomination and Elections Committee (2008-2010); Honors Committee (2006-2011); Dean's Undergraduate Research Fellowship Committee (2006-2011), Ad-Hoc Faculty Prize Committee

(2006, 2008, 2009), NYU Truman Committee (2008-present), Rudin Scholarship Selection Committee (2009-2011), FAS Selection Committee for Distinguished Teaching Award (2008, 2009, 2013, 2017), Assessment Council (2010-2016), Faculty Grievance Committee (2017-present).

· Associate Faculty, Medical Ethics Division (2012-present).

Author, 1998-present.

· *Virtual Unreality*. Viking, 2014.
· *Proofiness*. Viking, 2010.
· *Sun in a Bottle*. Viking, 2008.
· *Decoding the Universe*. Viking, 2006.
· *Alpha and Omega*. Viking, 2003.
· *Zero: The Biography of a Dangerous Idea*. Viking, 2000.

Consultant, 2003-2006.
Assisted with the following television documentaries:

· "The 100 Greatest Discoveries in Science." Thinkfilm. Aired on Discovery Science Channel in December, 2004.
· "The Story of 1." Impossible Pictures. Aired on PBS in March, 2006.

Science, Writer, 2000-2005.

· Specialties: physics, astrophysics, mathematics, computer science.

New Scientist, US Correspondent, 1997-1999.

· Specialties: astronomy, space exploration, physics, computer science, chemistry.

Freelance Journalist, 1994-1997.

· Specialties: science and technology.
· Contributing correspondent, *ScienceNOW*.

Pre-1996 employment includes internships at *Scientific American* and *The Economist*, as well as work at the National Security Agency, the Institute for Defense Analysis, and Yale University.

Education:

Columbia University School of Journalism, New York, NY.
1996 M.S. in Journalism. Recipient, Nate Haseltine Memorial Fellowship.

Yale University, New Haven, CT, 1993-1995
1995 M.S. in Mathematics.

Princeton University, Princeton, NJ. 1989-1993
1993 A.B. in Mathematics.

Selected Lectures, Talks, and Colloquia:

Invited talk, Tel Aviv University Summit on Fake News, May 14 2018. "Sockpuppets, Bots, and the Vectors for Fake News."

An analysis of the ways that sockpuppets and bots are being used to inject "Fake News" into social media streams.

Colloquium, Langone/NYU Medical Center, December 19, 2017. "Unorthodox Strategies to Clinical-Trial Success: Fibbing, Fraud, Fudging, and Friends in High Places."

A discussion of strategies for getting drugs approved that rely on FDA's lack of transparency.

Conference, Rockefeller University, September 6, 2017. "Science, Journalism, and Democracy: Grappling with a New Reality."

A discussion about FOIA and its role in science journalism.

Colloquium, Langone/NYU Medical Center, September 29, 2016. "Clinical Trials Transparency: Promises, Pitfalls, and Reform Efforts."

An exploration of the lack of transparency in clinical trials of drugs and drug candidates.

Invited talk, Festival della Communicazione, Camogli, Italy, September 9, 2016. "Virtual Reality: The Web, Big Data, Information, and Truth."

An exploration of the nature of truth on the web and in digital space.

Grand Rounds, University of Texas Southwestern, May 9, 2016: "Researchers behaving badly: (Unreported) misconduct in clinical trials."

An analysis of research misconduct that fails to get reported in the medical literature.

Keynote, Weissberg Forum for Discourse in the Public Square, Washington DC, April 19, 2016. "Information Battles: The Double-Edged Sword of Big Data."

An analysis of how big data is changing our society's relationship with information.

Keynote, Third Kavli Symposium on Science Coverage, Washington, DC, February 15, 2016. "Understanding clinical trials... despite heavy opposition."

A discussion of the barriers that prevent journalists (and clinicians) from accessing the full corpus of clinical research in an area and how to overcome them.

Invited talk, "Using investigative reporting and data analysis to make an argument." At the American Association for Advancement of Science annual meeting, 2016.

Colloquium, Langone/NYU Medical Center Department of Population Health, December 16 2015. "Anatomy of a retraction."

A case study of a retraction in the scientific literature.

Invited talk, 5th PharmedOut Conference at Georgetown University, June 12 2015. "Researchers Behaving Badly: Misconduct in Clinical Trials."

A lecture about unreported research misconduct uncovered through investigative journalism techniques.

Invited talk, 9th World Conference of Science Journalists in Seoul, South Korea, June 11 2015: "Data-Jitsu: How to go (way) beyond Excel."

A lecture to journalists about how to use spreadsheets to extract meaning from data.

Keynote address, Blue Waters/Petascale Science Symposium, 14 May 2014: "Information feast, information famine: Big data, big computing, and big trouble."

An examination of how big data is transforming science and society -- for better and for worse.

Isaac Asimov Memorial Debate, 20 March 2013.

A wide-ranging discussion on the subject of nothingness.

Sponsored lecture, Strategic Studies Group, Naval War College, 14 November 2012: "Lying with numbers: when to distrust quantitative data."

A discussion of why quantitative data is often used to hide the truth rather than reveal it.

Public lecture, Authors@Google, 1 December, 2011: "Proofiness."

A talk about deceptive numbers, politics, and medical research.

Guest lecture, Psychology Department, Georgetown University, 7 April 2011: "Phony numbers in the social sciences."

A colloquium about how numbers are made to lie in the social sciences.

Public discussion, Rubin Museum, 19 December 2010: "Talk about nothing."

A discussion with Laurie Anderson on the subject of zero and the void.

Talk at the National Association of Science Writers' annual meeting, 6 November 2010: "Character. "

A discussion of the use of characters in a nonfiction narrative.

Lecture at the Mount Sinai School of Medicine, 2 November 2010: "Quantum mechanics, Relativity, and Information. "

A talk about the overlap between relativity theory, quantum theory, and information theory.

Lecture at the Stevens Institute of Technology, 28 October 2009: "Sun in a Bottle: The Strange History of Fusion Energy."

A lecture about fusion energy, about science and pseudoscience, and about the media.

Colloquium at Johns Hopkins University/Applied Physics Laboratory, 10 April 2009: "Fusion, Politics, and the Press."

A presentation to physicists about fusion history as well as the role that politics and the press played in the struggle to generate fusion energy.

Miles Chair Lecture, Horace Greeley High School, 26 March 2009: "Good Science, Bad Science, and Mad Scientists."

A talk about how scientists are perceived by non-scientists -- and why.

Colloquium at Princeton Plasma Physics Laboratory Colloquium, PPPL, 4 February 2009: "Fusion, Politics, and the Press."

A presentation to plasma physicists about the history of fusion and how politics and the press have influenced the quest for fusion energy.

Journalism Department Colloquium, NYU, 31 October 2008: "Sun in a Bottle."

A lecture about fusion energy and about the media's role in scientific fiascos.

Scholars Lecture Series, NYU, 21 September 2007: "Bridging the Two Cultures." (Original title.)

A talk about rationality, the concept of *logos*, and science's role in illuminating the nature of the universe.

Thomas Jefferson High School for Science and Technology, Alexandria VA, 30 September 2005: "The Clash of the Two Cultures."

A lecture about how scientists and science are perceived by non-scientists.

American Physical Society April Meeting, Tampa FL, 19 April 2005: "Physics and the Press"

A talk intended for physicists about why physics is covered so poorly in the popular press.

Mathematical Association of America Section Spring Meeting, Salisbury MD, 24 April 2004: "Mathematics the Press, and the Art of Storytelling."

A lecture about why mathematics is so seldom covered in the media, at least compared to other scientific disciplines.

Selected Media Appearances:

AirTalk (KPCC), 7 April 2016: "What Buzzfeed Journalists Learned from a 4-month Study of FBI, DHS, Drone Flight Patterns."

An intervew regarding the "Spies in the Skies" article.

The Leonard Lopate show, 30 June 2014: "Virtual Unreality."

An interview about digital deception.

The World Science Festival, 17 June 2011: "The Illusion of Certainty: Risk, Probability and Chance."

A video presentation to accompany a panel discussion about risk.

More or Less (BBC Radio 4), 7 January 2011:

Discussion about flawed numerical thinking.

AirTalk (KPCC), 16 November 2010: "Statistics are facts, right?"

Conversation about whether numbers can be made to lie.

Roundtable (WAMC), 2 November 2010:
Discussion about how numbers are misused during elections.

Bloomberg News (Bloomberg TV), 8 October 2010:
Discussion about how to interpret economic indicators such as the unemployment rate.

America's News HQ (Fox News), 25 September 2010:
Interview about the misuse of numbers.

All Things Considered (NPR), 19 September 2010: "Lies, Damn Lies, and Proofiness."
Conversation about how numbers are being misused.

The Leonard Lopate Show (WNYC), 2 June 2010: "Unusual Spill Solutions: A Nuclear Bomb."
Interview about whether it would be possible to stop the ongoing Deepwater Horizon oil spill with a hydrogen bomb.

Coast to Coast AM, 9 December 2009: "CERN, Nukes, and New Science."
Conversation about the search for new particles at CERN as well as the quest for fusion energy.

Talk of the Nation/Science Friday, 8 May 2009:
Discussion about C. P. Snow's "The Two Cultures."

Radio Parallax (KDVS), 9 April 2009:
Interview about fusion and fusion energy.

The NewsHour with Jim Lehrer (PBS), 17 March 2009: "California Scientists Advance Toward Fusion Energy."
Comment on the status of the National Ignition Facility at the Lawrence Livermore National Laboratory.

Static Limit (KUSF), 14 March 2009:
Wide-ranging conversation about physics, mathematics, and science journalism.

The Leonard Lopate Show (WNYC), 6 January 2009: "Sun in a Bottle."
Discussion about the quest for fusion power.

Talk of the Nation (NPR), 8 December 2008: "Not Every Vote Counts."
Conversation about who really won the Coleman/Franken Senate race in Minnesota.

IEEE Spectrum Online (Podcast), 20 November 2008: "Fusion."
Interview about the history of fusion energy.

Explorations in Science with Michio Kaku (WBAI), 11 November 2008.
Discussion about the prospects for fusion as an energy solution.

Coast to Coast AM, 10 November 2008: "CERN Experiments, Science, and Fusion."
Conversation about the turn-on of the Large Hadron Collider and about fusion energy.

The Universe (History Channel), Winter 2007, "Beyond the Big Bang."
Interview about the history of astronomy and cosmology for the History Channel's flagship science program.

Redes (RTVE), 26 November 2007: "Universo y Conciencia más allá de la cuántica."
Interview about quantum theory and cosmology for Spanish TV program.

Coast to Coast AM, 27 January 2007: "Science Talk with Charles Seife."
A return appearance to continue the discussion about parallel universes and cosmology from the previous week.

Coast to Coast AM, 20 January 2007: "Parallel Universes and Quantum Science."
Conversation about information theory, quantum theory, and the possibility of parallel universes.

Coast to Coast AM, 15 June 2006: "Cosmology, Physics, and Science."
Update about what scientists are learning about the nature of the universe.

Coast to Coast AM, 5 February 2005: "Cosmological Theories."
Discussion of the ongoing revolution in modern cosmology.

Been There/Done That (WHYY), 3 January 2004: "Zero."
Interview about the number zero and its strange properties.

Q&A (CNN), 21 November 2003: "Time Travel."
Discussion -- along with physicist Ronald Mallett -- about whether time travel might be possible someday.

The Kojo Nnamdi Show (WAMU), 28 July 2003: "The Origin of the Universe."
Exploration of the current state of cosmological thought.

Science (BBC Radio 4), 11 March 2002: "Five Numbers -- Zero."
Interview about the number zero's place in history.

High Resolution (BBC Radio 4), 21 March 2001: "Making Something of Nothing."
Interview about the void, the vacuum, and about nothing.

Science Friday (NPR), 31 March 2000: "Sleep & Learning/Zero."
Conversation about the number zero.

Publications:

Note: this list does not include most online-only publications (several hundred of which were written between 1995-1997 and 2000-2005 for ScienceNOW, Science magazine's online news service.)

2018

•"In Washington-speak, Censorship is Called 'Transparency," *Scientific American*, 10 January 2018.

2017

•"Is the FDA Withholding Data About A Controversial Drug," *Scientific American*, 25 November 2017.
•"Big Pharma's Attempt to Ghostwrite for *STAT* Ended Badly, but Not Badly Enough." *Slate*, 11 September 2017.
•"Released FDA docs reveal details of agency's (failed) attempt to retract paper." *Retraction Watch*, 21 Aug. 2017.
•"FDA Documents Reveal Depths of Rancor over Drug's Approval Process." 2 August 2017.
•"The Domesticated Press Corps." *Slate*, 1 March 2017.

2016

•"How FDA manipulates the media." *Scientific American*, 21 September 2016.
•"Spies in the Skies." *Buzzfeed*, 7 April 2016. (With Peter Aldhous.)

2015

•"Ashley Madison and Using Stolen Data." Bioethics.net, 10 September 2015. (With Art Caplan.)
•"A Brief Guide to Writing Opinion." The Open Notebook, 10 September 2015.
•"Why it's OK for taxpayers to 'snoop' on scientists." The Los Angeles Times, 21 August 2015. (With Paul Thacker.)
•"The fight over transparency, round two." PLOS Biologue, 13 August 2015. (With Paul Thacker.) [Retracted over authors' objections , according to PLOS' editor-in-chief, "due to increasing pressure from scientists to remove [our] article from the site."]
•"Who's to blame when fake science gets published?" The Los Angeles Times, 28 May 2015.
•"Science's Big Scandal." Slate.com, 1 April 2015.
•"The revolution is digitized." Nature, 26 February 2015.
•"Are Your Medications Safe?" Slate.com, 23 February 2015.
•"Research Misconduct Identified by the US Food and Drug Administration: Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature." JAMA Internal Medicine, 19 February 2015.

2014

•"The Billionaires' Space Club." Slate.com, 30 December 2014.
•"For Sale: Your Name Here in a Prestigious Science Journal." ScientificAmerican.com, 17 December 2014.
•"Consent Matters." Bioethics.net, 29 July 2014. (With Art Caplan.)
•"Facebook Experiment Used Silicon-Valley Trickery." MSNBC.com, 30 June 2014. (With Art Caplan.)
•"What NASA is For: Straight from the Panda's Mouth." HuffingtonPost.com, 14 February 2014.
•"What is NASA For?" Slate.com, 5 February 2014.

2013

•"Twenty years ago, the NSA tried to protect you from spies, not spy on you." Pando.com, 6 December 2013.
•"23 and Me is Terrifying, but Not for the Reasons the FDA Thinks." ScientificAmerican.com, 27 November 2013.
•"An Open Letter to My Former NSA Colleagues." Slate.com, 22 August 2013.
•"Double Dose: In Second Case of Flawed Drug Resarch, FDA Response Was Slow and Secretive." ProPublica, 15 April 2013.
•"FDA Let Drugs Approved on Fraudulent Research Stay on the Market." ProPublica, 15 April 2013.
•"No Substitute: When a Generic Drug Isn't What It Seems." ProPublica, 15 April 2013.
•"A Military Fable." The Huffington Post, 26 February 2013.

•"Fusion Energy's Dreamers, Hucksters, and Loons." Slate.com, 3 January 2013.

2012
•"Is Drug Research Corrupt?" Scientific American, December 2012.
•"Jonah Lehrer's Journalistic Misdeeds at Wired.com." Slate.com, 31 August 2012.
•"Dr. Drew Cashes In." Slate.com, 9 July 2012.
•"James O'Keefe Attacked Me Because I Caught Him Breaking the Law." charlesseife.blogspot.com, 22 March 2012.
•"Seventeen Equations that Changed the World." Times Higher Education, March 2012.

2011
•"The Mind-Reading Salmon." Scientific American, August 2011.
•"Following the Thread." Bookforum, Feb/Mar 2011.

2010
•"The Science of Disestimation." Scientific American, December 2010.
•"Killing the Census." The Huffington Post, 23 September 2010.
•"Numbers Don't Lie, but People Do." Seed, 24 September 2010.
•"Sorry, Wrong Number." Spirit, September 2010.
•"Between Fact and Fantasy: Polling and the Media." The Huffington Post, 7 July 2010.

2008
•"Not Every Vote Counts. " The New York Times, 4 December 2008.
•"Can Engineers Achieve the Holy Grail of Infinite Energy?" Discover, October 2008.
•"One to Nine: The Inner Life of Numbers." Discover, May 2008.

2007
•"Signs of Life." Smithsonian, Fall 2007.

2006
•"Proof." The Washington Post, Oct. 15, 2006.
•"No strings attached." Seed magazine, Aug./Sept. 2006.
•"It came from outer space." The Washington Post, Feb. 26, 2006.

2005
•"Teaching Qubits New Tricks." Science, 8 July 2005.
•"What Is the Universe Made Of?." Science, 1 July 2005.
•"Can the Laws of Physics Be Unified?." Science, 1 July 2005.
•"What Are the Limits of Conventional Computing?." Science, 1 July 2005.
•"Do Deeper Principles Underlie Quantum Uncertainty and Nonlocality?." Science, 1 July 2005.
•"Senate Squeezes NSF's Budget." Science, 1 July 2005.
•"RHIC Gets Nod Over JLab in Worst-Case DOE Scenario." Science, 24 June 2005.
•"KEK Researchers Catch Glimpse of Outlandish Particles." Science, 10 June 2005.
•"Shakeup at SLAC." Science, 3 June 2005.
•"Physics Research Gets a Boost and a Warning From Its Funders." Science, 27 May 2005.
•"Neutron Stars Could Test Quantum Effect." Science, 20 May 2005.
•"Falling Budget Could Force Choice Between Nuclear Science Facilities." Science, 29 April 2005.
•"Tabletop Accelerator Breaks 'Cold Fusion' Jinx But Won't Yield Energy, Physicists Say." Science, 29 April 2005.
•"Counterattack Heats Up Dispute Over 'Dark Energy'." Science, 22 April 2005.
•"Latest Data Deal 'Pentaquark' Sightings a Fresh Blow." Science, 22 April 2005.
•"Unspeakable State of Matter Starts to Reveal Itself--But for How Long?." Science, 22 April 2005.
•"Magnetic Scope Angles for Axions." Science, 15 April 2005.
•"High-Energy Physics: Exit America?." Science, 1 April 2005.
•"Fermilab Experiment Shoots the Muon." Science, 11 March 2005.
•"Flaw Found in Data-Protection Method." Science, 4 March 2005.
•"Fiscal Woes Dog Gamma Ray Satellite." Science, 25 February 2005.
•"NSF Stunned by Higher Costs of Proposed DOE Facility." Science, 18 February 2005.

•"We're So Sorry, Uncle Albert." Science, 11 February 2005.
•"Safer Coin Tosses Point to Better Way for Enemies to Swap Messages." Science, 4 February 2005.
•"A Call to Verse" Science, 28 January 2005.
•"Cesium Collisions Help Create Colder Antihydrogen." Science, 7 January 2005.

2004
•"A Plasma Too Far? Researchers Hunt for Early State of Matter." Science, 24 December 2004.
•"The Runners-Up." Science, 17 December 2004.
•"Outlook for Cold Fusion Is Still Chilly." Science, 10 December 2004.
•"The Omnibus Bill Isn't Only About Dollars." Science, 3 December 2004.
•"Neutrinos Are All Flip-Floppers, Japanese Study Shows." Science, 26 November 2004.
•"Rara Avis or Statistical Mirage? Pentaquark Remains at Large." Science, 19 November 2004.
•"Gambling With Our Votes?." Science, 29 October 2004.
•"Fundamental Constants Appear Constant--At Least Recently." Science, 29 October 2004.
•"Seeing Waves in the Background." Science, 29 October 2004.
•"Researchers Build Quantum Info Bank By Writing on the Clouds." Science, 22 October 2004.
•"Swiveling Satellites See Earth's Relativistic Wake." Science, 22 October 2004.
•"Photons One-at-a-Time" Science, 22 October 2004.
•"Macroeconomists Showed Why Good Intentions Go Wrong." Science, 15 October 2004.
•"Laurels to Three Who Tamed Equations of Quark Theory." Science, 15 October 2004.
•"A Slanted View of the Early Universe." Science, 8 October 2004.
•"Firing Draws Protest at Los Alamos." Science, 24 September 2004.
•"South Korea Admits to Laser Enrichment Program." Science, 10 September 2004.
•"Physicists Pick a Cold Road for Accelerator Project." Science, 27 August 2004.
•"A General Surrenders the Field, But Black Hole Battle Rages On." Science, 13 August 2004.
•"Hubble Space Telescope Loses Major Instrument." Science, 13 August 2004.
•"Hawking Slays His Own Paradox, But Colleagues Are Wary." Science, 30 July 2004.
•"Physics Enters the Twilight Zone." Science, 23 July 2004.
•"Energy Curve Confirms Paired-Up Fermi Condensate." Science, 23 July 2004.
•"Top Quark Tips the Scale for a Heavier Higgs Boson." Science, 11 June 2004.
•"Solar Flares Reveal Surprising Recipe." Science, 14 May 2004.
•"Gravity Withstands Close-Up Scrutiny." Science, 14 May 2004.
•"Once Again, Dark Matter Eludes a Supersensitive Trap." Science, 14 May 2004.
•"Gravity Probe to Give Einstein a Pricey High-Precision Test." Science, 16 April 2004.
•"Gamma Rays Spotlight a Dark Horse for Dark Matter." Science, 19 March 2004.
•"Moon's 'Abundant Resources' Largely an Unknown Quantity." Science, 12 March 2004.
•"Galactic Stripling Gives a Glimpse of the Universe's Raw Youth." Science, 12 March 2004.
•"Light From Most-Distant Supernovae Shows Dark Energy Stays the Course." Science, 27 February 2004.
•"Big, Hot Molecules Bridge the Gap Between Normal and Surreal." Science, 20 February 2004.
•"New-Style Matter Opens Cool Middle Ground." Science, 6 February 2004.
•"Versatility Is the Object for New Crew Vehicle." Science, 30 January 2004.
•"Once Again, Muons Defy Reigning Theory." Science, 9 January 2004.
•"Wanted: One Good Cosmic Blast to Shake the Neighborhood." Science, 9 January 2004.

2003
•"Illuminating the Dark Universe." Science, 19 December 2003.
•"Perimeter's Threefold Way." Science, 5 December 2003.
•"At Canada's Perimeter Institute, 'Waterloo' Means 'Shangri-La'." Science, 5 December 2003.
•"Competing Research Teams Create Long-Sought State of Matter." Science, 14 November 2003.
•"Galaxy Maps Support Theory That the Universe Is Flying to Pieces." Science, 31 October 2003.
•"Cool Theories Garner Super Kudos." Science, 17 October 2003.
•"Clearer Forecasts for the Dismal Science." Science, 17 October 2003.
•"Polyhedral Model Gives the Universe An Unexpected Twist." Science, 10 October 2003.
•"Physics Tries to Leave the Tunnel." Science, 3 October 2003.
•"Lots of Reasons, But Few Lessons." Science, 3 October 2003.
•"'I Think I Added Something'." Science, 5 September 2003.
•"Will a Safer Shuttle Still Support Science?." Science, 5 September 2003.

•"Showdown Looms for Reigning Particle-Physics Theory." Science, 22 August 2003.
•"Visa Delay Foils Chinese Delegation." (with Ding Yimin) Science, 22 August 2003.
•"Souped-Up Archimedes Equation Torpedoes Submarine Paradox." Science, 8 August 2003.
•"'Terrorism Futures' Could Have a Future, Experts Say." Science, 8 August 2003.
•"Dark Energy Passes Another Test." Science, 25 July 2003.
•"Western Europe Joins Gravitational-Wave Search." Science, 18 July 2003.
•"Report Says Early Strikes Can't Shoot Down Missiles." Science, 18 July 2003.
•"Evidence for 'Pentaquark' Particle Sets Theorists Re-Joyce-ing." Science, 11 July 2003.
•"Dark Energy Tiptoes Toward the Spotlight." Science, 20 June 2003.
•"Has RHIC Set Quarks Free at Last? Physicists Don't Quite Say So." Science, 20 June 2003.
•"Environmental Report Paralyzes Italian Neutrino Lab." Science, 13 June 2003.
•"Calculations Pop the Cork on Travel Through Spacetime Tunnels." Science, 6 June 2003.
•"Pick Your Poison: U vs. Pu." Science, 30 May 2003.
•"North Korea's Not-So-Hidden Agenda Raises the Ante." Science, 30 May 2003.
•"In Clone Wars, Quantum Computers Need Not Apply." Science, 9 May 2003.
•"With Its Ingredients MAPped, Universe's Recipe Beckons." Science, 2 May 2003.
•"NASA's Hypersonic Lab Studies Factors Leading to Breakup." Science, 28 March 2003.
•"Recipe for Rocket-Free Space Travel: Dive In and Paddle, Patiently." Science, 28 February 2003.
•"Why Physicists Long for the Straight and Narrow." Science, 21 February 2003.
•"Gravity Waves Elude First Scrutiny." Science, 21 February 2003.
•"MAP Glimpses Universe's Rambunctious Childhood." Science, 14 February 2003.
•"Columbia Disaster Underscores the Risky Nature of Risk Analysis." Science, 14 February 2003.
•"United States Rejoins International Fusion-Research Project." Science, 7 February 2003.
•"New Skating System Fails Virtual Replay." Science, 31 January 2003.
•"How a Scribe Learned Math, ca. 1800 B.C.." Science, 31 January 2003.
•"Relativity Goes Where Einstein Sneered to Tread." Science, 10 January 2003.

2002
•"CERN Council Chooses ITER's Head as Chief." Science, 20 December 2002.
•"The Runners-Up." Science, 20 December 2002.
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