IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

CATALYST PHARMACEUTICALS, INC.,
355 Alhambra Circle, Suite 1250
Coral Gables, FL 33134

Plaintiff,

v.

ALEX AZAR, Secretary of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201;

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 Independence Avenue, SW
Washington, DC 20201;

NORMAN SHARPLESS, Acting Commissioner of Food and Drugs
10903 New Hampshire Avenue
Silver Spring, MD 20993; and

U.S. FOOD AND DRUG ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993,

Defendants.

Case No._____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff Catalyst Pharmaceuticals, Inc. brings this suit against Defendants Alex Azar, in his official capacity as Secretary of Health and Human Services; the U.S. Department of Health and Human Services (DHHS); Norman Sharpless, in his official capacity as Acting Commissioner of Food and Drugs; and the U.S. Food and Drug Administration (FDA), and alleges as follows:

PRELIMINARY STATEMENT

1. This suit challenges Defendants' approval of a new drug application and related drug labeling for Jacobus Pharmaceutical Company's (Jacobus) drug Ruzurgi (amifampridine) for treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in pediatric patients. Defendants' approval of that drug: (1) violated multiple provisions of FDA regulations regarding labeling, resulting in "misbranding" in violation of the Food Drug and Cosmetic Act (FDCA); (2) violated Plaintiff's statutory rights to Orphan Drug Exclusivity and to New Chemical Entity Exclusivity under the FDCA; and (3) was in multiple other respects arbitrary, capricious, and contrary to law, in violation of the Administrative Procedure Act (APA).

2. Under the FDCA, FDA must approve any new drug before it can be introduced into interstate commerce. 21 U.S.C. § 355(a). Truly new drugs typically go through the full new drug approval process, which requires an extensive showing of safety and efficacy. *Id.* § 355(b)(1). The FDCA also provides streamlined approval pathways for follow-on drug products, such as generics, that rely on FDA's previous approval of the same or a similar drug. *Id.* § 355(b)(2), (j).

3. The Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983), added to the FDCA a range of statutory benefits for drug developers, including most importantly the right to a seven-year period of market "exclusivity" to incentivize development of drugs to treat "rare diseases or conditions," *i.e.*, diseases or conditions affecting 200,000 or fewer persons in the United States. 21 U.S.C. §§ 360bb, 360cc. In enacting the Orphan Drug Act, Congress recognized that the significant costs of drug development, along with all the painstaking steps necessary for FDA approval, make such development prohibitively expensive for rare diseases without specialized incentives. Orphan drug designation, and the marketing exclusivity that it provides,

was Congress's way of incentivizing pharmaceutical companies to take the financial risks associated with developing and obtaining approval of drugs to treat rare conditions by providing a longer window to obtain a return on their investment. *See* 96 Stat. at 2049. Catalyst has spent more than $100 million developing Firdapse® (amifampridine phosphate). Firdapse® was designated by FDA as an orphan drug for LEMS in 2009, and FDA approved Firdapse® for treatment of adults with LEMS on November 28, 2018. Catalyst received a letter from FDA expressly recognizing its Orphan Drug Exclusivity (ODE) for LEMS on December 21, 2018.

4. Congress also recognized that certain exclusivity incentives were needed to protect drug developers' investment in "pioneer" drugs employing "new chemical entities" (*i.e.*, new active ingredients), and required that FDA refuse to accept certain applications for approval of other drugs employing the same active ingredient for five years (New Chemical Entity Exclusivity or NCEE). To obtain approval of Firdapse®, Catalyst was required to submit the results of more than 70 non-clinical and clinical studies, including two adequate and well-controlled clinical trials evaluating Firdapse® for the safe and effective treatment of LEMS. Catalyst's Firdapse® also meets the criteria for NCEE and was awarded that exclusivity by FDA on November 28, 2018.

5. FDA's regulations governing drug labeling are intended to ensure labeling is accurate and carefully explain the uses for the drug approved by FDA. Such regulations implement multiple statutory requirements, including the "misbranding" provisions of the FDCA, 21 U.S.C. § 352, which provide that FDA may not approve labeling that is "false or misleading in any particular." *See also id.* § 355(d) (providing that FDA "shall" refuse approval of drug labeling that is "false or misleading in any particular"); *id.* §§ 331, 333 (providing for criminal penalties for manufacturers that sell misbranded drugs). Among other things, FDA's labeling regulations prohibit any text on the labeling suggesting or implying that the drug can be used for any

unapproved uses, including any uses barred by ODE. *See* 21 C.F.R. §§ 201.57(c)(2)(iv) and (15)(i) (prohibiting drug labeling from "imply[ing] or suggest[ing] indications or uses or dosing regimens" not approved by FDA for the drug). So, for example, no drug approved only for adults can suggest or imply in its labeling that the drug is safe and effective for use in children, or vice versa. FDA cannot lawfully approve drug labeling that violates its own regulations.

6. Almost all LEMS patients are adults—and LEMS is typically diagnosed later in life. About half of LEMS patients also suffer lung cancer, most commonly small cell lung cancer. While there are approximately 3,000 LEMS patients in the United States (1,500 of which have been diagnosed with LEMS in claims data over the last two years), the number of pediatric LEMS patients is extremely small; Jacobus has indicated there are less than 15 pediatric patients total. Although Firdapse® is approved for adult use only, the few pediatric LEMS patients have been (and, in the absence of Ruzurgi's approval, can continue to be) treated with LEMS medication under FDA's "expanded access" investigational new drug program. Jacobus's LEMS drug Ruzurgi is the same drug as Catalyst's Firdapse®. Indeed, Ruzurgi's approval is based entirely on clinical efficacy data in the very same population for which Firdapse is approved—adult patients with LEMS.

7. FDA's approval of Ruzurgi should have been barred by multiple provisions of law. First, Jacobus's drug labeling unambiguously violates FDA's regulations by communicating in multiple separate provisions that the drug can be safely and effectively used for adult patients, notwithstanding the fact it has not been approved for use in adults but has instead only been approved for use in children. *Compare* Ruzurgi Labeling at 5-6 ("Use of RUZURGI in patients 6 to less than 17 years of age is supported by evidence from adequate and well-controlled studies of RUZURGI in adults with LEMS . . . .") *with* 21 C.F.R. § 201.57(c)(15)(i) ("[A]ny clinical study

that is discussed in prescription drug labeling . . . must not imply or suggest indications or uses" for which the drug is not approved). This misbranding facilitates illegal "off-label" marketing by Jacobus of its pediatric drug for adult patients.

8. Second, FDA impermissibly sidestepped Catalyst's statutory right to ODE. FDA specifically recognized that Jacobus is barred by Catalyst's ODE from approval for adult patients. *See* Tentative Approval Letter from FDA to Jacobus at 2 (May 6, 2019) ("Due to the orphan exclusivity granted to Catalyst Pharmaceuticals, Inc. for Firdapse, your application for Ruzurgi may not be finally approved for marketing under Section 505 of the [FDCA] until the period has expired."). There is no clinical distinction between adult LEMS and pediatric LEMS—it is the "same disease or condition" (LEMS). And because Jacobus's drug Ruzurgi is otherwise the same drug as Catalyst's drug, the plain statutory text of the ODE provision, 21 U.S.C. § 360cc(a), bars FDA approval of Jacobus's drug. A long line of administrative precedents confirms this result.

9. Third, even if a pediatric-only approval were possible under ODE (it is not), Jacobus also appears to lack sufficient clinical testing and other data for Ruzurgi to be lawfully approved under the full new drug approval process, and thus either explicitly or implicitly required a reference to either Catalyst's or another firm's data. Accordingly, Jacobus's new drug application should have been deemed a section 505(b)(2) follow-on application, *id.* § 355(b)(2), barred by Catalyst's NCEE statutory exclusivity, and could not have been lawfully approved by FDA. *See id.* § 355(c)(3)(E)(ii).

10. Fourth, in addition to each of those violations of law, FDA arbitrarily and capriciously applied different approval criteria for Jacobus than it applied to Catalyst even though the two drugs are and were similarly situated. FDA's rush to approve Jacobus's New Drug Application (NDA) for Ruzurgi did not include the review of all of the same pre-submission data

and studies that Catalyst was required by FDA to submit as part of its NDA. Ultimately, FDA approved Jacobus's NDA in a manner inconsistent with decades of FDA precedents. For example, while FDA required Catalyst to complete an animal toxicity study *before* approving Firdapse®, FDA permitted Jacobus to conduct a juvenile animal toxicology study *after* Ruzurgi has entered the market, even though FDA has (erroneously) permitted Jacobus to market Ruzurgi to pediatric patients.

11. On information and belief, FDA engaged in these acts based upon a misperception regarding the pricing of Firdapse®, but price is not a factor that Congress has allowed FDA to consider when rendering decisions. FDA was well aware that Jacobus could not hope to recoup the costs of pre- and post-approval clinical and non-clinical testing associated with approval of its pediatric drug (costing at least $15 million) without also illegally marketing off-label to adult patients. FDA also issued at least one official letter communicating to adult LEMS patients that they should consult their physicians regarding the potential use of Jacobus's product for LEMS—even though that drug was only approved for pediatric patients—rather than Catalyst's product, which is, pursuant to statute, the only LEMS drug that can be approved for adults.

12. On information and belief, FDA's actions are, in fact, facilitating "off-label" marketing by Jacobus. On the date Jacobus's drug was approved, an individual identified as a Jacobus paid consultant was quoted in the trade press directly urging adult patients and their physicians to instead use Jacobus's pediatric drug rather than the only adult approved drug available for LEMS—Catalyst's drug: "If it's [Ruzurgi] on the market for children, it can be prescribed for adults. . . . This sounds like a workaround." Scott Bloomer, *FDA Added Unexpected Twist to Dampen Controversy over a Drug That Costs $375,000*, MYHEALTHYCLICK (May 7, 2019), https://www.myhealthyclick.com/fda-added-unexpected-twist-to-dampen-controversy-

over-a-drug-that-costs-375000.[1] Almost immediately after Jacobus's approval, Catalyst's stock price dropped by 40%.

13. In these and other ways, FDA's actions violate multiple provisions of the FDCA, and are arbitrary and capricious, an abuse of discretion, and/or contrary to law in violation of the APA. Without a remedy, these violations will facilitate illegal marketing by Jacobus to adult patients, which in multiple material respects threatens irreparable harm to Catalyst.

14. Catalyst is entitled to declaratory and injunctive relief in the form of (i) a declaration declaring FDA's approval of Jacobus's Ruzurgi unlawful, (ii) a vacatur setting aside FDA's Ruzurgi approval, and (iii) appropriate preliminary and permanent injunctive relief prohibiting FDA from approving any application for a drug that violates Firdapse®'s statutory exclusivities.

PARTIES

15. Plaintiff Catalyst Pharmaceuticals, Inc. is the owner of New Drug Application No. 208078 for Firdapse®. Catalyst is a publicly-traded company with its principal place of business at 355 Alhambra Circle, Suite 1250, Coral Gables, FL 33134. Catalyst advertises, sells, and distributes its drugs in this District and nationwide.

16. Alex Azar is the Secretary of Health and Human Services and the head of DHHS. In this capacity, Secretary Azar has ultimate responsibility for activities at DHHS, including the actions complained of herein. His governmental activities occur nationwide.

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[1] *See also* Donald B. Sanders, MD, et al., *Reliability of the triple-timed up-and-go test*, MUSCLE & NERVE (Jan. 2018) (identifying Dr. Sanders as "a paid consultant to [Jacobus]"), https://onlinelibrary.wiley.com/doi/pdf/10.1002/mus.25700.

17. DHHS is a department of the United States. Its headquarters and principal place of business are at 200 Independence Avenue, S.W., Washington, D.C. 20201. Its governmental activities occur nationwide.

18. Norman Sharpless is the Acting Commissioner of Food and Drugs and the head of FDA. His governmental activities occur nationwide.

19. FDA is an agency of the United States and a division of DHHS. FDA's headquarters and principal place of business are at 10903 New Hampshire Avenue, Silver Spring, MD 20903. Its governmental activities occur nationwide.

JURISDICTION, EXHAUSTION, AND FINAL AGENCY ACTION

20. This Court has jurisdiction pursuant to 28 U.S.C. § 1331. This action arises under the APA, 5 U.S.C. §§ 701-06. Plaintiff's prayers for a declaratory judgment and preliminary and permanent injunctive relief are authorized by the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; the APA, 5 U.S.C. §§ 701-06; and 28 U.S.C. § 1361.

21. Venue is proper in this District under 28 U.S.C. § 1391(e)(1) because Catalyst resides in this District and there is no real property involved in this action.

22. FDA's approval of Ruzurgi is a final agency action reviewable under the APA. 5 U.S.C. § 704.

23. There is no statutorily mandated requirement that Catalyst seek relief from the agency before bringing suit in this Court. There is also no regulatory pathway to challenge the approval under which the approval would remain "inoperative" during the period of agency review. *See id.* (providing that this is a mandatory condition for any agency rule seeking to compel agency review before judicial challenge). Thus, administrative exhaustion is not a prerequisite to suit.

24. In any event, immediate judicial review is warranted because Catalyst has previously made extensive efforts to obtain relief from FDA on the matters addressed by this Complaint. In multiple communications with FDA prior to Ruzurgi's approval, Catalyst urged FDA to both treat any similarly situated competitor the same way FDA treated Catalyst, and to respect Catalyst's statutory right to exclusivity, and FDA has failed or refused to do so. Thus, any further attempt to seek relief directly from FDA would be futile.

25. Moreover, Catalyst faces the threat of immediate and irreparable harm from FDA's actions. Jacobus has recently published the price of Ruzurgi, and, on information and belief, is preparing to imminently launch its competing product. Because Ruzurgi is priced lower than Firdapse® but both drugs are the same, Catalyst's small number of adult customers may have a compelling economic incentive to switch from Firdapse®, the product approved for them, to Ruzurgi, the product that FDA did not approve for these adult patients.

BACKGROUND

A. Statutory and Regulatory Framework for New Drug Approvals

26. Regardless of whether another drug is presently enjoying statutory exclusivity, generally *no* "new drug" may enter the market without first obtaining FDA approval. 21 U.S.C. § 355(a).

27. The principal pathway for premarket approval is through a full New Drug Application (NDA) submitted pursuant to section 505(b)(1) of the FDCA. *Id.* § 355(b)(1). This NDA must contain, among other things, complete reports of investigations of the safety and effectiveness of the product candidate gathered through expensive clinical trials. *Id.*[2] "Such

[2] *See also id.* § 355(b)(1)(A)-(G) (requiring an NDA applicant to submit "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; a full list of the articles used as components of such drug; a full

reports rely in large measure on clinical trials with human subjects." *Abigail All. for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 697 (D.C. Cir. 2007). And "before a sponsor can even begin human testing, it must" separately "submit for the FDA's approval an" investigational new drug application (IND). *See id.* at 697; 21 U.S.C. § 355(i)(1). Drugs approved pursuant to this process are commonly referred to as "pioneer drugs."

28. The Hatch-Waxman Amendments added more streamlined pathways to approval for follow-on drugs that generally rely at least in part on the application of an already-approved pioneer drug. As relevant here, section 505(b)(2) of the FDCA provides a streamlined pathway that allows a follow-on drug applicant to rely on the investigations that the pioneer drug performed in circumstances where the follow-on applicant has "not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 U.S.C. § 355(b)(2).

29. Both pioneer drug applicants and section 505(b)(2) applicants must also submit "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b). The labeling must contain voluminous content. *See* 21 C.F.R. § 201.57. Among other things, it must contain "[a] concise statement of each of the product's indications," *id.* § 201.57(a)(6), specifically, that "the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition," *id.* § 201.57(c)(2). The "Clinical Studies" section, in turn "must not imply or suggest indications or uses . . . not stated in the 'Indications and Usage' . . . section." 21 C.F.R. § 201.57(c)(15)(i).

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statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; such samples of such drug and of the articles used as components thereof" as required; "specimens of the labeling proposed to be used for such drug;" and any required assessments regarding pediatric uses of the drug).

30. The FDCA also provides multiple circumstances under which FDA must refuse approval for an application. Among other things, FDA "shall" "refus[e] to approve an application" if (1) "the investigations," relied on for the application "do not include adequate tests . . . to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling"; (2) "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"; or (3) the "labeling is false or misleading in any particular." 21 U.S.C. § 355(d).

31. Post-approval, the FDCA also regulates the manufacturers of approved drugs and empowers FDA to oversee manufacturers of approved drugs in many ways. First, as relevant here, section 505(o)(3) of the FDCA, 21 U.S.C. § 355(o)(3), authorizes FDA to require holders of approved drug applications to conduct post-approval studies and clinical trials. FDA may do so "to address [a] serious safety concern." *See* Office of Commc'ns, Div. Drug Info, FDA, *Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the [FDCA]* at 6 (Apr. 2011).

32. Second, through its prohibition of "misbranded" drugs, the FDCA imposes a continuing obligation on drug manufacturers to ensure that their labeling never becomes misleading. 21 U.S.C. § 352 (providing that labeling that is "false or misleading in any particular" is misbranded); *see also id.* § 331(a) (prohibiting misbranding). And it equally prohibits "manufacturers from promoting or marketing their drugs for off-label uses." *See Ironworkers Local Union 68 v. AstraZeneca Pharms., LP*, 634 F.3d 1352, 1356 n.5 (11th Cir. 2011). As FDA has recently explained, a manufacturer's provision of any "[i]nformation about the use of a product to treat or diagnose patients who are not included in the product's approved patient population"

would not be considered consistent with the FDA-required labeling. *See* Ctr. For Drug Evaluation & Research, Office of the Comm'r, FDA, *Guidance for Industry; Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers* at 10 (June 2018).

B. The Orphan Drug Act

33. The Orphan Drug Act was enacted on January 4, 1983 to incentivize the increased development of drugs across all rare diseases and conditions. Pub. L. No. 97-414, § 1(b), 96 Stat. at 2049 (1983). The Orphan Drug Act amended the FDCA at 21 U.S.C. §§ 360aa-360ee. By enacting the Orphan Drug Act, Congress provided financial incentives to encourage investment in the development of drugs that may otherwise not be developed because the market for their use is too small to be profitable.

34. The principal financial incentive established by the Orphan Drug Act is a promise of a seven-year period of marketing exclusivity for designated orphan drugs that are ultimately approved for rare diseases or conditions. During this period of exclusivity, FDA may not approve another marketing application for the "same drug for the same disease or condition." 21 U.S.C. § 360cc(a), and LEMS (whether for adults or children) is, in all respects, the same disease or condition.

35. The seven-year period during which FDA is prohibited from approving another application for the "same drug for the same disease or condition" is often referred to as a period of "marketing exclusivity" for the successful orphan drug applicant because no new entity is permitted to manufacture or sell the same drug in interstate commerce for the same disease or condition during that time. Congress's decision to grant the holders of successful orphan drug applications seven years of marketing exclusivity upon approval was the result of purposeful consideration of the extent of benefits needed to incentivize drug manufacturers to advance

treatments for orphan diseases. *See* H.R. Rep. No. 100-473, at 6 (1987) (discussing that Congress weighed the potential benefits and drawbacks of offering seven years of market exclusivity); *see also* 96 Stat. at 2049 (recognizing that manufacturers of drugs for rare diseases or conditions could "reasonably expect the drug to . . . incur a financial loss" absent exclusivity). If FDA can create workarounds that limit the value of orphan drug exclusivity, it would undermine the key incentive Congress created for pharmaceutical companies to invest the millions of dollars that it takes to bring an orphan drug to market.

36. Section 526 of the Orphan Drug Act, 21 U.S.C. § 360bb, establishes the process by which a drug may receive orphan designation. That section permits a drug sponsor to request that FDA designate a drug as an "orphan drug" if the drug, when approved, would treat a "rare disease or condition." The Act essentially codifies in its definition of what is a "rare disease or condition" the concept of whether a drug would have a broad enough patient population to recoup development and other costs *in the absence of* the seven-year exclusivity. First, it recognizes as a matter of law that a disease or condition that "affects less than 200,000 persons in the United States" is a rare disease or condition and that a company that designs a drug to treat a population this small would presumptively not be able to recoup its costs without the seven year exclusivity. Second, the Orphan Drug Act provides that a disease or condition that "affects *more* than 200,000 in the United States" may also be considered "rare" if "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (again, absent seven year exclusivity). 21 U.S.C. § 360bb(a)(2).

37. Once FDA *approves* an orphan-designated drug, there are only three circumstances under which the Orphan Drug Act permits FDA to approve a third party's

application for the same drug for the same disease or condition: (1) if the sponsor of the first-approved drug cannot sufficiently supply the market and meet the needs of the orphan patient population; (2) if the third party obtains the written consent of the orphan drug sponsor; or (3) if the third party can demonstrate that its drug is "clinically superior" to the first because it "provides a significant therapeutic advantage . . . in terms of efficacy, greater safety, or by providing a major contribution to patient care." 21 U.S.C. § 360cc(b), (c). None of these exceptions apply in this case.

C. New Chemical Exclusivity

38. The FDCA also has other exclusivity provisions. As relevant here, the NCEE provision provides that:

> **If** an application submitted under subsection (b) for a drug, no active ingredient . . . of which has been approved in any other application under subsection (b) is approved" **then** "no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations [required] and relied upon by the applicant for approval of the application were not conducted by or for the applicant for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) before the expiration of five years form the date of the approval of the application under subsection (b).

See 21 U.S.C. § 355(c)(3)(E)(ii) (emphasis added); *see also id.* § 355(j)(5)(F)(ii) (same for other types of follow-on drugs).

39. In other words, as FDA has explained through regulation: "If a drug product that contains a new chemical entity [i]s approved . . . in an application submitted under section 505(b) of the [Act], no person may submit a 505(b)(2) application . . . for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved [new drug application]." 21 C.F.R. § 314.108(b)(2).

D. Catalyst's Firdapse® Is Approved for and Given Orphan Drug Exclusivity Regarding Treatment of LEMS

40. Catalyst's predecessor-in-interest requested an orphan drug designation for amifampridine phosphate for LEMS in accordance with 21 U.S.C. § 360bb, which FDA granted on November 12, 2009. In granting the designation, FDA drew no distinction between LEMS affecting adult patients and LEMS in pediatric patients, and LEMS does not present differently in the two populations.

41. Catalyst first submitted its New Drug Application (NDA) under 21 U.S.C. § 355(b)(1) for amifampridine phosphate on November 16, 2015, and later resubmitted this NDA on March 28, 2018 in response to FDA's February 12, 2016 Refusal to File letter.[3] Although Catalyst had already thoroughly studied the effect of amifampridine in LEMS patients when the company first submitted its NDA in November 2015, FDA stated that Catalyst had not included "[s]ufficiently detailed information" regarding its first clinical trial for LEMS patients, referred to in the approved Firdapse® labeling as LEMS-002. *See* Letter from FDA to Catalyst at 1 (Feb. 12, 2016). Before resubmitting the NDA, Catalyst discussed the design of a second clinical trial—LEMS-003—extensively with FDA at an April 7, 2016 meeting. The results of both LEMS-002 and LEMS-003 were submitted as part of Catalyst's March 2018 NDA resubmission and included in the proposed Firdapse® labeling.

42. Based in part on the results of these two clinical trials—which both involved adult patients—FDA approved Firdapse® as "indicated for the treatment of . . . LEMS in adults" on November 28, 2018. Firdapse® Labeling at 1. The Clinical Studies section of the labeling

[3] Under 21 C.F.R. § 314.101, FDA may refuse to file an NDA when, among other things, "[t]he NDA . . . is incomplete because it does not on its face contain information required" by the FDCA or implementing regulations.

describes LEMS-002 and LEMS-003 as "two randomized, double-blind, placebo-controlled discontinuation studies," in which "64 adults (age 21 to 88 years)" were enrolled. This section also discusses the results of the both studies:

> [P]atients randomized to placebo had a significantly greater worsening of muscle weakness and of global impression of the effects of the study treatment on their physical well-being, compared to patients who continued FIRDAPSE in the double-blind period.

Id. at 8-9. These studies, which were funded by Catalyst, were additionally published in two well-respected journals. *See* Shin J. Oh, MD, et al., *Amifampridine Phosphate (Firdapse) Is Effective and Safe in a Phase 3 Clinical Trial in LEMS*, MUSCLE & NERVE (Mar. 2016) (discussing the results of LEMS-002); Perry Shieh, MD, PhD, et al., *Amifampridine Phosphate (Firdapse) Is Effective in a Confirmatory Phase 3 Clinical Trial in LEMS*, J. CLINICAL NEUROMUSCULAR DISEASE (Mar. 2019) (discussing the results of LEMS-003). Catalyst also conducted extensive non-clinical safety and toxicology testing to support its NDA. *See* Firdapse® Labeling. Catalyst, however, has never granted another party a right of reference to any of the results of its non-clinical safety and toxicology studies, as well as the data underlying its published studies.

43. In its letter approving Firdapse®, FDA listed three post-approval activities that Catalyst is required to conduct: (1) an animal carcinogenicity study; (2) a pregnancy surveillance program; and (3) a clinical trial evaluating the effect of Firdapse® on liver function. *See* November 28, 2018 Approval Letter from FDA to Catalyst at 2-4 (Nov. 28, 2018). FDA often requires successful NDA applicants to conduct similar studies so that the agency can review additional safety data as the drug is used by a larger patient population.

44. On December 21, 2018, FDA's Office of Orphan Products Department confirmed to Catalyst that, as the first sponsor of an amifampridine drug to obtain marketing approval for the

treatment of LEMS in adults, the Company is entitled to seven years of ODE for Firdapse®, and that this exclusivity expires on November 28, 2025.

45. FDA also published as part of its Approved Drug Products with Therapeutic Equivalence Evaluations (colloquially known as the Orange Book), that Catalyst has NCEE for amifampridine phosphate, which will expire on November 28, 2023.

46. After FDA approved Firdapse®, some physicians and LEMS patients expressed concern about the perceived high cost of the approved drug, although Catalyst's pricing of the drug was in line with the pricing of other products that promote significant clinical benefits in treating orphan diseases of similar severity and prevalence. The price of Firdapse® was the subject of significant media and trade press attention.

47. Politicians also waded into the pricing discussion. For example, on February 4, 2019, Senator Bernie Sanders announced that he was "investigat[ing]" the price of Firdapse. *See* Press Release, Sen. Bernie Sandes, *Sanders Investigates a $375,000 Price Spike on Old Drug* (Feb. 4, 2019), https://www.sanders.senate.gov/newsroom/press-releases/sanders-investigates-a-375000-price-spike-on-old-drug. His premise was that Firdapse® was a re-purposed drug in use for over 30 years. In fact, before the approval of Firdapse®, it was an unapproved drug only available to a small group of patients until Catalyst performed the required testing to obtain approval. Catalyst's pricing is set in a manner that recognizes its commitment of $100 million for development of the drug.

48. Contrary to the misperceptions in the media, however, Catalyst established in conjunction with the launch of Firdapse® a comprehensive patient insurance navigation and financial assistance program, which allows most patients to pay $10 or less per month for

Firdapse®, and committed to distribute the drug for no cost to patients who are unable to get insurance coverage.

49. After announcing his investigation, Senator Sanders also sent a letter to DHHS Secretary Azar and then-Commissioner Scott Gottlieb asking FDA "not [to] take enforcement action against pharmacies and manufacturers who were previously providing 3,4-DAP [the chemical name of amifampridine] to patients and are able to resume the distribution of this drug." February 26, 2019 Letter from Sanders to Azar and Gottlieb. In other words, Senator Sanders urged FDA to ignore Congress's mandated exclusivities for Firdapse®.

E. FDA Approves Ruzurgi for Treatment of LEMS

50. On May 6, 2019, in a letter to Jacobus regarding Ruzurgi, FDA recognized that Catalyst's "orphan exclusivity" prohibited Ruzurgi from being "finally approved for marketing" for the adult patient population—the only population upon which safety and efficacy clinical studies have been performed. Tentative Approval Letter from FDA to Jacobus (May 6, 2019). Catalyst's "orphan exclusivity" prohibited Ruzurgi's approval because Firdapse® is the same drug as Ruzurgi. *See id.* While tentative approval letters are not uncommon when an NDA applicant is awaiting expiration of another NDA holder's exclusivity, Plaintiff is aware of no precedent for issuing such letters in the specific context presented here, where FDA is effectively using Catalyst's ODE to facilitate off-label sales. In releasing Jacobus' tentative approval at the same time as the pediatric indication approval letter, FDA has essentially told the public that the Agency would have approved Ruzurgi as safe and effective in adults but for Catalyst's exclusivity—again in effect signaling that Ruzurgi can be used in the patient population for which Catalyst has exclusivity.

51. On the very same day that FDA recognized Catalyst's ODE for Firdpase® for the treatment of LEMS, however, FDA approved Ruzurgi for the treatment of LEMS in patients 6 to less than 17 years of age. *See* May 6, 2019 Approval Letter from FDA to Jacobus (Ruzurgi Approval Letter); *see also* Ruzurgi Labeling at 1 (Ruzurgi is "indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age."). FDA also informed Catalyst on May 6 that Jacobus's NDA was allegedly submitted as a stand-alone 505(b)(1) application, meaning it allegedly was approved without reference to any of Catalyst's clinical studies and so did not implicate Catalyst's NCEE.[4] Upon information and belief, Jacobus lacked and therefore could not submit to FDA sufficient clinical and non-clinical study data to appropriately be considered a (b)(1) applicant.

52. Under 21 U.S.C. § 355(b) and 21 C.F.R. § 201.57, Jacobus was required to submit "a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits." The Clinical Studies section of the Ruzurgi labeling states that Ruzurgi's efficacy "for the treatment of LEMS was established by Study 1, a randomized, double-blind, placebo-controlled, withdrawal study" and that "patients who were randomized to placebo perceived a worsening of weakness compared to those who remained on RUZURGI." *See* Ruzurgi Labeling at 11. Study 1 did not include any pediatric patients.

[4] For the purposes of NCEE, Firdapse®, with the active ingredient amifampridine phosphate, and Ruzurgi, with the active ingredient amifampridine, are chemically identical. *See, e.g.*, Shieh, et al. at 112 ("Amifampridine phosphate (Firdapse®) is the name of the nonproprietary salt form of the active ingredient for 3,4 DAP [diaminopyridine]."). FDA's definition of active moiety specifies that a salt form of a molecule is the same active moiety as the molecule itself. *See* 21 C.F.R. § 314.3(b) ("Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.").

53. The Use in Specific Populations section, which discusses the use of Ruzurgi in different subsets of patients, states, with respect to the pediatric patient subpopulation, that the safety and efficacy of Ruzurgi "have been established in patients 6 to less than 17 years of age." *See id*. at 6. Jacobus, however, did not submit any data from clinical studies in which pediatric patients participated. In fact, the patients who participated in the single clinical study upon which Jacobus relied were between the ages of 23 and 83 years (just like Catalyst's two Phase 3 trials). *See id*. at 11. Yet the Ruzurgi labeling states that the safety and efficacy of the drug in the **pediatric** subpopulation "is supported by evidence from adequate and well-controlled studies of RUZURGI in **adults** with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and safety data from pediatric patients 6 to less than 17 years of age." *See id*. at 6 (emphasis added). To make this even clearer, the Ruzurgi labeling, as approved by FDA, indicates that FDA feels Ruzurgi is safe and effective in children with LEMS because it is safe and effective in adults with LEMS.

54. On information and belief, FDA has never approved ODE for a pediatric orphan drug subpopulation when the same applicant was barred by ODE from marketing to adult patients for the same disease. FDA precedents indicate that FDA has only done so previously where an exception to ODE existed—either due to waiver pursuant to 21 U.S.C. § 360cc(b), or pursuant to a finding of clinical superiority, *id.* § 360cc(c). *Cf.* Humira Supplement Approval Letter (June 30, 2016) (ODE approval for treatment of certain disease in adults); Humira Supplement Approval Letter (Sept. 28, 2018) (ODE approval for *same sponsor* for treatment of same disease in pediatrics); Bob Pollock, *Raptor's Procysbi Receives 7 Year Orphan Drug Exclusivity*, LACHMAN CONSULTANTS (June 27, 2013) (discussing drug that received ODE for pediatrics because deemed "clinically superior to the original product"). In other contexts, FDA will not approve an "orphan

subset" solely for pediatric patients without (1) a finding that the drug cannot be utilized for adults, and (2) specific pediatric clinical studies. *See* Office of Orphan Prods. Dev., FDA, *Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases; FDA Guidance for Industry* at 2 & n.3 (July 2018). Here, FDA approved a pediatric subpopulation based solely on efficacy in adults, without any efficacy data in pediatric patients and no safety data from clinical trials for pediatric patients.

55. In the Ruzurgi Approval Letter, FDA listed the post-approval activities that Jacobus is required to conduct. Whereas Catalyst is required to complete only three relatively common post-approval activities, as noted above, Jacobus is required to complete **ten** post-approval activities, including a pre- and postnatal development animal study; an animal fertility study; two animal embryofetal development studies; two animal carcinogenicity studies; a clinical trial evaluating the effect of Ruzurgi on the kidneys; and, notably, a "*juvenile animal toxicology study* of amifampridine in rat." *See* Ruzurgi Approval Letter at 3-6 (emphasis added). On information and belief, FDA required Catalyst to submit much of this data as part of its NDA **before** FDA would even accept and review the NDA for Firdapse®—much less approve it, while Jacobus is being allowed to submit its own corresponding data **after** receiving approval for its drug.

56. On the day that FDA approved Ruzurgi, an individual who has been identified as a Jacobus paid consultant, stated that Ruzurgi is a "workaround" because "it can be prescribed for adults." Scott Bloomer, *FDA Added Unexpected Twist to Dampen Controversy over a Drug That Costs $375,000*, MYHEALTHYCLICK (May 7, 2019), https://www.myhealthyclick.com/fda-added-unexpected-twist-to-dampen-controversy-over-a-drug-that-costs-375000 (quoting Dr. Donald Sanders). That individual has continued to encourage the off-label use of Ruzurgi; as recently as

June 10, 2019, he reportedly stated that "there would be nothing unusual about prescribing the Jacobus drug for adults." Ed Silverman, *Jacobus prices its rare disease drug at half of what Catalyst charges, but will doctors prescribe it?*, STAT NEWS (June 10, 2019).

57. Senator Bernie Sanders similarly praised FDA's approval of Ruzurgi, explaining that it was a "blow to the greed of Big Pharma" and a "victory for patients with LEMS." Press Release, Sen. Bernie Sanders, *Sanders Statement on FDA Approval of Drug to Treat Pediatric LEMS* (May 8, 2019), https://www.sanders.senate.gov/newsroom/press-releases/sanders-statement-on-fda-approval-of-drug-to-treat-pediatric-lems. Senator Sanders's comments make it clear that he expects the Ruzurgi approval to significantly harm the financial recovery that should be arising from Catalyst's ODE exclusivity.

58. According to Jacobus, Ruzurgi is being priced between approximately $175,200[5] per year. *See* Natalie Grover, *UPDATED: With a substantial discount to Catalyst's Firdapse, is Jacobus poised to win physician, payer support for off-label adult LEMS use?*, ENDPOINTS NEWS (June 11, 2019). As such, allowing Jacobus to market their product in violation of Catalyst's exclusivities will cause irreparable harm to Catalyst for which there is no adequate remedy.

59. On information and belief, FDA has communicated directly to adult LEMS patients that Rugurzi may be a safe and effective alternative to Firdapse® and that patients should consult their physicians regarding their treatment options.

[5] Based on an average dose of 60 mg.

CLAIM I: VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT AGENCY ACTION THAT IS ARBITRARY AND CAPRICIOUS AND NOT IN ACCORDANCE WITH LAW
Violation of 5 U.S.C. § 706(2)(A); 21 U.S.C. § 355(d)

60. Catalyst incorporates and realleges Paragraphs 1 through 59 above as if fully set forth herein.

61. The Administrative Procedure Act prohibits Defendants from acting in any way that is arbitrary and capricious or an abuse of discretion, or that is not in accordance with law.

62. The FDCA provides that FDA may not approve a drug whose labeling is "false or misleading in any particular." 21 U.S.C. § 355(d).

63. FDA has provided by regulation that labeling is false or misleading if it implies or suggests any use not approved by FDA. 21 C.F.R. §§ 201.57(c)(2)(iv) and (15)(i).

64. Although FDA has approved Ruzurgi for pediatric use only, it approved labeling for Ruzurgi that plainly implies and suggests that it may be used for adults.

65. FDA's simultaneous publication of a tentative approval for Ruzurgi for adults with LEMS was a way for FDA to encourage and facilitate off-label marketing and use.

66. Among other statements, Ruzurgi's labeling provides that its safety and effectiveness has "been established" in the pediatric subpopulation, in part, from "evidence from adequate and well-controlled studies of RUZURGI in **adults** with LEMS."

67. For the foregoing reasons, FDA's approval of Ruzurgi is arbitrary, capricious, an abuse of discretion, and/or not in accordance with law.

CLAIM II: VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT AGENCY ACTION NOT IN ACCORDANCE WITH LAW
Violation of 5 U.S.C. § 706; 21 U.S.C. § 360cc

68. Catalyst incorporates and realleges Paragraphs 1 through 59 above as if set forth in full herein.

69. The Administrative Procedure Act prohibits Defendants from acting in any way that is not in accordance with law.

70. The Orphan Drug Act prohibits FDA from approving any "same drug for the same disease or condition" within seven years of the approval of an orphan drug. 21 U.S.C. § 360cc(a).

71. FDA designated Catalyst's amifampridine drug—Firdapse®—as an "orphan drug" for the treatment of LEMS on November 12, 2009.

72. FDA approved Firdapse® for treatment of LEMS on November 28, 2018, and confirmed on December 21, 2018, that Firdapse® was entitled to seven year ODE under the Orphan Drug Act.

73. On May 6, 2019, in disregard of Firdapse®'s ODE, FDA approved the "same drug"—Ruzurgi—for the "same disease or condition"—LEMS.

74. To the extent FDA may argue that its regulations permit the Agency to approve Ruzurgi notwithstanding Firdapse®'s ODE, those regulations are inconsistent with the Orphan Drug Act and cannot apply here.

75. For the foregoing reasons, FDA's approval of Ruzurgi is not in accordance with law.

CLAIM III: VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT AGENCY ACTION THAT IS ARBITRARY AND CAPRICIOUS AND NOT IN ACCORDANCE WITH LAW

Violation of 5 U.S.C. § 706; 21 U.S.C. § 355

76. Catalyst incorporates and realleges Paragraphs 1 through 59 above as if set forth in full herein.

77. The Administrative Procedure Act prohibits Defendants from acting in any way that is arbitrary and capricious or an abuse of discretion, or that is not in accordance with law.

78. The FDCA provides if a drug product that contains a new chemical entity is approved in an NDA under section 505(b), 21 U.S.C. § 355(b), then FDA may not approve an NDA under section 505(b)(2) for a drug product with the same active moiety as the new chemical entity for a period of five years from approval of the first approved NDA. *See* 21 U.S.C. § 355(c)(3)(E)(ii); 21 C.F.R. § 314.108(b)(2).

79. By definition, an NDA submitted under section 505(b)(2) of the FDCA, 21 U.S.C. § 355(b)(2), relies upon investigations conducted by someone other than the applicant, and for which the applicant has not obtained a right of reference or use.

80. FDA approved Firdapse®, which contains the new chemical entity amifampridine phosphate, under section 505(b) of the FDCA, 21 U.S.C. § 355(b), on November 28, 2018.

81. FDA has recognized in its Orange Book that Catalyst has NCEE for amifampridine phosphate, which will expire on November 28, 2023.

82. FDA nevertheless approved Ruzurgi, which contains the same active moiety as Firdapse®, on May 6, 2019.

83. On information and belief, Ruzurgi was improperly approved under section 505(b)(1) of the FDCA instead of section 505(b)(2) even though Jacobus's application relied, directly or by implication, upon studies conducted and data collected and submitted by Catalyst for the Firdapse® approval without a right of reference or use to rely upon those studies and data. In essence, because FDA concluded that Firdapse® was safe and effective, it knew Ruzurgi was as well. But had Ruzurgi been adjudicated under the correct pathway, it would be blocked by Firdapse®'s NCEE.

84. For the foregoing reasons, FDA's approval of Ruzurgi is arbitrary, capricious, an abuse of discretion, and/or not in accordance with law.

CLAIM IV: VIOLATION OF THE ADMINISTRATIVE PROCEDURE ACT AGENCY ACTION THAT IS ARBITRARY AND CAPRICIOUS AND NOT IN ACCORDANCE WITH LAW
Violation of 5 U.S.C. § 706

85. Catalyst incorporates and realleges Paragraphs 1 through 59 above as if set forth in full herein.

86. The Administrative Procedure Act prohibits Defendants from acting in any way that is arbitrary and capricious or an abuse of discretion, including by according "disparate treatment [to] similarly situated" regulatees. *See Mahon v. U.S. Dep't of Agric.*, 485 F.3d 1247, 1260 (11th Cir. 2007).

87. Catalyst and Jacobus are similarly situated with regard to their applications for Firdapse® and Ruzurgi, because both drugs contain the same active moiety and are intended to treat the same disease or condition.

88. On information and belief, however, FDA arbitrarily treated Catalyst differently than Jacobus. For example, FDA allowed Jacobus to submit studies and clinical trials ***post-approval*** that it required Catalyst to submit before FDA would even consider an NDA submitted by Catalyst for Firdapse®. Specifically, Catalyst was required to submit the results of an animal toxicology study and a clinical trial to evaluate the effect of Firdapse® on kidneys before Firdapse® was reviewed, while FDA permitted Jacobus to conduct a juvenile animal toxicology study and a clinical trial to evaluate the effect of Ruzurgi on kidneys after the Agency approved Ruzurgi. FDA also accelerated the time for Jacobus to submit its NDA by not requiring the same testing data it required before even reviewing Plaintiff's NDA—much less approving it.

89. For the foregoing reasons, FDA's approval of Ruzurgi is arbitrary, capricious, an abuse of discretion, and/or not in accordance with law.

REQUEST FOR RELIEF

Catalyst respectfully requests that the Court enter judgment in its favor and grant the following relief:

1. A declaration pursuant to 28 U.S.C. § 2201 that:
   a. Defendants' approval of Ruzurgi is arbitrary, capricious, an abuse of discretion, and/or not in accordance with law because its labeling is false or misleading;
   b. Defendants' approval of Ruzurgi violates Plaintiff's ODE because Ruzurgi is the same drug as Firdapse® and is approved to treat the same disease or condition as Firdapse®;
   c. Defendants' approval of Ruzurgi violates Plaintiff's NCEE because Ruzurgi was approved directly or by implication in reliance on investigations conducted by Catalyst for Firdapse®'s approval; and
   d. Defendants' approval of Ruzurgi is arbitrary, capricious, an abuse of discretion, and/or not in accordance with law because it was held to a lower approval standard than the similarly situated Firdapse®.
2. An order vacating Defendants' approval of Ruzurgi.
3. An order enjoining FDA from approving any amifampridine drug for treatment of LEMS until the expiration of Catalyst's ODE on November 28, 2025.
4. An order enjoining FDA from approving any amifampridine drug that relies on Catalyst's investigations, either directly or by implication, without a right of reference or use from Catalyst until the expiration of Catalyst's NCEE on November 28, 2023.

5. An order awarding Catalyst its costs and attorneys' fees pursuant to 28 U.S.C. § 2412.

6. Such other and further relief as the Court deems just and proper.

Dated: June 12, 2019

Respectfully submitted,

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**Pro Hac Vice* to be filed