



Office of Orphan Products Development
Food and Drug Administration
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1501 K Street, N.W.
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Attention: Sean C. Griffin and Kwaku A. Akowuah

Re: Determination that Xywav's (NDA 212690) unexpired orphan-drug exclusivity ("ODE") does not block approval of Lumryz (NDA 214755)

Dear Mr. Griffin and Mr. Akowuah:

We have considered the submissions described in greater detail herein from Jazz Pharmaceuticals, Inc. ("Jazz") and Sidley Austin LLP ("Sidley") as counsel to Jazz. FDA's Office of Orphan Products Development ("OOPD" or "we") provides the response below.

I. Introduction

Herein, this analysis evaluates whether the ODE for Xywav (calcium, magnesium, potassium, and sodium oxybates) blocks the approval of NDA 214755 for Lumryz (sodium oxybate) for extended-release oral suspension submitted by Avadel CNS Pharmaceuticals, LLC ("Avadel") for the treatment of cataplexy or excessive daytime sleepiness ("EDS") in adults with narcolepsy. Xywav became eligible for ODE for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy because its sponsor, Jazz, demonstrated at the time of approval that Xywav was clinically superior to Xyrem, which was previously approved for the same indication. Under section 527(a) of the Federal Food, Drug, & Cosmetic Act ("FD&C Act"), the ODE for Xywav prevents FDA from approving a new drug product that is the "same drug" as Xywav for the same use or indication until its exclusivity expires on July 21, 2027.¹ By regulation, a drug is the "same drug" as Xywav if it contains the same active moiety (oxybate)

¹ Section 527(a) of the FD&C Act; *see also* 21 CFR § 316.31. *See also* FDA, Clarification of Orphan-Drug Exclusivity Following *Catalyst Pharms., Inc. v. Becerra*, 88 Fed. Reg. 4086 (Jan. 24, 2023).

for the same use or indication (the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy)² unless the new drug product is clinically superior to Xywav.³ For the reasons described below, we conclude that Lumryz is clinically superior to Xywav and is thus not considered to be the “same drug” as Xywav within the meaning of 21 CFR § 316.3(b)(14) and section 527(a) of the FD&C Act. Therefore, Xywav’s ODE does not block approval of NDA 214755 for Lumryz for the treatment of cataplexy or EDS in adults with narcolepsy.

We also conclude that Lumryz is eligible for its own term of ODE because it is clinically superior to both Xywav and Xyrem. Under section 527(c)(1) of the FD&C Act, if FDA has previously approved a drug that is otherwise the same drug for the same use or indication, the subsequent drug may be eligible for its own term of ODE if the sponsor demonstrates that its product is clinically superior to every such previously approved drug.⁴ As set forth below, we have determined that Avadel has demonstrated Lumryz’s clinical superiority to every previously approved oxybate drug for the same use or indication, i.e., both Xywav and Xyrem. Therefore, Lumryz is eligible for its own term of ODE for the treatment of cataplexy or EDS in adults with narcolepsy.

OOPD consulted with agency sleep experts and the Division of Neurology 1 (“DN1”) in making this determination,⁵ and their scientific thinking and expert opinions have been integral to this decision. As discussed below, FDA’s determination is based on careful consideration of the relevant scientific, legal, and regulatory issues raised and the materials submitted by outside parties. On December 15, 2020, Avadel submitted to OOPD and to the file for NDA 214755 an “exclusivity claim.”⁶ On July 14, 2021, Avadel submitted to OOPD and to the file for NDA 214755 a supplement to its “exclusivity claim.”⁷ On July 21, 2021, Avadel sent a letter to OOPD and to FDA’s Office of Chief Counsel (“OCC”) presenting arguments why Lumryz’s NDA should be eligible for approval notwithstanding Xywav’s ODE.⁸ On October 25, 2021, Latham & Watkins LLP as counsel to Avadel sent OCC a letter presenting arguments about the approvability of Lumryz’s NDA.⁹ On August 30, 2022, Avadel sent a letter to OOPD with additional arguments about clinical superiority.¹⁰

² The indication for Lumryz is “the treatment of cataplexy or EDS in adults with narcolepsy,” which is not co-extensive with, but falls entirely within, the scope of Xywav’s ODE because Xywav’s ODE includes a broader age range.

³ 21 CFR § 316.3(b)(14).

⁴ Section 527(c)(1) of the FD&C Act; *see also* 21 CFR § 316.34(c).

⁵ *See* Mahadevappa Hunasikatti MD FCCP and Nargues Weir MD FCCP FAASM ATSF, *Consult request on Lumryz* (Apr. 29, 2023) [hereinafter Sleep Expert Consult]; DN1, *Office of Orphan Products Development Consult Request #16-5302* at (May 1, 2023) [hereinafter DN1 Lumryz Consult].

⁶ Avadel, *Exclusivity Claim* (Dec. 15, 2020).

⁷ Avadel, *Exclusivity Claim – Supplemental Information in Demonstration of Clinical Superiority of FT218* (Jul. 14, 2021).

⁸ Letter from Jerad G. Seurer to Nicole Wolanski and Mark Raza, *Approval and Orphan Drug Exclusivity for FT218 (sodium oxybate for extended-release oral suspension)* (Jul. 21, 2021).

⁹ Letter from John R. Manthei to Elizabeth Dickinson, *Lumryz (sodium oxybate) for extended-release oral suspension (NDA 214755)* (Oct. 25, 2021).

¹⁰ Letter from Jennifer Gudeman to Sandra Retzky, *Orphan Drug Considerations for LUMRYZ (sodium oxybate) for Extended-Release Oral Suspension – DRU 2016-5302* (Aug. 30, 2022).

In addition to the submissions OOPD received from Avadel and its counsel, OOPD received submissions from Jazz. On September 16, 2021, Jazz sent a letter to OOPD presenting arguments why Lumryz is not clinically superior to Xywav (“Jazz’s September 2021 Letter”).¹¹ On December 6, 2022, Sidley as counsel to Jazz sent OCC a letter presenting arguments why Lumryz is not clinically superior to Xywav (“Sidley Letter”) and requested a meeting with OCC.¹² On January 18, 2023, FDA met with Sidley during which Sidley presented a slide deck (“Sidley Slides”).¹³ In this analysis, the arguments presented in Jazz’s September 2021 Letter, the Sidley Letter, and the Sidley Slides are collectively referred to as Jazz’s arguments.¹⁴

II. Legal Background

A. Orphan-Drug Designation (“ODD”)

Congress enacted the Orphan Drug Act in 1983 to provide incentives for the development of drugs for rare diseases or conditions that would not otherwise be developed due to the small patient population and lack of profitability of such drugs.¹⁵ Section 526 of the FD&C Act defines a “rare disease or condition,” in relevant part, as any disease or condition that affects less than 200,000 persons in the United States.¹⁶ To be eligible for ODD incentives — including tax credits for qualified clinical testing, exemption from the application user fee, and, potentially, ODE — the sponsor of a drug must request ODD for a rare disease or condition under section 526 of the FD&C Act, and FDA must grant ODD.¹⁷ FDA’s regulations at 21 CFR Part 316 lay out the requirements for an ODD submission.¹⁸ A sponsor of a drug that is “otherwise the same as an already approved drug may seek and obtain ODD for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.”¹⁹

¹¹ Letter from Dennis Ahern to Sandra Retzky, *Considerations Regarding Clinical Superiority for Oxybate Products* (Sep 16, 2021) [hereinafter Jazz’s September 2021 Letter].

¹² Letter from Sean C. Griffin to Shoshana Hutchinson, *Orphan Drug Exclusivity for NDA 212690* (Dec. 6, 2022) [hereinafter Sidley Letter].

¹³ See Sidley, Presentation to the Office of Chief Counsel of behalf of Jazz Pharmaceuticals, Inc. (Jan. 18, 2023) [hereinafter Sidley Slides]. This meeting was listening only for FDA.

¹⁴ We also note that on November 29, 2022, TREND Community, a patient advocacy organization, sent a letter to OOPD presenting arguments and patient testimonials why there is a need for a once-nightly oxybate therapy. Letter from Maria Picone to FDA (Nov. 29, 2022). Then on January 2, 2023, Clete A. Kushida, M.D., Ph.D. sent a letter to OOPD to present arguments that Lumryz is clinically superior to the existing oxybate therapies, Xyrem and Xywav. Letter from Clete A. Kushida to Sandra Retzky (Jan. 3, 2023). These letters did not serve as a basis for FDA’s decision.

¹⁵ Pub. L. No. 97-414, 96 Stat. 2049 (1983).

¹⁶ See section 526(a)(2)(A) of the FD&C Act.

¹⁷ See section 526(a)(1) of the FD&C Act. A sponsor must request ODD prior to submitting a marketing application for the drug for the relevant disease.

¹⁸ See, e.g., 21 CFR §§ 316.20-21.

¹⁹ 21 CFR § 316.20(a).

B. ODE

One important incentive Congress provided in the Orphan Drug Act for sponsors developing drugs for rare diseases is the potential for a drug to become eligible for ODE. Section 527(a) states, in relevant part:

Except as provided in subsection (b), if the Secretary-

(1) approves an application filed pursuant to section 505, or

(2) issues a license under section 351 of the Public Health Service Act

for a drug designated under section 526 for a rare disease or condition, the Secretary may not approve another application . . . or issue another license . . . for the same drug for the same disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license. . . .

In short, ODE prevents FDA from approving or licensing the same drug for the same use or indication for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of approval or licensure.²⁰

The statute provides two exceptions to ODE at section 527(b), under which FDA may approve an application for the same drug as a drug with ODE for the same use or indication. First, FDA may approve such an application if the agency finds that the sponsor of the drug with ODE cannot “ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition.”²¹ Second, FDA may also approve such an application if the sponsor of the drug with ODE consents to the approval of the application.²²

As explained below, FDA interprets section 527(a) in two contexts: 1) to determine whether a drug is eligible for ODE and 2) to determine whether certain pending drugs may be approved during an approved drug’s unexpired ODE (i.e., the scope of ODE).

i. Eligibility for ODE

An orphan-designated drug becomes eligible for ODE under section 527(a) of the FD&C Act once FDA approves or licenses it for the designated rare disease or condition, subject to the additional condition of clinical superiority in section 527(c) of the FD&C Act, when applicable. Section 527(c)(1) states:

If a sponsor of a drug that is designated under section 526 and is otherwise the same, as determined by the Secretary, as an already approved or licensed drug is seeking exclusive approval or exclusive licensure described in subsection (a) for the same rare disease or condition as the already approved drug, the Secretary shall require such sponsor, as a

²⁰ See section 527(a) of the FD&C Act; *see also, e.g.*, 21 CFR §§ 316.31, 316.34, 316.3(b)(14).

²¹ Section 527(b)(1) of the FD&C Act.

²² Section 527(b)(2) of the FD&C Act.

condition of such exclusive approval or licensure, to demonstrate that such drug is clinically superior to any already approved or licensed drug that is the same drug.

When applicable, FDA requires the sponsor of a subsequent drug to demonstrate clinical superiority to all (i.e., each and every) previously approved drugs with the same active moiety for the same indication or use to be eligible for its own term of ODE.²³

Section 527(c)(2) of the FD&C Act defines “clinically superior” for the purposes of meeting the condition of clinical superiority in section 527(c)(1) to mean “the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care.”²⁴ The orphan-drug regulations at 21 CFR § 316.3(b)(3) define “clinically superior” as follows:

Clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:

- (i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or
- (ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or
- (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.²⁵

Section 527(c) of the FD&C Act was enacted by Congress under the FDA Reauthorization Act of 2017 (“FDARA”), and the applicability of the section was clarified in the Consolidated Appropriations Act, 2021 (2020). Prior to FDARA, FDA had relied upon its regulations to require a drug that is otherwise the same drug as a previously approved drug for the same use or indication to demonstrate clinical superiority to the previously approved drug for it to be eligible for ODE. *See, e.g.*, 21 CFR § 316.34(c) stating that “If a drug is otherwise the same drug as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug.” *See also* 21 CFR § 316.3(b)(3) & § 316.3(b)(14). In

²³ 21 CFR § 316.3(b)(14) defines “same drug” to mean, in relevant part, “a drug that contains the same active moiety as a previously approved drug and is intended for the same use . . . except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.” Further discussion of this definition appears in the subsequent subsection.

²⁴ Section 527(c)(2) of the FD&C Act.

²⁵ 21 CFR § 316.3(b)(3).

response to court losses on the specific issue of whether FDA could impose such a clinical superiority requirement as a precondition for eligibility for ODE, Congress amended the statute to give the agency explicit statutory authority to do so.

Section 527(c)(1) states that if a sponsor “is seeking exclusive approval or exclusive licensure described in subsection (a)” for an otherwise same drug that has already been approved or licensed for the same disease or condition, “as a condition of such exclusive approval or licensure,” the sponsor must demonstrate “that such drug is clinically superior to any already approved or licensed drug that is the same drug.” As the text demonstrates, section 527(c) only concerns potential eligibility of a subsequent drug for its own period of ODE and does not address whether a subsequent drug’s approval is blocked by another drug’s ODE even where clinical superiority of the subsequent drug has been shown. As described further below, the blocking effect of ODE of a previously approved drug is instead described in 527(a) of the FD&C Act.

ii. Scope of ODE

As explained above, under section 527(a) of the FD&C Act, ODE prevents FDA from approving or licensing the same drug for the same use or indication for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of approval or licensure. FDA looks to the definition of “same drug” at 21 CFR § 316.3(b)(14) in determining whether a subsequent drug is the same drug for the same indication or use as a previously approved drug with unexpired ODE. That regulation defines “same drug” to mean, in relevant part, “a drug that contains the same active moiety as a previously approved drug and is intended for the same use . . . except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.”²⁶ Thus, under FDA’s validly promulgated and longstanding regulations, the “same drug” definition has a chemical and clinical component. In the 1992 Final Rule for the orphan-drug regulations, FDA explained that “two drugs would be considered the same drug if the principal, but not necessarily all, structural features of the two drugs were the same, unless the subsequent drug were shown to be clinically superior” and that “either differences in active moiety or clinical superiority will be sufficient to make two micromolecular drugs different.”²⁷ Accordingly, if the sponsor of the subsequent drug for the same indication or use can demonstrate that its drug has a different active moiety²⁸ or is clinically superior²⁹ to the drug with ODE (i.e., the “first drug”), the subsequent drug will not be considered to be the “same drug” as the drug with ODE, and that drug’s ODE will not block approval of the application for the subsequent drug for the same indication or use.³⁰

Interpreting section 527(a) of the FD&C Act in this manner does not create an exception to ODE analogous to those codified at section 527(b) of the FD&C Act that were discussed above; the

²⁶ 21 CFR § 316.3(b)(14).

²⁷ See FDA, *Orphan Drug Regulations, Final Rule*, 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) [hereinafter 1992 Final Rule].

²⁸ See 21 CFR § 316.3(b)(2) for orphan-drug definition of “active moiety.”

²⁹ See 21 CFR § 316.3(b)(3) defining “clinically superior.”

³⁰ 1992 Final Rule, 57 Fed. Reg. at 62078 (“Assuming that a subsequent drug’s marketing application is otherwise approvable, FDA will not interpret the Orphan Drug Act to block approval of any drug proved to be clinically superior to a drug with currently effective exclusive marketing rights.”).

exceptions at 527(b) concern instances where FDA determines that a drug is the same drug for the same indication or use but is approvable nonetheless despite another same drug's unexpired ODE. Drugs that are approved under the exceptions at section 527(b) would be chemically and clinically the same as the drug with unexpired ODE and would not include clinically superior drugs.

In summary, for a determination under section 527(a) as to whether a drug's unexpired ODE blocks approval of a subsequent drug, FDA compares the subsequent drug to the drug with unexpired ODE. In circumstances in which the subsequent drug contains the same active moiety for the same indication or use as the drug with unexpired ODE, FDA determines whether the subsequent drug is clinically superior to the drug with ODE. If it is clinically superior, the subsequent drug is not considered to be the "same drug," and thus its approval for the same indication or use is not blocked. By contrast, for a determination under section 527(c) of the FD&C Act as to whether a subsequent drug with the same active moiety for the same indication or use as a previously approved drug is eligible under section 527(a) for its own term of ODE, FDA compares the subsequent drug to all such previously approved drugs, even if ODE for those drugs has expired. If the subsequent drug is clinically superior to each, then it is eligible for its own term of ODE.

C. Clinical Superiority

As explained above, section 527(c)(2) of the FD&C Act defines clinically superior to mean that "the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, *or* by providing a [MCTPC]," and 21 CFR § 316.3(b)(3) defines clinically superior to mean that "a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in *one or more* of the following ways:" greater effectiveness, greater safety, or a MCTPC (emphasis added). In both definitions, the subsequent drug must provide a significant therapeutic advantage "over and above" an already approved drug in just one way—greater efficacy, greater safety, *or* by providing a MCTPC—to be considered clinically superior. Neither the plain reading of the statute nor that of the regulation imposes an additional requirement that in order to provide a significant therapeutic advantage in one of the three measures, the drug must also be at least comparable in the other two measures.

There is at least one instance in which FDA determined that a subsequent drug is clinically superior based on greater efficacy even though the drug was less safe in one measure than the previously approved drug with ODE. Specifically, FDA considered whether different interferon beta products for relapsing remitting multiple sclerosis ("RRMS") were clinically superior to one another. This situation involved three interferon beta products for the same use. The first interferon beta for treatment of RRMS, Betaseron, was approved on July 23, 1993, and was eligible for ODE until July 23, 2000. During Betaseron's period of ODE, a different sponsor, Biogen, sought marketing approval for another interferon beta product for RRMS called Avonex. FDA determined that Biogen demonstrated that Avonex was clinically superior to Betaseron because Avonex was safer due to elimination of skin necrosis at injection sites.³¹ As a result,

³¹ FDA, *Memorandum, Clinical Superiority of Biogen's interferon product, Avonex*, DRU-1991-627 (Apr. 16, 1996).

Avonex was a different drug than Betaseron under the orphan-drug regulations, and Betaseron's ODE did not block its approval. On May 17, 1996, FDA approved Avonex for RRMS, and it was eligible for its own term of ODE until May 17, 2003. Subsequently, during Avonex's period of ODE, a third sponsor, Serono, sought approval for an interferon beta product for RRMS called Rebif. Serono demonstrated that Rebif was more effective than Avonex based on a study showing that patients taking Rebif were less likely to experience multiple sclerosis exacerbations than patients taking Avonex.³² However, Rebif patients experienced skin necrosis at injection sites that Avonex patients did not (i.e., the same adverse event that was present with Betaseron that led to the determination that Avonex was clinically superior to Betaseron based on safety).³³

FDA concluded that Rebif was clinically superior to Avonex based on greater effectiveness, and that the safety considerations of Rebif compared to Avonex were "not directly relevant" to the clinical superiority determination.³⁴ In making its decision, FDA explained the following:

[T]he regulations do not state that clinical superiority must be based on overall risk benefit being deemed superior for the subsequent product compared to the prior product. In fact, the regulations indicate that only a selected aspect may constitute a sufficient basis to reach a conclusion of clinical superiority. That is, the aspects not selected by the sponsor for focus (e.g., safety when efficacy is selected; efficacy when safety is selected) do not require a comparative assessment. The regulations require neither that all aspects of known efficacy nor all aspects of safety be shown to be superior. Nor do the regulations indicate that other aspects of safety or efficacy be shown "comparable" when only one specific aspect of safety or efficacy is shown to be superior.³⁵

FDA also stated:

There is no additional requirement that the subsequent product, although clinically superior in one parameter, must also be shown to be at least equal in all others. This would set an inappropriate and nearly impossible burden (in terms of clinical trial design) on the sponsor of a second product. A more meaningful standard is a significant therapeutic benefit in terms of increased effectiveness and adequate safety, or increased safety and adequate effectiveness. The balancing of risks and benefits embodied in a drug product as a whole is done when the agency determines whether the drug may be approved for the particular use.³⁶

D. MCTPC

³² See FDA, *BLA STN 103780/0 Comparative Study of Rebif to Avonex and Orphan Exclusivity* at 20 (Mar. 7, 2002) [hereinafter CBER Rebif memo].

³³ *Id.*

³⁴ *Id.*

³⁵ *Id.* at 3-4. See also *id.* at 10-11 ("Orphan drug regulations do not state that all known clinical actions of a product must be shown superior to the competitor."); *id.* at 20 ("[T]he orphan drug regulations do not require that safety be superior or even identical between two drugs when a clinical efficacy comparison is employed for the demonstration of being not the 'same drug.'").

³⁶ FDA, *Memorandum, OOPD Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif* at 3 (Mar. 7, 2002) [hereinafter OOPD Rebif memo].

Because of the diverse ways in which drugs may qualify as clinically superior (and therefore not the “same drug”) under the law, FDA evaluates clinical superiority on a case-by-case basis.³⁷ Specifically, with respect to MCTPC, to preserve the statutory incentive to develop orphan drugs, the agency has stated that MCTPC is “intended to constitute a narrow category.”³⁸ Regarding how to demonstrate a MCTPC, the agency has also stated:

- “There is no way to quantify such superiority in a general way. The amount and kind of superiority needed would vary depending on many factors, including the nature and severity of the disease or condition, the quality of the evidence presented, and diverse other factors.”³⁹
- “The following factors, when applicable to severe or life-threatening diseases, may in appropriate cases be taken into consideration when determining whether a drug makes a major contribution to patient care: convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration.”⁴⁰
- MCTPC “determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product.”⁴¹

Relative effectiveness and safety of the drug may be relevant in assessing whether a drug makes a MCTPC, and a drug must meet FDA’s safety and effectiveness standards to obtain approval, but, as explained above, nothing in the statute or regulation requires comparable effectiveness and safety. In the Rebif example noted above, FDA stated with respect to MCTPC:

This analysis may involve multiple aspects of the drug product, since the benefit to the patient is likely to be greater convenience or less discomfort, and the very term “major contribution to patient care” implies a more global assessment. So, for example, an assessment of the safety or effectiveness of the new form of the subsequent product might be considered in determining whether the drug made a major contribution to patient care. However, even in this instance, there can not [sic] be an infinite number of comparison criteria if this provision of the regulation is to be meaningful.⁴²

For example, if the administration of a drug were changed from intravenous (IV) to oral, FDA would consider, if appropriate, whether any adverse events diminished the advantage of the

³⁷ See FDA, *Orphan Drug Regulations, Proposed Rule*, 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991) [hereinafter 1991 Proposed Rule] (“The content of this evidence [needed for a demonstration of clinical superiority] will depend on the nature of the superiority claimed.”); see also 1992 Final Rule, 57 Fed. Reg. at 62079 (stating that a major contribution to patient care “determination will have to be made on a case-by-case basis.”).

³⁸ 1991 Proposed Rule, 56 Fed. Reg. at 3343.

³⁹ 1992 Final Rule, 57 Fed. Reg. at 62078.

⁴⁰ FDA, *Orphan Drug Regulations, Final Rule*, 78 Fed. Reg. 35117, 35125 (Jun. 12, 2013) [hereinafter 2013 Final Rule].

⁴¹ *Id.* at 35124.

⁴² CBER Rebif memo, *supra* note 32, at 3.

change in administration from IV or oral. In that respect, safety concerns could inform the MCTPC analysis, but a safety concern present in a subsequent drug that was not present in the previous drug would not automatically defeat a MCTPC finding. That determination would be made on a case-by-case basis and depend upon the nature of the safety concern weighed against the benefits of the MCTPC.

III. Factual Background

This matter involves three different drug products that contain the same active moiety (oxybate)⁴³ for the treatment of cataplexy or EDS in patients with narcolepsy. Jazz is the current sponsor of Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates). Avadel is the sponsor of Lumryz (sodium oxybate).

A. Normal Sleep and Narcolepsy

The following background concerning normal sleep and narcolepsy is based on OOPD's consultation with two board certified sleep experts in FDA ("Sleep Expert Consult").⁴⁴

Adequate sleep is essential for humans as it physically and psychologically restores bodily functions.⁴⁵ Without adequate sleep, humans function poorly and may die prematurely.⁴⁶ Chronic sleep loss, sometimes called sleep debt, is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health.⁴⁷

Normal sleep architecture is characterized in adults as a progression of 90 to 120 minute sleep cycles starting with non-REM Stage 1 sleep (NREM or N1 sleep), then non-REM Stage 2 (NREM or N2) sleep, then non-REM Stage 3 (NREM or N3) sleep, and ending in Rapid Eye Movement (REM or Stage R) sleep.⁴⁸ Rapid eye movements and dreaming occur during Stage R.⁴⁹ After Stage R, the normal adult has a very brief return to Stage Wake (Stage W), in the transition of going from cycle to cycle, though this awakening is not typically remembered, is normal and does not contribute to sleep fragmentation, sleep loss, or daytime sleepiness.⁵⁰ The

⁴³ The active moiety oxybate may also be referred to as gamma-hydroxybutyrate (GHB).

⁴⁴ Sleep Expert Consult, *supra* note 5. These physicians are boarded in (1) internal medicine; (2) pulmonology; (3) critical care medicine; (4) and sleep. One of the consultants continues to see patients in a sleep clinic. Statements in this subsection of the document are based on statements in this consult.

⁴⁵ Kiran Maski, *Insufficient sleep: Evaluation and management*, UpToDate (May 23, 2022), <https://www.uptodate.com/contents/insufficient-sleep-evaluation-and-management>.

⁴⁶ Chiara Cirelli, *Insufficient sleep: Definition, epidemiology, and adverse outcomes*, UpToDate (Oct 10, 2022), <https://www.uptodate.com/contents/insufficient-sleep-definition-epidemiology-and-adverse-outcomes>.

⁴⁷ *Id.*

⁴⁸ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022), <https://www.uptodate.com/contents/stages-and-architecture-of-normal-sleep>.

⁴⁹ James A. Rowley & M. Safwan Badr, *Chapter 1: Normal Sleep*, in *Essentials of Sleep Medicine* 3, at 5 (M. Safwan Badr & Jennifer L. Martin eds., 2nd ed. 2022).

⁵⁰ Mary A. Carskadon & William C. Dement, *Monitoring and staging human sleep, Chapter 2—Normal Human Sleep: An Overview*, in *Principles and practice of sleep medicine* at 12 (M.H. Kryger et al., eds., 5th ed. 2011); *see also* Rowley, *supra* note 49, at 5 (Fig. 1.2).

normal sleep cyclical pattern typically repeats four to five times per night.⁵¹ Cycling progression through these stages is the basic structural organization of normal sleep and is called “sleep architecture.”⁵²

Each sleep stage has unique features. Stage N1 sleep is light sleep (easily arousable), Stage N2 sleep is intermediate in depth (less light sleep), and Stage N3 is deep sleep, otherwise known as restorative sleep, slow-wave sleep (SWS), or delta sleep.⁵³ Brain activity is low during Stage N3 sleep, and importantly, many recovery functions in the body occur only in this stage of sleep.⁵⁴ Normally, the sleep cycles progress through the night with increasing time in Stage N3 during initial sleep cycles and increasing REM sleep in each later sleep cycle during the night.⁵⁵

Stage N3 sleep has a unique and important role in restoring the mind and body.⁵⁶ With sleep loss or deprivation or interruption, one enters Stage N3 sleep earlier and with increased quantity during the night.⁵⁷ Thus, the body attempts to achieve sleep equilibrium by rapidly restoring this critical stage of sleep.⁵⁸ On polysomnography (PSG)—a diagnostic full sleep study with an electroencephalogram (EEG)—REM sleep is a time of active brain EEG waves and physiological instability characterized by somewhat irregular heart rate and breathing patterns.⁵⁹ REM is associated with paralysis of all muscles except the essential respiratory muscles (e.g., the diaphragm).⁶⁰

When an arousal occurs (e.g., when waking up to take medication during the night after falling asleep), there is a shift in an EEG pattern—one that leads to a longer Stage W with alertness or consciousness, even if not remembered.⁶¹ That duration of time in Stage W is prolonged and will adversely impact a clinical measure called Wake After Sleep Onset (WASO)—a metric of how much wakefulness happens in a night of sleep.⁶² In treating sleep disorders, including narcolepsy, the goal is to maximize the time in sleep and minimize wake time (i.e., minimize WASO).⁶³ Disruption of sleep leads to the inability to enter Stage N3, or disruption of N3, and such individuals will revert back to Stage W and subsequently progress to Stage N1 sleep and so

⁵¹ Kirsch, *supra* note 48.

⁵² Rowley, *supra* note 49, at 5.

⁵³ Carskadon, *supra* note 50, at 11.

⁵⁴ Derk-Jan Dijk, *Regulation and Functional Correlates of Slow Wave Sleep*, Supp. To Vol. 5 No. 2 Journal of Clinical Sleep Medicine, S6, at S6 (2009).

⁵⁵ Carskadon, *supra* note 50, at 11.

⁵⁶ Lixia Chen et al., *The association between sleep architecture, quality of life, and hypertension in patients with obstructive sleep apnea*, 27 Sleep and Breathing 191, at 192 (2023).

⁵⁷ Kirsch, *supra* note 48; *see also* Carskadon, *supra* note 50, at 15.

⁵⁸ *See* Sleep Expert Consult, *supra* note 5, at 4.

⁵⁹ Ye Zhang et al., *Polysomnographic nighttime features of narcolepsy: A systematic review and meta-analysis*, 58 Sleep Medicine Reviews at 1 (2021); *see also* David W. Carley & Sarah S. Farabi, *Physiology of Sleep*, 29 Diabetes Spectr. 5, at 6; *see also* Kirsch, *supra* note 48; *see also* Carskadon, *supra* note 50, at 3-4.

⁶⁰ Rowley, *supra* note 49 at 5.

⁶¹ Kirsch, *supra* note 48; *see also* Pierre Philip et al., *Sleep Fragmentation in Normals: A Model for Sleepiness Associated with Upper Airway Resistance Syndrome*, 17 Sleep 242, at 244-245 (1994).

⁶² Eric Suni, *Wakefulness After Sleep Onset*, Sleep Foundation (updated Jan. 18, 2023), <https://www.sleepfoundation.org/sleep-studies/wakefulness-after-sleep-onset>.

⁶³ *See* Sleep Expert Consult, *supra* note 5, at 5.

forth.⁶⁴ The disruption changes sleep architecture and will increase WASO.⁶⁵ This disruption is something to be avoided in the narcoleptic patient, if possible.⁶⁶

Narcolepsy is a disorder of REM intrusion into wakefulness.⁶⁷ Sudden REM sleep onset during wakefulness causes loss of motor tone (i.e., sleep paralysis) along with a dream like state called cataplexy.⁶⁸ REM intrusion can also occur during sleep, disrupting the normal sleep architecture described above.⁶⁹ Individuals with narcolepsy “generally fall asleep rapidly but can spontaneously awaken several times during the night and have difficulty returning to sleep. This sleep maintenance insomnia seems paradoxical in a disorder characterized by daytime sleepiness, and it may reflect a low threshold to transition from sleep to wakefulness.”⁷⁰ REM intrusion in sleep shifts sleep stages and prevents sleep continuity (also called sleep consolidation), fragments normal sleep architecture, and prevents sufficient deep sleep (i.e., prevents N3 restorative sleep from occurring because the sleep stages keep shifting to lighter sleep).⁷¹ Often Stage N1 increases at the debt of Stage N3 sleep given the increased number of shifts between sleep stages.⁷² This results in daytime sleepiness with the consequences of sleep fragmentation or sleep deprivation (i.e., altered sleep architecture which may affect daytime performance).⁷³

EDS is the most common and chronic symptom of narcolepsy.⁷⁴ Per Scammell: “[t]he sleepiness may be so severe that patients with narcolepsy can rapidly doze off with little warning; these episodes are commonly referred to as ‘sleep attacks.’”⁷⁵ Another symptom of narcolepsy, cataplexy, is an “emotionally-triggered transient muscle weakness” that can cause a patient to collapse.⁷⁶

For narcolepsy, the goals of therapy are “to achieve ‘normal’ alertness during conventional waking hours or to maximize alertness at important times of the day, (e.g., during work, school, or while driving),” and to the extent possible, promote normal sleep at night.⁷⁷ Management of narcolepsy is multimodal and includes non-pharmacologic and pharmacologic treatment.⁷⁸ Non-pharmacologic care, including “sleep hygiene,” is “critical to obtaining adequate, quality sleep

⁶⁴ Richard Berry et al., *The AASM Manual for the Scoring of Sleep and Associated Events, Rules, Terminology and Technical Specifications*, American Academy of Sleep Medicine (AASM) (2020), version 2.6 at 22-33.

⁶⁵ See Sleep Expert Consult, *supra* note 5, at 6.

⁶⁶ *Id.*

⁶⁷ Thomas E Scammell, *Clinical features and diagnosis of narcolepsy in adults*, UpToDate (Jul. 12, 2022), <https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-narcolepsy-in-adults>.

⁶⁸ *Id.*

⁶⁹ Imran Ahmed & Michael Thorpy, *Chapter 15: Narcolepsy and Idiopathic Hypersomnia*, in *Essentials of Sleep Medicine* 327, at 328 (M. Safwan Badr & Jennifer L. Martin eds., 2nd ed. 2022).

⁷⁰ Scammell, *Clinical*, *supra* note 67.

⁷¹ Michelle T. Cao & Christian Guilleminault, *Chapter 90: Narcolepsy: Diagnosis and Management*, in *Neurologic Disorders* 873, at 873; see also Zhang, *supra* note 59 at 11.

⁷² Sleep Expert Consult, *supra* note 5, at 6.

⁷³ *Id.* at 6-7.

⁷⁴ Scammell, *Clinical*, *supra* note 67; see also Cao, *supra* note 71, at 873.

⁷⁵ Scammell, *Clinical*, *supra* note 67.

⁷⁶ *Id.*

⁷⁷ Thomas E Scammell, *Treatment of narcolepsy in adults*, UpToDate (Nov. 14, 2022), <https://www.uptodate.com/contents/treatment-of-narcolepsy-in-adults>.

⁷⁸ Kiran Maski et al., *Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline*, 17 *Journal of Clinical Sleep Medicine* 1881, at 1892 (2021).

on an ongoing basis.”⁷⁹ Sleep hygiene means consistent sleep scheduling, a bedtime routine of personal care, napping, daily exercise, and a sleep environment conducive to sleep without interruptions.⁸⁰

In addition to behavioral changes promoting good sleep hygiene, most patients with narcolepsy also require pharmacotherapy.⁸¹ Oxybate salts are one class of drugs that improves symptoms of EDS and decreases episodes of cataplexy.⁸² Per Scammell, especially for patients with severe and disabling sleepiness:

Oxybates have a different mechanism of action than other narcolepsy medications and act primarily through *consolidating nighttime sleep*. Although risks and side effects, as well as cost, may be higher with oxybates, they can offer the best chance of optimal symptom control with monotherapy. For patients with a good response to oxybates, other wake-promoting medications may be able to be tapered.⁸³

As explained above, “consolidating nighttime sleep” means ensuring sleep continuity through the normal stages of sleep architecture. Therefore, oxybate products are intended to decrease nocturnal arousals (also known as nighttime or nocturnal awakenings) to decrease sleep fragmentation that leads to poor quality sleep. Importantly, as explained in more detail below, the effectiveness of Xyrem and Xywav wanes during the night, so their labeling recommends that patients awaken for a second dose. Lumryz, as a once nightly formulation, will eliminate such nocturnal arousal, thus minimizing disturbances and decreasing sleep fragmentation.

B. Regulatory History of Oxybate Products for Narcolepsy

On November 7, 1994, FDA granted ODD to Jazz’s predecessor Orphan Medical, Inc. for oxybate⁸⁴ for the treatment of narcolepsy. On July 17, 2002, FDA approved Xyrem for the treatment of cataplexy associated with narcolepsy, and Xyrem was eligible for ODE for the treatment of cataplexy associated with narcolepsy until July 17, 2009. On November 18, 2005, FDA approved Xyrem for a new indication, the treatment of EDS in patients with narcolepsy, and Xyrem was eligible for a new term of ODE for the treatment of EDS in patients with narcolepsy until November 18, 2012. Both of those periods of ODE have since expired. Finally, on October 26, 2018, FDA approved Xyrem for the treatment of cataplexy or EDS in pediatric patients 7 years of age and older with narcolepsy. Prior to this approval, the safety and effectiveness of Xyrem in pediatric patients had not been established, and therefore this approval

⁷⁹ Maski, *Insufficient*, *supra* note 45.

⁸⁰ See National Sleep Foundation, *10 Tips for a Better Night’s Sleep*, <https://www.thensf.org/sleep-tips/>; see also American Academy of Sleep Medicine, *How to sleep better*, https://aasm.org/resources/pdf/products/howtosleepbetter_web.pdf; see also Ahmed, *supra* note 69 at 340.

⁸¹ Timothy I. Morgenthaler et al., *Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin*, 30 *Sleep* 1705 at 1705-1711 (2007).

⁸² Scammell, *Treatment*, *supra* note 77.

⁸³ *Id.* (emphasis added).

⁸⁴ We note that ODD letters and the ODD database often refer to the generic name of the drug the sponsor uses in its request for designation rather than the active moiety, but the ODD applies to the active moiety (here, oxybate for the treatment of narcolepsy).

expanded the indication to a new patient population. Xyrem was eligible for ODE for the treatment of cataplexy or EDS in pediatric patients 7 years of age and older with narcolepsy, which will run until October 26, 2025.⁸⁵

Xyrem has a concentration of 0.5 grams (g)/milliliter (mL) of sodium oxybate, equivalent to 0.413 g/mL of oxybate.⁸⁶ Xyrem is taken in 2 doses at night, the first dose at bedtime with the second dose taken 2.5 to 4 hours later.⁸⁷ For adults, the initial starting dose is 4.5 g per night, which can be increased in increments of 1.5 g per night at weekly intervals to a maximum of 9 g per night.⁸⁸ The maximum dose of 9 g contains approximately 1,640 milligrams (mg) of sodium.⁸⁹ This amount can make up a large portion of the maximum daily recommended sodium (for example, CDC guidelines recommend less than 2,300 mg of sodium each day as part of a healthy eating pattern).⁹⁰ Due to its high sodium content, Xyrem's labeling includes a Warning and Precaution on use of the drug in patients sensitive to high sodium intake and recommends consideration of the amount of daily sodium intake in each dose of Xyrem for patients sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment).⁹¹ The sodium warning is listed last of eight warnings, and warnings are listed in order of relative clinical significance.⁹²

Subsequently, Jazz developed a low-sodium alternative to Xyrem called Xywav. Xywav consists of 4 active ingredients, all of which have oxybate as the active moiety: calcium oxybate (0.234 g/mL), potassium oxybate (0.130 g/mL), magnesium oxybate (0.096 g/mL), and sodium oxybate (0.040 g/mL) — equivalent to 0.413 g/mL of oxybate, the same as Xyrem.⁹³ The total salt concentration is 0.5 g/mL.⁹⁴ Also like Xyrem, the recommended starting dosage for Xywav in adults is 4.5 g per night administered orally, divided into two doses, one at bedtime with the second dose to be taken 2.5 to 4 hours later.⁹⁵ Xywav can be titrated by increments of up to 1.5 g per night per week to the recommended maximum dosage of 9 g per night.⁹⁶ At the maximum

⁸⁵ Pediatric exclusivity extends Xyrem's ODE until April 26, 2026.

⁸⁶ Xyrem FDA-Approved Labeling at Section 3 (Apr. 2023), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021196s042lbl.pdf [hereinafter Xyrem 2023 Labeling].

⁸⁷ *Id.* at section 2.1. Note that the labeling describes dosage “per night” regardless of whether the patient primarily sleeps during the day or night. This analysis will also use the word “night” to refer to the patient's bedtime.

⁸⁸ *Id.* at section 2.1.

⁸⁹ *Id.* at section 5.8.

⁹⁰ See CDC, *About Sodium*, available at: <https://www.cdc.gov/salt/food.htm>.

⁹¹ Xyrem 2023 Labeling, *supra* note 86, at section 5.8. The warning states, “Xyrem has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of Xyrem. Table 3 provides the approximate sodium content per Xyrem dose.”

⁹² See FDA, *Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* at 7 (Oct. 2011) (available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/warnings-and-precautions-contraindications-and-boxed-warning-sections-labeling-human-prescription>) (“The order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the adverse reactions”).

⁹³ Xywav FDA-Approved Labeling at section 3 (Apr. 2023), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212690s011lbl.pdf [hereinafter Xywav 2023 Labeling].

⁹⁴ *Id.*

⁹⁵ *Id.* at section 2.1.

⁹⁶ *Id.*

dose for adults, the sodium content of Xywav is 131 mg.⁹⁷ Therefore, unlike Xyrem, there are no Warnings and Precautions in Xywav’s labeling related to that drug’s use in patients sensitive to high sodium intake.

Because the active moiety in Xywav is also oxybate, Xywav is covered by Jazz’s ODD for oxybate for the treatment of narcolepsy. On July 21, 2020, FDA approved Xywav for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. In order for Xywav to be eligible for ODE, Jazz was required to demonstrate that Xywav was clinically superior to Xyrem.⁹⁸ OOPD determined that Xywav was clinically superior to Xyrem because the reduced sodium in Xywav provides greater safety in a substantial portion of the target population.⁹⁹ Specifically, at the effective daily dose of 6 g to 9 g, Xyrem adds approximately 1,100 mg to 1,640 mg of sodium to each patient’s daily sodium intake, compared to Xywav, which adds only 87 to 131 mg of sodium to each patient’s daily sodium intake for the same recommended daily dose.¹⁰⁰ OOPD concluded, “the differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.”¹⁰¹ OOPD noted that whether sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy has never been specifically or adequately investigated; however, the general base of knowledge about the effects of sodium support that the amount of sodium in Xyrem would increase cardiovascular risks in patients with narcolepsy.¹⁰²

Because FDA found Xywav to be clinically superior to Xyrem, Xywav was eligible for ODE.¹⁰³ On June 24, 2021, OOPD sent a letter to Jazz stating that it is eligible for ODE for Xywav for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy, effective as of the July 21, 2020, approval of NDA 212690.¹⁰⁴ Xywav’s ODE for this indication will run until July 21, 2027.

⁹⁷ NDA 212690 Clinical Review at 7 (available at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212690Orig1s000MedR.pdf).

⁹⁸ Section 527(c)(1) of the FD&C Act.

⁹⁹ See FDA, *Exclusivity Memorandum DRU-1994-858, Xywav (calcium, magnesium, potassium, and sodium oxybates)* at 6 (Sep. 30, 2021) [hereinafter Xywav Exclusivity Memo]. During OOPD’s assessment of Xywav’s clinical superiority over Xyrem, OOPD received and considered two letters from Jazz containing arguments why Xywav is clinically superior to Xyrem. See letter from Arthur Merlin d’Estreux to Janet Maynard, *Orphan Drug Exclusivity for JZP-258, NDA No. 212690* (Apr. 24, 2020); see also letter from Robert Iannone to Janey Maynard, *Request to Expedite Recognition of Orphan Drug Exclusivity for XYWAV (NDA 212690)* (Apr. 19, 2021). Additionally, OOPD received and considered a letter from Avadel providing arguments why Xywav is not clinically superior to Xyrem. See letter from Jennifer Gudeman to Janet Maynard, *Sodium Oxybate for the Treatment of Narcolepsy* (Dec. 8, 2020). OOPD also consulted with the Division of Neurology 1 (“DN1”) in the Center for Drug Evaluation and Research (“CDER”). See DN1, *Consult Request NDA 212690 Xywav* (Nov. 27, 2020) [hereinafter DN1 2020 Xywav Consult]; See also DN1, *Consult Request NDA 212690 Xywav* (Mar. 8, 2021).

¹⁰⁰ Xywav Exclusivity Memo, *supra* note 99, at 3.

¹⁰¹ FDA, *Clinical Superiority Findings*, available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings>.

¹⁰² Xywav Exclusivity Memo, *supra* note 99, at 5.

¹⁰³ See section 527(c) of the FD&C Act.

¹⁰⁴ Letter from Nicole Wolanski to Jazz Pharmaceuticals, Inc., *Orphan-Drug Exclusivity Letter DRU-1994-858* (June 24, 2021). OOPD also responded to Avadel’s letter to explain that we considered their arguments before concluding that Xywav was eligible for ODE. See letter from Nicole Wolanski to Jennifer Gudeman, *Sodium Oxybate for the Treatment of Narcolepsy* (Jun. 24, 2021).

Concurrently, Avadel developed Lumryz, an extended-release oral suspension version of sodium oxybate for the treatment of narcolepsy. The active moiety in Lumryz, like both Xyrem and Xywav, is oxybate. While Xyrem and Xywav are both dosed twice per night, with the patient instructed to wake from sleep to take the second dose, Lumryz is dosed once per night before sleep. Therefore, Lumryz’s labeling does not advise an awakening to take a second dose for proper administration.¹⁰⁵ At the recommended daily dose of 6 g to 9 g, Xyrem and Lumryz both have the same sodium content (approximately 1,100 mg to 1,640 mg). As explained above, at the same recommended daily dose of 6 g to 9 g, Xywav has a lower sodium content of 87 mg to 131 mg. See Table 1 for a summary of the differences among the drugs.

Table 1: Comparison of Xyrem, Xywav, and Lumryz Dosing and Sodium Content per Daily Dose

Drug	Dosing	Amount of sodium at the recommended daily dose of 6 g to 9 g
Xyrem	Twice-per-night	1,100 mg to 1,640 mg
Xywav	Twice-per-night	87 mg to 131 mg
Lumryz	Once-per-night	1,100 mg to 1,640 mg

On April 20, 2016, Avadel¹⁰⁶ requested ODD for oxybate¹⁰⁷ for the treatment of narcolepsy. At the time of the request for designation, Xyrem was already approved for a narcolepsy indication, but Xywav was not yet approved. Because Avadel was seeking ODD for oxybate for the same disease for which Xyrem was approved, Avadel was required to provide a plausible hypothesis that its drug was clinically superior to Xyrem to be eligible for ODD.¹⁰⁸

Upon review of the initial request for designation, OOPD asked Avadel to provide additional support for its hypothesis for clinical superiority.¹⁰⁹ Avadel submitted an amendment to its request for designation on October 13, 2017. At that time, to determine whether the plausible hypothesis standard for ODD had been met, OOPD consulted with clinical experts in the Division of Neurology Products (DNP) regarding the benefit of Lumryz’s once-per-night dosing over Xyrem’s twice-per-night dosing.¹¹⁰ DNP stated that if a formulation of sodium oxybate can be administered only once each night, it would have advantages over a sodium oxybate drug administered twice-per-night, like Xyrem.¹¹¹ DNP cited several reasons such a formulation could be clinically superior, including that a drug administered once per night would be much more convenient and less disruptive for patients, and that a drug administered once-per-night may present less risk to patients, for example risks from falls when waking up to take the second

¹⁰⁵ Lumryz, FDA-Approved Labeling (May 2023) [hereinafter Lumryz Labeling].

¹⁰⁶ Avadel submitted the request for designation under the name Flamel Ireland Limited. In 2017, there was a cross-border merger of Flamel and Avadel; the latter entity survived the merger as the public holding company.

¹⁰⁷ At the time, Avadel referred to its product as FT218 or sodium oxybate for extended-release oral suspension. See also *supra* note 84.

¹⁰⁸ 21 CFR § 316.20(a).

¹⁰⁹ FDA, *Review of Request for ODD for sodium oxybate, DRU-2016-5302* at 5 (Jul. 28, 2016); see also Letter from Gayatri R. Rao to The Weinberg Group, Inc., *Deficiency Letter, DRU-2016-5302* (Aug. 23, 2016).

¹¹⁰ As the result of a reorganization of the CDER, the review division responsible for oxybate drug products for the treatment of narcolepsy is now called the Division of Neurology 1 (DN1).

¹¹¹ Division of Neurology Products, *Sodium Oxybate Consultation Request* at 9 (Nov. 24, 2017).

dose.¹¹² DNP’s response supported OOPD’s conclusion that there was a plausible hypothesis that Lumryz may be clinically superior to Xyrem based on providing greater safety or by making a MCTPC over Xyrem.¹¹³ Therefore, on January 8, 2018, FDA granted Avadel’s request for ODD for oxybate for treatment of narcolepsy.¹¹⁴

On December 15, 2020, Avadel submitted NDA 214755 for Lumryz. On July 18, 2022, FDA tentatively approved Lumryz for the treatment of cataplexy or EDS in adults with narcolepsy. The Tentative Approval Letter stated, “This letter does not address whether any orphan drug exclusivity (ODE) recognized for Xyrem under NDA 021196 or for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution under NDA 212690 affects the approvability of Avadel’s application.”¹¹⁵ On March 1, 2023, Avadel submitted an amendment to NDA 214755 requesting final approval.

IV. Discussion

A. Applicability of the Clinical Superiority Standard

Xywav currently has ODE for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy, and as such, FDA may not approve another sponsor’s marketing application for the same drug for the same use or indication until its exclusivity expires on July 21, 2027.¹¹⁶ Lumryz contains the same active moiety as Xywav (oxybate), and Avadel is seeking approval for Lumryz for an indication covered by Xywav’s unexpired ODE (the treatment of cataplexy or EDS in adults with narcolepsy). Under the orphan-drug regulations, Lumryz is the “same drug” as Xywav unless Lumryz is clinically superior to Xywav.¹¹⁷ If Lumryz is clinically superior to Xywav, then it is not the “same drug” as Xywav, and Xywav’s ODE will not block Lumryz’s approval.¹¹⁸

¹¹² *Id.* at 8-9.

¹¹³ FDA, *Review of Amended Request for Orphan Drug Designation for sodium oxybate, DRU-2016-5302* at 4-6 (Dec. 21, 2017). The standard for ODD is a “plausible hypothesis” that the subsequent drug may be clinically superior to the first drug. When FDA grants ODD to a drug that is otherwise the same drug as a previously approved drug for the same rare disease or condition based on a plausible hypothesis of clinical superiority, that means FDA agrees that the sponsor “may be able to produce a clinically superior drug,” not that the sponsor has provided evidence that its drug in fact would be clinically superior. *See* 1991 Proposed Rule, 56 Fed. Reg. at 3340. This is a lower standard than is required to demonstrate clinical superiority for the purposes of determining whether a drug’s ODE blocks approval of another drug or determining eligibility for ODE.

¹¹⁴ Letter from Debra Y. Lewis to The Weinberg Group Inc., *Designation letter for sodium oxybate, DRU-2016-5302* (Jan. 8, 2018). *See also supra* note 84.

¹¹⁵ Letter from Teresa Buracchio to Marla E. Scarola, *Tentative Approval Letter* (Jul. 18, 2022).

¹¹⁶ Section 527(a) of the FD&C Act; 21 CFR §§ 316.31 & 316.3(b)(14).

¹¹⁷ 21 CFR § 316.3(b)(14).

¹¹⁸ Jazz asserts that for FDA to approve Lumryz, Lumryz must be clinically superior to Xywav. *See* Sidley Letter, *supra* note 12, at 5-8. We agree with this conclusion but note that Jazz at one point appears to arrive at this conclusion based on an incorrect interpretation of the law, citing to section 527(c) of the FD&C Act (the condition of clinical superiority to be eligible for ODE) as an exception to ODE. *See, e.g., id.* at 7 (“Thus, section 527(c)(1) provides that a later-in-time applicant can break through unexpired exclusivity (or obtain new exclusivity) only by demonstrating that its proposed drug will be ‘clinically superior to *any already approved or licensed drug that is the same drug.*’ 21 U.S.C. § 360cc(c)(1) . . .”). Later, Jazz changed its position during the meeting between Sidley and OCC. *See* Sidley Slides, *supra* note 13, at 10 (stating that section 527(c) cannot be read as a third exception to ODE

Avadel is not seeking approval for Lumryz for an indication covered by Xyrem’s unexpired ODE.¹¹⁹ Upon approval, in order to be eligible for its own term of ODE, an orphan-designated drug must be clinically superior to all otherwise same drugs previously approved for the same use or indication.¹²⁰ Accordingly, if Lumryz is clinically superior to Xywav and Xyrem, then it will be eligible for its own term of ODE.

i. Clinical superiority can overcome ODE

As explained above, the definition of “same drug” in the orphan-drug regulations states that if a subsequent drug that has the same active moiety and is for the same use as a previously approved drug “can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.”¹²¹ Accordingly, if a subsequent drug is clinically superior to a drug with ODE that has the same active moiety and is for the same indication or use, approval of the subsequent drug is not blocked by that drug’s ODE. Jazz provides three arguments why FDA cannot apply the definition of “same drug” here to determine that Lumryz is a different drug than Xywav, and thus not blocked by Xywav’s ODE.

First, Jazz argues that *Depomed* and *Eagle* struck down FDA’s definition of “same drug.”¹²² As a threshold matter, *Depomed* and *Eagle* concerned a different set of facts and a distinct legal issue. Those cases addressed FDA’s authority to require a demonstration of clinical superiority as a condition for eligibility for ODE prior to the addition of section 527(c) to the FD&C Act. Jazz acknowledges this, stating, “Section 527(c) thus addresses the specific factual scenario at issue in *Depomed*, *Eagle*, and *United Therapeutics* by providing that subsequent periods of ODE cannot be obtained without proof of clinical superiority.”¹²³ Thus, the holdings of these cases concern eligibility for ODE, not the scope of ODE (i.e., what ODE blocks). The district court in *Eagle Pharms* explicitly stated: “[t]he scope of Bendeka’s exclusivity is an issue that the FDA must determine in the first instance.”¹²⁴

and that section 527(c) addresses only serial grants of exclusivity). Section 527(c) only concerns potential eligibility of a subsequent drug (like Lumryz) for its own period of ODE; it does not address whether a subsequent drug’s (Lumryz’s) approval is blocked by Xywav’s ODE. See section II.B of document for further explanation.

¹¹⁹ Avadel is only seeking approval for the treatment of cataplexy or EDS in the adult population with narcolepsy, and Xyrem’s ODE only blocks approval of the same drug for the treatment of cataplexy or EDS in the pediatric population. Jazz acknowledges that “[. . .] the unexpired ODE for XYREM is not at issue (because Avadel’s proposed labeling omits pediatric use).” Sidley Slides, *supra* note 13, at 7.

¹²⁰ Section 527(c)(1) of the FD&C Act.

¹²¹ 21 CFR § 316.3(b)(14)(i); *see also* similar language in 316.3(b)(14)(ii).

¹²² Sidley Letter, *supra* note 12, at 6; *see also* Sidley Slides, *supra* note 13, at 14.

¹²³ Sidley Slides, *supra* note 13, at 10.

¹²⁴ *Eagle Pharms., Inc. v. Azar*, No. CV 16-790 (TJK), 2018 WL 3838223, at *3 (D.D.C. Aug. 1, 2018). *See also id.* at *2 (“But the Order did not adopt Eagle’s (or any other party’s) interpretation of the scope of Bendeka’s exclusivity.”); *id.* (“And as Defendants repeatedly and correctly assert, the scope of Bendeka’s exclusivity was not before the Court in this litigation. *See, e.g.,* Defs.’ Mot. at 7 (‘Eagle repeatedly emphasized that the scope of exclusivity for Bendeka was a separate issue from the existence of any such exclusivity, indicating that only the latter was properly before this Court.’). Rather, the issue was whether Bendeka should enjoy orphan-drug exclusivity at all. Accordingly, that was the only issue that the Court’s Opinion and Order addressed, as Defendants acknowledge. *See id.* at 2, 9; Defs.’ Reply at 2. And doing so did not require the Court to address whether Bendeka is the same drug as Treanda under either the FDA’s regulations or the statute.”). *See also* FDA, *Dear Applicants for*

Jazz nonetheless points to several quotations from the cases in looking for support, but these quotations do not speak directly to the situation at issue with Lumryz. The first quotation,¹²⁵ from the background section of the *Depomed* decision, simply describes how the definition of “same drug” “effectively limits the scope of exclusivity,” but neither *Depomed* nor *Eagle* addressed the scope of the plaintiffs’ exclusivity (i.e., whether approval of another sponsor’s drug was blocked by the plaintiffs’ exclusivity).¹²⁶ Jazz also quotes language in the *Depomed* decision stating, “This Court will not impute to Congress an intention to authorize an exception that Congress itself did not think worth enacting.”¹²⁷ However, the regulatory definition of “same drug” does not create an extra-statutory “exception” to ODE. As explained in section II.B above, under section 527(a), FDA may not approve another sponsor’s application for the same drug for the same use or indication as a drug with ODE.¹²⁸ Exceptions to ODE describe situations where FDA can nevertheless approve another sponsor’s application for the same drug for the same use or indication during a period of unexpired ODE.¹²⁹ Instead of creating such an exception to ODE where same drugs for the same indications or uses can be approved despite a drug’s unexpired ODE, the definition of “same drug” identifies certain drugs that are not the same (e.g., clinically superior drugs) and, in this context, helps clarify the scope of ODE once it has attached. When a subsequent drug that is otherwise the same drug (i.e., contains the same active moiety and is for the same use or indication) as a drug with unexpired ODE and is found to be clinically superior to that drug with unexpired ODE, then the subsequent drug is not the “same drug,” and the unexpired ODE cannot block approval of that drug under section 527(a) of the FD&C Act (because such ODE can only block same drugs for the same uses or indications).¹³⁰ That section 527(b) enumerates two exceptions to ODE does not undermine the

Certain Products Containing Bendamustine Letter, Docket No. FDA-2018-N-3773 (Feb. 20, 2019) (“FDA has . . . determined that the agency will continue to apply its existing ‘same drug’ regulation when determining the scope of Bendeka’s exclusivity (i.e., exclusivity prevents the approval of any other drug with the same active moiety (here, bendamustine) for the exclusivity-protected indications.”).

¹²⁵ Sidley Slides, *supra* note 13, at 14 (quoting *Depomed v. HHS*, 66 F. Supp. 3d 217 (D.D.C. 2014) (“FDA’s ‘insertion of the ‘same drug’ concept . . . effectively limits the scope of exclusivity protection because under the regulations, only if a new drug uses the same [active moiety] to treat the same disease or condition . . . and the new drug is also not found to be ‘clinically superior’ to the existing orphan drug will the FDA . . . forbid its marketing within the exclusivity period.”)).

¹²⁶ *Depomed v. HHS*, 66 F. Supp. 3d 217 (D.D.C. 2014); *see also Eagle Pharms., Inc. v. Azar*, 952 F.3d 323 (D.C. Cir. 2020).

¹²⁷ Sidley Letter, *supra* note 12, at 6; *see also* Sidley Slides, *supra* note 13, at 14. Similarly, the Sidley Letter also later quotes from *Depomed*, “Where Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied.” Sidley Letter, *supra* note 12, at 8.

¹²⁸ Section 527(a) of the FD&C Act.

¹²⁹ The exceptions to 527(a) of the FD&C Act are enumerated in section 527(b).

¹³⁰ This distinction between an exception to ODE and a definitional exclusion from the term “same drug” is a meaningful one. The exceptions to ODE under section 527(b) set forth the circumstances under which FDA may approve an application even though it is for the same drug for the same indication or use as the drug that has ODE. Meanwhile, a subsequent drug that is clinically superior to the drug with ODE is simply not the same drug as the drug that has ODE and is therefore excluded from the scope of subsequent drugs that are blocked by that ODE. A standard illustration of this distinction, familiar to most law students, is the evidentiary rule against hearsay. Federal Rule of Evidence 802 provides that hearsay is generally inadmissible. Rules 801(c)-(d) exclude certain statements from the definition of hearsay: 801(c) limits hearsay to out-of-court statements offered for their truth, while 801(d) further specifies certain statements that are “not hearsay.” Meanwhile, Rules 803, 804, and 807 provide for certain exceptions to the rule against hearsay—statements that meet the definition of hearsay, but that are nevertheless not

agency's conclusion that a clinically superior drug is definitionally not the "same drug," and therefore its approval is not blocked by ODE.

Jazz also cites quotations from *Eagle* critiquing "FDA's imposition of its clinical-superiority requirement" and that FDA's "interpretation reads a limitation into the text that is not there."¹³¹ Again, *Eagle* concerned FDA's imposition of the condition of clinical superiority for a sponsor to be eligible for its own period of ODE, which is not at issue here. We have already recognized that Xywav is eligible for ODE. Xywav's ODE, however, only blocks approval of the same drug for the same indication or use.

Second, Jazz argues that the enactment of section 527(c) of the FD&C Act superseded and invalidated the regulatory definition of "same drug." Specifically, Jazz argues that the regulatory definition of "same drug" is inconsistent with section 527(c)(1), because the statute does not contain what Jazz refers to as the "'not-the-same' fiction."¹³² However, Jazz ignores crucial words in the statute. As explained above, Section 527(c)(1) requires a demonstration of clinical superiority when the sponsor of a drug is seeking ODE for "a drug that is designated under section 526 and *is otherwise the same*, as determined by the Secretary, as an already approved or licensed drug" for the same use or indication.¹³³ The orphan-drug regulations, which predate section 527(c)(1), use this same phrase; *see, e.g.*, 21 CFR § 316.3(b)(3) (stating "that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is *otherwise the same drug*)" (emphasis added)); 21 CFR § 316.34(c) ("If a drug is *otherwise the same drug* as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug." (emphasis added)); Congress legislated against this backdrop. Black's Law Dictionary defines "otherwise" as:

otherwise *adv.* (bef. 12c) **1.** In a different way; in another manner <David Berkowitz, otherwise known as Son of Sam>. **2.** By other causes or means <to succeed by hard work and otherwise>. **3.** In other conditions or circumstances <to know him otherwise than through law practice>. **4.** Except for what has just been mentioned <page 99 was illegible; otherwise, the records were easy to decipher>. **5.** Busy doing something else <she was otherwise engaged that day>. **6.** To the contrary; differently <although the economists say that legal markets are soft, many law-firm leaders think otherwise>. • The term *otherwise* tends to be quite broad in scope.

subject to the rule against hearsay. Exceptions to the rule against hearsay and exclusions from its definition are therefore addressed separately. The same is true here.

¹³¹ Sidley Letter, *supra* note 12, at 6; see also Sidley Slides, *supra* note 13, at 14.

¹³² Sidley Slides, *supra* note 13, at 15-16. *Id.* at 15 (arguing that "[t]he statute does not rely on any legal fiction and does not pretend that a clinically superior product is no longer 'the same' as prior drugs that contain the same active moiety; that '[i]nstead, the statute created a clinical superiority requirement that embraces 'sameness;'" that "[p]ursuant to section 527(c)(1), a second or further period of ODE is conditioned on a demonstration that the proposed drug is 'clinically superior to any already approved or licensed drug that is the same drug;'" and that "[p]er the statute XYWAV remains 'the same drug' as other oxybates even though it is clinically superior").

¹³³ Section 527(c)(1) of the FD&C Act (emphasis added).

These dictionary definitions make clear that “otherwise” connotes difference. By using the phrase “otherwise the same” the statute (and regulations) acknowledges that a clinically superior drug is not, in fact, considered to be the same as a previously approved drug. The orphan-drug regulations defining “same drug” state that “if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug,” which is entirely consistent with section 527(c)’s description of a clinical superior drug as one that is “otherwise the same” as (i.e., different than) a previously approved drug. FDA has previously considered whether the enactment of the FDARA provisions at section 527 conflicted with its regulations and concluded that “FDA’s current regulations are consistent with FDARA.”¹³⁴

Third, Jazz argues that allowing a clinically superior drug to overcome the ODE of an otherwise same drug goes against the intent of Congress and renders ODE meaningless.¹³⁵ FDA disagrees. As Jazz itself acknowledges, Congress expressed an interest in incentivizing the development of clinically superior products.¹³⁶ The ODE framework executes that intention in two ways: first, clinically superior drugs can be eligible for their own terms of ODE; second, clinically superior drugs can be approved during the ODE period for a drug that is otherwise the same as the clinically superior drug because they fall outside the scope of that drug’s ODE. Although ODE does not block as much as Jazz would prefer in this instance, that does not render ODE “meaningless.” Xywav’s ODE blocks FDA approval of all applications from other sponsors for the same drug for the same use or indication for seven years (subject to the exceptions in section 527(b)), a valuable benefit that is not just limited to blocking FDA’s approval of generic drugs referencing Xywav.

ii. MCTPC in Relation to Safety

As explained above, Lumryz may demonstrate clinical superiority to Xywav by showing that it provides a significant therapeutic advantage through greater effectiveness, greater safety, or by making a MCTPC. Doing so would render Lumryz a different drug than Xywav such that Xywav’s ODE would not block Lumryz’s approval. Importantly, as explained above, one drug can demonstrate a MCTPC over a previously approved drug even if the drug is not as effective or safe in every respect as the previously approved drug. Jazz tries to argue otherwise. Jazz claims that “longstanding FDA policy requires the second-in-time drug to achieve at least comparable safety as the earlier drug” in order to be clinically superior.¹³⁷ Additionally, Jazz claims that “to be eligible for clinical superiority a drug must also provide safety at least comparable to the approved drug” and that “a new drug that is less safe than an already approved orphan drug cannot be considered ‘clinically superior’ to the first drug.”¹³⁸ The same argument is also made in the Sidley Letter, which states, “clinical superiority cannot be demonstrated through tradeoffs—a later drug is not clinically superior if it sacrifices the safety or efficacy

¹³⁴ *Dear Applicants for Certain Products Containing Bendamustine Letter*, *supra* note 124. Jazz points to section 527(d) of the FD&C Act to suggest that the agency cannot apply its definition of “same drug” to interpret the statute and its regulations at Subpart D of Part 316. As noted here, FDA has previously considered this issue and concluded that FDA’s current regulations are consistent with FDARA.

¹³⁵ Sidley Letter, *supra* note 12, at 8; *see also* Sidley Slides, *supra* note 13, at 17.

¹³⁶ Sidley Slides, *supra* note 13, at 17.

¹³⁷ Jazz’s September 2021 Letter, *supra* note 11, at 1.

¹³⁸ *Id.* at 2.

achieved by its predecessors.”¹³⁹ In the Sidley Slides, Jazz relies on the words “over and above” in section 527(c)(2) to argue that clinical superiority requires “progress” and thus a drug cannot be clinically superior to a previously approved drug if it is also less safe than the previously approved drug. These assertions are not correct.

First, the words “over and above,” in the context of the statute and regulation at 21 CFR § 316.3(b)(3), cannot be read to mean a drug must be as safe as a previously approved drug to make a MCTPC. As explained in section II.C above, section 527(c)(2) of the FD&C Act defines clinically superior to mean that “the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, *or* by providing a [MCTPC],” and 21 CFR § 316.3(b)(3) defines clinically superior to mean that “a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in *one or more* of the following ways:” greater effectiveness, greater safety, or a MCTPC (emphasis added). Jazz conveniently ignores the italicized statutory and regulatory language in these definitions. In both definitions, the subsequent drug must provide a significant therapeutic advantage “over and above” an already approved drug in just one way—greater efficacy, greater safety, *or* by providing a MCTPC—to be considered clinically superior. The plain reading of both the statute and the regulation does not impose an additional requirement that in order to provide a significant therapeutic advantage in one of the three measures, the drug must also be at least comparable in the other two measures. The relative effectiveness and safety of the drug may be relevant in assessing whether a drug makes a MCTPC, and a drug must meet FDA’s fundamental safety and effectiveness thresholds to obtain approval (see section II.D above), but nothing in the statute or regulation requires comparable effectiveness and safety in every respect.

In fact, in the 2011 proposed rule for amending the orphan-drug regulations, FDA proposed adding such a requirement to the regulation.¹⁴⁰ Specifically, FDA proposed adding that a demonstration of MCTPC must also include “a demonstration that the drug provides safety and effectiveness comparable to the approved drug.”¹⁴¹ In the 2013 final rule, however, FDA did not adopt that proposed change, so as not to create “a new standard” for MCTPC.¹⁴² Instead, FDA stated that MCTPC “determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product.”¹⁴³

Jazz points to the 2011 proposed rule to argue that a “comparable safety showing” is “consistent with longstanding FDA policy.”¹⁴⁴ To the contrary, as discussed above, the final rule makes clear that requiring a showing of comparable safety and effectiveness for a MCTPC would create a “new standard.”¹⁴⁵ Jazz also claims that it “could find no precedent where FDA has endorsed a

¹³⁹ Sidley Letter, *supra* note 12, at 8-9; *see also* Sidley Slides, *supra* note 13, at 29.

¹⁴⁰ FDA, *Orphan Drug Regulations, Proposed Rule*, 76 Fed. Reg. 64868, 64871 (Oct. 19, 2011) [hereinafter 2011 Proposed Rule].

¹⁴¹ *Id.* at 64878.

¹⁴² 2013 Final Rule, 78 Fed. Reg. at 35124.

¹⁴³ *Id.*

¹⁴⁴ Jazz’s September 2021 Letter, *supra* note 11, at 2 footnote 4 (referencing 2011 Proposed Rule, 76 Fed. Reg. at 64876).

¹⁴⁵ 2013 Final Rule, 78 Fed. Reg. at 35124.

comparably effective but less safe product as clinically superior.”¹⁴⁶ However, more importantly, based on our review, agency precedent is devoid of instances in which we refused to find a MCTPC for a drug based on a failure to show comparable safety or efficacy.¹⁴⁷ As explained above, safety concerns could inform a MCTPC analysis, but a safety concern present in a subsequent drug that was not present in the previous drug would not automatically defeat a finding of MCTPC. That determination would be made on a case-by-case basis and depend upon the nature of the safety concern weighed against the benefits of the MCTPC. As described in detail in section II.C, FDA’s ODE determination regarding Rebif provides at least one instance where we found a drug to be clinically superior based on greater efficacy even though the drug was less safe in one measure than the previously approved drug with ODE. As noted above, Rebif patients experienced skin necrosis at injection sites that patients on a previously approved drug (Avonex) did not (i.e., the same adverse event that was present with the previously approved drug Betaseron that led to the determination that Avonex was clinically superior to Betaseron based on safety).¹⁴⁸ While this clinical superiority determination was not based on a MCTPC finding, the example nonetheless demonstrates that the agency does not require comparable safety and efficacy to be considered clinically superior.

Jazz claims that FDA’s clinical superiority analyses include an assessment of whether the subsequent drug is at least “not less safe than” the previously approved drug to support its assertion that “a new drug that is less safe than an already approved orphan drug cannot be considered ‘clinically superior’ to the first drug.”¹⁴⁹ To support these claims, Jazz cites examples where FDA considered whether a previously approved drug is at least not less safe.¹⁵⁰ As discussed below, although these examples discuss the relative safety of two drugs, they do not support a conclusion that a drug *must* be at least “not less safe” than an already approved drug to be clinically superior to that drug. FDA has considered whether a subsequent drug has comparable safety and efficacy to the previously approved drug as part of an overall assessment of whether the subsequent drug makes a MCTPC. For example, to reiterate what we said above, where certain adverse events associated with a change in administration raise safety concerns for a subsequent drug that are not present for a previous drug, FDA could consider such information to determine whether the safety concerns affect the agency’s finding that certain benefits of the drug create a MCTPC, but such safety concerns would not automatically lead FDA to deny the drug approval or exclusivity based on a finding that the drug was not clinically superior.

The specific examples provided by Jazz do not counsel otherwise. First, Jazz cites to OOPD’s statements, in determining that Revcovi (elapegademase-lvlr) is clinically superior to Adagen (pegademase bovine), that “OOPD does not need to determine whether Revcovi is in fact more safe than Adagen. Clinical superiority based on effectiveness has been demonstrated, and

¹⁴⁶ Jazz’s September 2021 Letter, *supra* note 11, at 1.

¹⁴⁷ We are aware of certain language in agency documents that could be interpreted as suggesting FDA has such a policy. As described further below, despite these statements, none of FDA’s past precedents that OOPD reviewed manifest application of such a policy upon approval when FDA is determining eligibility for ODE or when it is considering whether a drug may be approved in light of another sponsor’s ODE. Given the quantum of information suggesting otherwise, it is clear that those statements do not reflect such an agency policy.

¹⁴⁸ CBER Rebif memo, *supra* note 32, at 20.

¹⁴⁹ Jazz’s September 2021 Letter, *supra* note 11, at 2.

¹⁵⁰ *Id.* at 2 footnote 4; *see also* Sidley Slides, *supra* note 13, at 30.

Revcovi is at least not less safe than Adagen.”¹⁵¹ Revcovi and Adagen are both enzyme replacement therapies used to treat adenosine deaminase (“ADA”) deficiency in patients with severe combined immunodeficiency. Adagen is derived from a bovine source, while Revcovi is recombinant (i.e., made in a laboratory). OOPD determined that Revcovi is clinically superior to Adagen based on a consult with expert clinicians in the review division, who found that Revcovi is more effective as it provides more stable plasma ADA activity, more consistently above the therapeutic threshold associated with clinical benefit associated with long term survival.¹⁵² Because OOPD found Revcovi to be clinically superior based on greater efficacy, it did not need to determine if Revcovi also provided greater safety. Efficacy and safety are alternative prongs for clinical superiority. Nothing in OOPD’s reasoning suggests that the fact that Revcovi was “not less safe than Adagen” was a factor in OOPD’s finding of clinical superiority based on greater effectiveness or that if Revcovi had been less safe, then Revcovi could not have been found to be clinically superior. Nor do OOPD’s statements mean that FDA has a policy that in order to be clinically superior based on efficacy, a subsequent drug must also provide safety at least comparable to the previously approved drug.

Second, Jazz cites an ODD memo regarding a potential plausible hypothesis of clinical superiority of enteric-coated cysteamine (later named Procysbi (cysteamine bitartrate)) over another cysteamine product for the treatment of cystinosis.¹⁵³ Enteric-coated cysteamine had ODD for the treatment of cystinosis based on a plausible hypothesis that enteric-coated cysteamine may be clinically superior to the previously approved cysteamine product for the same disease based on safety by causing less nausea and vomiting.¹⁵⁴ Note that at the time of the cited memo, OOPD was not conducting an analysis of whether the sponsor had, in fact, demonstrated clinical superiority. The memo responded to a June 23, 2008, letter from the sponsor asking to update the hypothesis that was the basis of the ODD.¹⁵⁵ OOPD reviewed this request, and in the memo cited by Jazz, explained that OOPD assesses MCTPC “individually” (on a case-by-case basis) and considers factors including “the nature of the orphan indication, course of treatment for the indication, and benefits that could be obtained from the new product.”¹⁵⁶ The memo then states, as cited by Jazz, “Inherent in this analysis is the general assumption that changes in drug administration would maintain a similar or improved adverse event profile and similar efficacy.”¹⁵⁷ As explained below, this statement is consistent with and reflects the MCTPC standard we described above.

At the ODD stage, as is the case in the Procysbi memo, FDA does not have full safety, efficacy, and other data for the drug necessary to make a definitive determination about clinical

¹⁵¹ Jazz’s September 2021 Letter, *supra* note 11, at 2 footnote 4.

¹⁵² FDA, *Exclusivity Memorandum, DRU-2014-4675, Revcovi (elapegademase-lvlr)* at 3 (Oct. 14, 2020).

¹⁵³ Jazz’s September 2021 Letter, *supra* note 11, at 2 footnote 4; *see also* Sidley Slides, *supra* note 13, at 30.

¹⁵⁴ FDA, Review of Request for ODD for enteric-coated cysteamine, DRU-2006-2310 (Oct. 10, 2006) [hereinafter Procysbi Designation Memo].

¹⁵⁵ Letter from Ted Daley to Timothy Cote, *Orphan Drug Exclusivity Determination for Delayed-release Cysteamine Bitartrate Capsules (i.e., enteric-coated beads) for Treatment of Cystinosis, DRU-2006-2310* (Jun. 23, 2008). Note that there is no requirement for a sponsor to update the hypothesis of clinical superiority upon which an ODD is based. This sponsor seemingly wanted to know if OOPD would accept the hypothesis for clinical superiority as it anticipated later submitting a marketing application for which it wanted ODE.

¹⁵⁶ FDA, *Memorandum, Request for OOPD Opinion, DRU-2006-2310* (Mar. 3, 2009) [hereinafter Procysbi 2009 memo].

¹⁵⁷ *Id.*

superiority; therefore, for the plausible hypothesis analysis at the ODD stage, unless a safety or efficacy concern is readily apparent to the agency absent receipt of safety and efficacy data in the sponsor's application for approval, we generally assume that the drug provides comparable safety and efficacy.¹⁵⁸ At the approval stage, once such safety and efficacy data about the drug has been submitted in an application for marketing approval, that general assumption may or may not still apply, depending on what the submitted data shows. As we stated above, FDA may consider whether, for example, any adverse events documented within the drug's safety data submitted in its application for approval diminish the advantages of, for example, a change in route or frequency of administration. In that respect, as explained above, safety concerns could inform the MCTPC analysis, but a safety concern present in a subsequent drug that was not present in the previous drug would not automatically disqualify the drug from obtaining a MCTPC finding. As stated above, clinical superiority analyses can "vary depending on many factors"¹⁵⁹ and MCTPC "implies a more global assessment."¹⁶⁰

In the case of Procysbi, upon approval, FDA found that Procysbi was clinically superior to the previously approved cysteamine product Cystagon based upon a MCTPC finding. The reviewer noted that the safety profile for Procysbi and Cystagon were similar "although a higher incidence of GI AEs were observed in the pivotal trial with delayed-release cysteamine in comparison to Cystagon."¹⁶¹ If anything, this example shows that FDA has made a MCTPC finding upon approval where a drug was potentially less safe in at least one respect than the previously approved drug.

Third, Jazz cites to a memo about the clinical superiority of BeneFix (coagulation factor IX (recombinant)) based on safety to previously approved factor IX products for the prevention of bleeding in hemophilia B.¹⁶² The memo considers whether a demonstration of greater safety under 21 CFR § 316.3(b)(3)(ii) requires a demonstration of a single safety advantage without regard for other safety considerations, or a demonstration of an overall increase in safety considering all aspects of safety.¹⁶³ The memo does not conclude which standard is applicable, but finds that BeneFix provides greater safety under both standards.¹⁶⁴ Each of the quotations

¹⁵⁸ Jazz also cites to FDA's review of a request for ODD for Ravicti as another example of a requirement for comparable safety. See Sidley Slides, *supra* note 13, at 30. This is another example of FDA considering whether there is a plausible hypothesis of clinical superiority, not a demonstration of clinical superiority. In this example, FDA was concerned that the sponsor did not adequately explain why the new dosage form would represent a significant advantage over the previous dosage form, and FDA was concerned that the new dosage form could introduce new safety risks that were not accounted for in the sponsor's hypothesis. See FDA, *Review of Request for Orphan-Drug Designation*, 05-2035, Glycerol tri(4-phenylbutyrate) at 4 (Sep. 2, 2005) ("[I]t is unclear whether the glycerol byproduct of GT4P metabolism would pose its own safety risk in chronic use of the drug."). Thus, a safety concern was readily apparent to the agency at the designation stage absent receipt of safety data in the sponsor's application for approval. Without additional information about the potential safety of the drug and without additional information about the advantages of the drug, FDA was unable to determine there was a plausibly hypothesis of clinical superiority that would warrant ODE.

¹⁵⁹ 1992 Final Rule, 57 Fed. Reg. at 62078.

¹⁶⁰ OOPD Rebif memo, *supra* note 36, at 3.

¹⁶¹ FDA, *Review of an Amended Request for Orphan Drug Designation, 2006-2310, Procysbi (enteric-coated cysteamine)* at 6 (May 28, 2013) [hereinafter Procysbi Exclusivity Memo].

¹⁶² Jazz's September 2021 Letter, *supra* note 11, at 2 footnote 4.

¹⁶³ FDA, *Memorandum, Orphan Product Status of BeneFix Coagulation Factor IX (Recombinant)* (Jan. 21, 1997) [hereinafter "BeneFix memo"].

¹⁶⁴ *Id.*

that Jazz cites are in the context of considering whether one safety advantage needs to be compared to safety concerns in order to make an assessment about greater safety under 21 CFR § 316.3(b)(3)(ii). This is a different question than whether a drug can be clinically superior overall if it is less safe in one respect than the previously approved drug. The first quotation (i.e., “A significant risk associated with the new drug, that is not shared by the approved orphan, would likely render the new drug unapprovable”) is making the obvious point that significant new safety risks inform FDA’s evaluation of the fundamental safety of a drug for marketing approval under section 505 of the FD&C Act. The other two quotations (i.e., “it would be unreasonable to ignore an apparent risk that may outweigh the purported advantage of a new drug,” and “[s]ince there is no established risk to ‘outweigh’ the enhanced viral safety of BeneFix, the significant therapeutic advantage of BeneFix has not been outweighed by anything”) describe a situation where a safety risk associated with the subsequent drug would need to be considered in an overall assessment of safety, but not necessarily prevent a finding of greater safety. These quotations do not support Jazz’s position.

Fourth, Jazz cites FDA’s determination that Signifor LAR (pasireotide)—a “long-acting release” formulation—made a MCTPC by providing once-per-month dosing as compared to twice-per-day pasireotide to treat Cushing’s disease.¹⁶⁵ Specifically, Jazz cites to the statement that “[t]here are no notable differences in the safety and efficacy profiles between the immediate release and long-acting formulations.”¹⁶⁶ Again, stating that there are no notable differences in safety is not the same as stating that if Signifor LAR were less safe then it could not make a MCTPC. The exclusivity memorandum for Signifor LAR does not state that having comparable safety was a requirement to finding a MCTPC.¹⁶⁷

Overall, none of these examples support that FDA will consider a new drug to be clinically superior to a previously approved drug only if the new drug is at least as safe as the previously approved drug.

Finally, Jazz tries to argue from a policy perspective that finding clinical superiority based on one significant advantage to patients even if the drug is less safe in some other measure would undermine the value of the ODE incentive.¹⁶⁸ FDA disagrees. FDA interprets the purpose of the Orphan Drug Act to incentivize the development of better versions of drugs for the treatment or prevention of rare diseases or conditions. FDA believes that a drug may provide a significant therapeutic advantage to patients over a previously approved drug even if, for example, it is less safe in one measure than the previously approved drug. If new drugs were required to be at least as safe as the previously approved drugs, that would prevent a drug that provides a significant therapeutic advantage and otherwise meets FDA’s approval standard from coming to the market during the duration of the previously approved drug’s ODE. Implementing ODE requires balancing the need to incentivize the development of drugs for rare diseases or conditions and the need for patients to access better versions of such drugs. Requiring comparable safety on

¹⁶⁵ Sidley Slides, *supra* note 13, at 30.

¹⁶⁶ *Id.* (quoting clinical superiority findings available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings>).

¹⁶⁷ FDA, *Exclusivity Memorandum*, 09-2887 Signifor LAR (Apr. 3, 2019) [*hereinafter* Signifor Exclusivity Memo].

¹⁶⁸ Jazz’s September 2021 Letter, *supra* note 11, at 20. *See also id.* at 1 (“Because the concept of clinical superiority does not include regression, longstanding FDA policy requires the second-in-time drug to achieve at least comparable safety as the earlier drug”).

every measure before a drug can be found to be clinically superior would be an arbitrarily rigid requirement that would significantly delay approval of drugs with important therapeutic advantages for patients with rare diseases.

FDA has adopted a more nuanced approach to clinical superiority, where a potential MCTPC is considered in the overall context of the safety, efficacy, and other features of the drug to determine if there is an overall significant therapeutic advantage of the new drug. As FDA has stated, MCTPC “determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product.”¹⁶⁹ Improvements to drugs are not necessarily linear, where every version of a drug builds off and is better in every respect than the one that came before. An improvement in one respect may benefit patients, even if there is a disadvantage in another aspect of the drug. As FDA has stated, “there can not [sic] be an infinite number of comparison criteria if this provision of the regulation is to be meaningful.”¹⁷⁰ That is not to say that a small advantage provided by a new drug should overcome a large disadvantage also introduced by the drug; however, it would not serve the purpose of the Orphan Drug Act—and public health—if a drug were automatically disqualified from being clinically superior if it were less safe in one regard, while still meeting FDA’s approval standards for safety.

B. Lumryz is Clinically Superior to Xyrem and Xywav

Avadel has not contended that Lumryz has greater effectiveness than Xyrem and Xywav, and DN1 has concluded that “[t]here is no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav.”¹⁷¹ Avadel did present arguments why it believes that Lumryz provides greater safety than Xyrem and Xywav,¹⁷² but OOPD concludes that Avadel has not demonstrated that Lumryz provides greater safety than either Xyrem or Xywav.¹⁷³ DN1 has also concluded that Avadel’s arguments do not support a finding of greater safety of Lumryz over either Xyrem or Xywav.¹⁷⁴ Because Avadel has not demonstrated either greater effectiveness or greater safety, Lumryz can be deemed to be clinically superior over Xyrem and Xywav only if Lumryz makes a MCTPC over the previously approved drugs.¹⁷⁵ As explained below, FDA concludes that Lumryz makes a MCTPC over Xyrem and Xywav.

Based on a review of the arguments submitted by Avadel and Jazz, consultation with DN1,¹⁷⁶ and consultation with two board certified sleep experts in FDA,¹⁷⁷ OOPD finds that Lumryz makes a MCTPC over Xyrem and Xywav by providing a once-nightly dosing regimen that

¹⁶⁹ 2013 Final Rule, 78 Fed. Reg. at 35124.

¹⁷⁰ See OOPD Rebif memo, *supra* note 36, at 3 (emphasis added).

¹⁷¹ DN1 Lumryz Consult, *supra* note 5, at 3. There has been no head-to-head study to directly compare Lumryz to Xyrem or Xywav.

¹⁷² See Avadel’s Exclusivity Claim, *supra* note 6; see also Avadel’s Exclusivity Claim Supplement, *supra* note 7.

¹⁷³ For the purposes of this analysis, OOPD will not include a response to each of Avadel’s claims of greater safety. OOPD ultimately finds Lumryz to be clinically superior to Xyrem and Xywav based on making a MCTPC, and Avadel’s arguments about greater safety do not factor into the MCTPC finding.

¹⁷⁴ DN1 Lumryz Consult, *supra* note 5, at 3.

¹⁷⁵ 21 CFR § 316.3(b)(3)(iii).

¹⁷⁶ DN1 Lumryz Consult, *supra* note 5.

¹⁷⁷ See Sleep Expert Consult, *supra* note 5.

avoids a nocturnal arousal to take a second dose. Crucial to this finding is that the three oxybate products are for the treatment of symptoms of narcolepsy—a chronic sleep disorder. The purpose of oxybate treatment is to consolidate a narcoleptic’s sleep to improve daytime symptoms of EDS and cataplexy.¹⁷⁸ As explained in more detail below, waking up to take a second dose of Xyrem and Xywav is antithetical to the goal of improving sleep. This is compounded by the fact that narcolepsy is a chronic condition and patients may need treatment for the remainder of their lives.

As explained by FDA’s sleep experts in greater detail in their consult, even with a single nocturnal arousal, there can be impairment of alertness and decline in cognitive performance the following day.¹⁷⁹ It is known that disrupting sleep, even briefly, changes sleep architecture—the normal pattern of NREM and REM cycles requisite for daily restoration.¹⁸⁰ As explained in section III.A of this document and by FDA’s sleep experts, when an arousal occurs (e.g., when waking up to take medication during the night after falling asleep), there is a shift in an EEG pattern—one that leads to a longer Stage W with alertness or consciousness, even if not remembered.¹⁸¹ The duration of time in Stage W necessary to take the second dose and fall back asleep is prolonged and will adversely impact WASO.¹⁸² In treating sleep disorders, including narcolepsy, the goal is to maximize the time in sleep and minimize wake time (i.e., minimize WASO).¹⁸³ Hence, nocturnal arousals should be avoided—especially in those with sleep disorders—as the goal of treatment is to restore normal sleep architecture.¹⁸⁴

Xyrem and Xywav are administered in two divided doses, with the first dose taken at bedtime and second dose taken 2.5 to 4 hours later. FDA’s sleep experts have concluded that awakening to take a second dose of Xyrem or Xywav is not optimally supportive of the continual sleep necessary for narcolepsy patients to restore sleep architecture and daytime alertness with more normal functioning.¹⁸⁵ Such dosing necessitates awakening from sleep, prompting a nocturnal arousal.¹⁸⁶ Both Xyrem and Xywav labeling explain that after a dose, it usually takes at least 5 to 15 minutes to fall asleep, which means it usually takes at least 5 to 15 minutes to fall back asleep after taking the second dose.¹⁸⁷ Awakening to take a second dose necessarily disrupts sleep and causes fragmented sleep.¹⁸⁸ A person with disrupted sleep cannot simply return to sleep and resume their normal sleep cycle.¹⁸⁹ Disruption of sleep leads to the inability to enter Stage N3, or disruption of N3, and such individuals will revert back to Stage W and subsequently progress to Stage N1 sleep and so forth.¹⁹⁰ So, upon taking a second dose of Xyrem or Xywav,

¹⁷⁸ Scammell, *Treatment*, *supra* note 77.

¹⁷⁹ See Sleep Expert Consult, *supra* note 5, at 7-8; see also Cirelli, *supra* note 46.

¹⁸⁰ Sleep Expert Consult, *supra* note 5, at 8; see also Philip, *supra* note 61, at 244-245.

¹⁸¹ Kirsch, *supra* note 48; see also Philip, *supra* note 61, at 244-245.

¹⁸² Sleep Expert Consult, *supra* note 5, at 5; see also Suni, *supra* note 62.

¹⁸³ Sleep Expert Consult, *supra* note 5, at 5.

¹⁸⁴ *Id.* at 6; see also Scammell, *Treatment*, *supra* note 77.

¹⁸⁵ See Sleep Expert Consult, *supra* note 5, at 7.

¹⁸⁶ *Id.* at 7 footnote 45 (“It is self-evident that an arousal occurs upon taking the second dose of Xyrem or Xywav because some degree of consciousness or alertness is needed for the voluntary movements involved in taking medicine”).

¹⁸⁷ Xyrem 2023 Labeling, *supra* note 86, at section 2.3; Xywav 2023 Labeling, *supra* note 93, at section 2.4.

¹⁸⁸ Sleep Expert Consult, *supra* note 5, at 5.

¹⁸⁹ Sleep Expert Consult, *supra* note 5, at 8.

¹⁹⁰ *Id.* at 6; see also Berry *supra* note 64, at 22-33.

after the minimum 5-15 minutes to return to sleep, such sleep does not resume where the patient left off to take their medication.¹⁹¹ If patients do not intentionally awaken to take the second dose (e.g., by setting an alarm), the effect of the drug will wear off, and the patients may awaken anyway and need the second dosing to return to sleep.¹⁹² As explained above, the disruption changes sleep architecture and will increase WASO and is something to be avoided in the narcoleptic patient, if possible.¹⁹³

In contrast to Xyrem and Xywav, Lumryz is an extended-release formulation that is indicated to be administered once daily at bedtime. Importantly, patients on Lumryz do not need to wake mid-sleep to take a second dose. The dosing regimen of Lumryz “provides an opportunity for narcolepsy patients to achieve normal sleep architecture, which is not a possibility for a patient on Xyrem or Xywav who must either wake up to take a second dose (disrupting sleep architecture) or allow the drug to wear off after 2.5-4 hours (reverting patients back to their naturally occurring, disrupted sleep architecture).”¹⁹⁴ This is medically relevant because the purpose of oxybate therapy is to improve sleep consolidation.¹⁹⁵ Additionally, the benefit provided by the dosing regimen of Lumryz is germane to several of the factors that FDA may consider when determining if a drug makes a MCTPC.¹⁹⁶ Lumryz’s extended release properties provide for longer periods between doses, which is significant not only because it reduces the nightly number of doses from two to one but also because it eliminates the need to awaken in the middle of sleep to take a second dose. FDA considers this to be significantly more convenient for patients, an advancement in the ease of drug administration, and a reduction in treatment burden. As explained by FDA’s sleep experts, patients taking Xyrem and Xywav typically prepare both doses before bed, may need to set an alarm to wake up at the proper time to take the second dose, and then may require 5-15 or more minutes to return to sleep. Aside from the medical benefits of not having to awaken to take a second dose already explained above, it is inherently more convenient, easier, and less burdensome for patients to forgo that process on a nightly basis. Importantly, this is in the context of a chronic neurological condition that requires potentially lifelong treatment.

i. MCTPC Finding Consistent with Past Precedent

Our basis for finding a MCTPC for Lumryz is similar to FDA’s MCTPC finding for Procysbi. As introduced above, Procysbi is an enteric-coated cysteamine product that has ODD for the treatment of cystinosis. The ODD was based in part on a plausible hypothesis that enteric-coated cysteamine would be clinically superior to the previously approved cysteamine product, Cystagon, for the same disease based on safety by causing less nausea and vomiting.¹⁹⁷ Procysbi

¹⁹¹ Sleep Expert Consult, *supra* note 5, at 8.

¹⁹² *Id.* at 7.

¹⁹³ *Id.* at 6.

¹⁹⁴ *Id.* at 8.

¹⁹⁵ Scammell, *Treatment*, *supra* note 77.

¹⁹⁶ *See, e.g.*, 2013 Final Rule, 78 Fed. Reg. at 35125 (“The following factors, when applicable to severe or life-threatening diseases, may in appropriate cases be taken into consideration when determining whether a drug makes a major contribution to patient care: convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration”).

¹⁹⁷ Procysbi Designation Memo, *supra* note 154.

was first approved on April 20, 2013, and to be eligible for ODE, FDA required a demonstration of clinical superiority over Cystagon. Cystagon was labeled to be dosed every six hours, whereas Procysbi was labeled to be dosed every 12 hours (a reduction of 50%).¹⁹⁸ By requiring dosing every six hours, patients taking Cystagon would be required to awaken from sleep to take a dose in order to administer the drug as labeled.¹⁹⁹ FDA concluded that many patients taking Cystagon were unable to follow the strict six-hour-dosing schedule, and that strict six-hour-dosing was required for the drug to be clinically beneficial (by maintaining white blood cell cystine levels below 1.0 nmol/½ cystine/mg protein).²⁰⁰ FDA found that Procysbi made a MCTPC over Cystagon, because Procysbi is effective at 12-hour-dosing, and many patients are unable to follow Cystagon's strict six-hour-dosing, especially due to the need to awaken from sleep to ensure a timely dose.²⁰¹ Similar to Procysbi, Lumryz provides for 50% reduction in dosing frequency that eliminates the need to awaken to take a dose in order to achieve the medication's intended benefit.

ii. Consideration of Sodium Differences

OOPD has also considered whether other relevant factors inform whether Lumryz makes a MCTPC over Xyrem and Xywav.²⁰² Specifically, we considered the sodium differences between Lumryz and Xywav. At the recommended daily dose of 6 g to 9 g, Lumryz contains approximately 1,100 mg to 1,640 mg of sodium whereas Xywav contains 87 mg to 131 mg.

At the recommended daily dose of 6 g to 9 g, Xyrem and Lumryz both have the same sodium content (approximately 1,100 mg to 1,640 mg). The difference in sodium content between Xywav and Xyrem was explained in a DN1 consult for OOPD's Xywav ODE determination:

Given the differences in sodium content between Xywav and Xyrem, Xywav is safer and thus clinically superior to Xyrem in the following: all patients with narcolepsy; the substantial proportion of the narcolepsy population that is salt-sensitive (i.e., individuals who have greater changes in blood pressure with changes in salt intake than those who are not salt sensitive, representing about 50% of the general population); the substantial proportion of the narcolepsy population that is hypertensive (about 30% of the general population is hypertensive); and the substantial proportion of the narcolepsy population (39%) who cannot be prescribed Xyrem due to co-existing medical conditions that can be made worse as a result of the high sodium content of Xyrem.²⁰³

This division consult also states:

¹⁹⁸ Procysbi Exclusivity Memo, *supra* note 161, at 9-10.

¹⁹⁹ *Id.* at 5.

²⁰⁰ *Id.* at 9.

²⁰¹ *Id.* at 10. The reviewer also observed that the safety profile for Procysbi and Cystagon were similar "although a higher incidence of GI AEs were observed in the pivotal trial with delayed-release cysteamine in comparison to Cystagon." *Id.* at 6. The clinical superiority finding for Procysbi reflects multiple MCTPC factors, such as longer period between doses, increased ease of administration, and reduced treatment burden.

²⁰² See OOPD Rebif memo, *supra* note 36, at 3 ("an assessment of the safety or effectiveness of the new form of the subsequent product might be considered in determining whether the drug made a major contribution to patient care").

²⁰³ DN1 2020 Xywav Consult, *supra* note 99, at 6.

The relationship between daily salt intake and cardiovascular morbidity is widely accepted, as is the need for salt intake to be generally restricted and not only in subjects with conditions such as hypertension, cardiac failure, and impaired renal function. The difference in sodium content between Xywav and Xyrem is both substantial and clinically meaningful when daily sodium intake requires restriction in patients who concomitantly have conditions such as cardiac failure, hypertension, and renal impairment. Xywav rather than Xyrem will be the medication of choice in such patients. Such patients, especially those with hypertension, may constitute a significant proportion of those with cataplexy and excessive daytime sleepiness in narcolepsy. The difference in sodium content between Xywav and Xyrem is also very likely to be clinically meaningful in all patients with narcolepsy, including those who are salt sensitive.²⁰⁴

OOPD found Xywav to be clinically superior (within the meaning of the orphan-drug regulations) to Xyrem because the reduction of sodium “will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.”²⁰⁵

OOPD acknowledges that the sodium content of Lumryz raises the same safety concern that was present for Xyrem and that is not present with Xywav. The agency stated in the consult response quoted above that the difference in sodium content between Xywav and Xyrem is “very likely to be clinically meaningful in all patients with narcolepsy”²⁰⁶ and that “[g]iven the differences in sodium content between Xywav and Xyrem, Xywav is safer and thus clinically superior to Xyrem in [. . .] all patients with narcolepsy.”²⁰⁷ The logic of these statements, if extended here, would mean that the difference in sodium content between Xywav and Lumryz is likely to be clinically meaningful in all patients with narcolepsy and that Xywav is safer than Lumryz in all such patients, albeit based solely on one specific measure, i.e., reduced sodium. Nonetheless, FDA has concluded that Lumryz is clinically superior to Xywav as a MCTPC given the benefit of Lumryz’s once-nightly dosing despite Xywav’s greater safety due to reduced sodium. First, as explained above, there is no requirement for comparable safety when making a MCTPC finding, and finding clinical superiority based on one parameter — greater safety, greater efficacy, or a MCTPC — is sufficient to meet the clinical superiority standard.²⁰⁸ Second, for the reasons explained below, we believe that the benefit of Lumryz’s once-nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy patients. Neither the statute nor regulations require a MCTPC to benefit the entire patient population for which a drug is intended.

Although it is widely accepted that individuals should limit sodium intake generally, the warning in Lumryz’s labeling regarding sodium is directed only at “patients sensitive to sodium intake”

²⁰⁴ *Id.* at 9-10.

²⁰⁵ FDA, Clinical Superiority Findings, available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings>.

²⁰⁶ DN1 2020 Xywav Consult, *supra* note 99, at 10.

²⁰⁷ *Id.* at 6.

²⁰⁸ As OOPD stated in the Rebif example above, for one drug to be clinically superior in one parameter, it does not also need to be at least equal in all others. See OOPD Rebif memo, *supra* note 36, at 3.

such as “those with heart failure, hypertension, or renal impairment.”²⁰⁹ For narcolepsy patients who are not sensitive to sodium intake, OOPD concludes that a once-nightly dosed oxybate drug will provide a significant therapeutic advantage. It is true that patients who are not sensitive to sodium could also benefit from a reduction in sodium, but we consider the benefit offered by once-nightly dosing to outweigh the risk of increased sodium intake in such patients because having to wake up to take a second dose is antithetical to oxybate’s goal of improving sleep; disrupting sleep contributes to chronic sleep loss, which is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health; and there are other ways such patients may reduce sodium in their diet.²¹⁰ For narcolepsy patients who are sensitive to sodium, healthcare practitioners would need to weigh the benefits of once-nightly dosing against the severity of the patient’s sodium sensitivity and the nature of their comorbidities to determine whether, in the practitioners’ judgment, use of Lumryz or Xywav was appropriate. For certain sodium-sensitive patients with narcolepsy, the benefit offered by once-nightly dosing would outweigh the risk of increased sodium intake for the same reasons (e.g., having to wake up to take a second dose is antithetical to oxybate’s goal of improving sleep; disrupting sleep contributes to chronic sleep loss, which is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health; and there are other ways such patients may reduce sodium in their diet).²¹¹

For a drug to make a MCTPC, the drug should provide adequate safety to meet the approval standard (not necessarily the same or greater safety as a previously approved drug). FDA has weighed the benefits and the risks of Lumryz and determined that the safety profile is adequate to meet the requirements for marketing approval.²¹² Thus, although Lumryz has an increased sodium burden compared to Xywav, the safety risk from such an increase is not significant enough to preclude Lumryz from meeting the requirements for marketing approval. The safety risk associated with sodium for Lumryz is mitigated by labeling with an appropriate warning and precaution for patients sensitive to high sodium intake,²¹³ as has been done for Xyrem.²¹⁴

In summary, OOPD concludes that the benefits of Lumryz’s once-nightly dosing rise to the level of making a MCTPC because Lumryz’s dosing provides for oxybate therapy that does not involve disrupting or fragmenting sleep, whereas Xyrem and Xywav necessitate a nocturnal awakening to take a second dose, which disrupts sleep architecture in patients with known sleep

²⁰⁹ Lumryz labeling, *supra* note 105, at section 5.8.

²¹⁰ Sleep Expert Consult, *supra* note 5, at 2. Jazz argues that approving Lumryz would undermine FDA’s policy regarding the benefits of reducing daily sodium intake. Jazz’s September 2021 Letter, *supra* note 11, at 20. FDA acknowledges the importance of reducing sodium intake generally, and this determination does not erode that stance merely because we have concluded that sodium can be reduced by other means for patients who would benefit from taking this drug.

²¹¹ We note that the DN1 Lumryz Consult explains that “the available safety data for Lumryz do not indicate that the higher sodium content of each dose of that drug is reflected in a greater incidence of adverse events than is observed with equivalent doses of Xywav.” DN1 Lumryz Consult, *supra* note 5, at 3.

²¹² DN1 Lumryz Consult, *supra* note 5, at 3 (“the safety profile of Lumryz meets the Agency’s standards for approval.”). *See also* OOPD Rebif memo, *supra* note 36, at 3 (“A more meaningful standard is a significant therapeutic benefit in terms of increased effectiveness and adequate safety, or increased safety and adequate effectiveness.”).

²¹³ *See* Lumryz Labeling, *supra* note 105, at section 5.8.

²¹⁴ *See* Xyrem 2023 Labeling, *supra* note 86, at section 5.8.

disorder. This decision is based on consultations with DN1 and FDA sleep experts and relies on the scientific understanding about treating narcolepsy by minimizing nocturnal arousals and consolidating sleep. OOPD believes that the science supports a finding that the MCTPC provided by Lumryz over Xyrem and Xywav has been demonstrated.

V. Jazz's Arguments Are Not Persuasive

A. Safety

Jazz argues that Lumryz does not provide greater safety than Xyrem and Xywav and is less safe than Xyrem and Xywav in several ways.²¹⁵ As explained above, OOPD's determination that Lumryz is clinically superior to Xyrem and Xywav is not based on Lumryz providing greater safety than Xyrem and Xywav. Therefore, OOPD has not responded to each safety argument from Jazz.²¹⁶ In addition, OOPD has acknowledged above that Lumryz has a higher sodium content than Xywav and addressed why Lumryz is still clinically superior to Xywav. Finally, as explained below, OOPD is not convinced by Jazz's remaining arguments that there are additional ways that Lumryz is less safe than Xyrem and Xywav.

First, Jazz argues that the risk of falls may be greater with Lumryz than with Xyrem and Xywav.²¹⁷ Jazz characterizes its argument as speculation ("one can equally speculate about alternate scenarios in which nocturnal awakenings and falls increase due to [Lumryz's] extended-release formulation") and hypothesis ("[Lumryz] introduces its own hypothetical fall risks").²¹⁸ Jazz speculates that because Lumryz is an extended release formulation, if a patient were to awaken and get out of bed, the patient using Lumryz would have more active drug in their blood compared to Xyrem and Xywav and could be at a higher risk for falls.²¹⁹ Jazz also states that Lumryz has "apparently higher rates of enuresis" (i.e., bedwetting), which may lead to more falls.²²⁰ Jazz's claim is based on a cross-study comparison showing a higher rate of enuresis with Lumryz compared to Xyrem and Xywav. Cross-study comparisons refers to drug studies in which a given drug is independently investigated from a second drug and does not allow direct comparison of results from one study to the other. Inferences cannot be reliably drawn as the two study populations and conditions of each study may not be the same. OOPD consistently has rejected use of such comparisons to conclude one drug has a higher rate of an adverse event than another drug. Nevertheless, even if Lumryz were to have a higher rate of enuresis than Xyrem and Xywav, Jazz's argument is based on speculation that enuresis may lead to falls, because the patient may wake up, get out of bed, and change their sheets.²²¹ DN1 agrees

²¹⁵ Jazz's September 2021 Letter, *supra* note 11, at 6-15.

²¹⁶ See Jazz's September 2021 Letter, *supra* note 11, at 6-15. These arguments include that the pivotal REST-ON study was not designed to detect superiority (at 7-8), that findings of greater safety for other drugs were based on more data than is available for Lumryz (at 8-9), that there is insufficient evidence to support that the risk of falls is reduced with Lumryz compared to Xyrem and Xywav (at 10-13), that there is insufficient evidence to support that Lumryz will have better rates of adherence than Xyrem and Xywav (at 13-15), and that there is insufficient evidence to support that Lumryz will have lower rates of diversion (i.e., illegally transferring the drug to another person) than Xyrem and Xywav (at 15).

²¹⁷ Jazz's September 2021 Letter, *supra* note 11, at 12-13.

²¹⁸ *Id.*

²¹⁹ *Id.* at 12.

²²⁰ *Id.*

²²¹ *Id.*

that Jazz's arguments are speculative and is not aware of any data to support their arguments.²²² Ultimately, as Jazz admits, its arguments are based on speculation and hypotheses, and there are no scientific data to support a conclusion that there is a higher risk for falls with Lumryz compared to Xyrem and Xywav.

Second, Jazz argues that Lumryz may have worse adherence rates than Xyrem and Xywav.²²³ Jazz states that patients taking Lumryz may decide to skip taking their medication on nights when they do not expect to get 8-10 hours of sleep before they need to awaken the next day, or on nights where they do not limit fluid intake or consume alcohol.²²⁴ Jazz contrasts this with patients taking Xyrem or Xywav who, according to Jazz, in similar situations may choose to forgo the second dose on a given night instead of forgoing oxybate treatment entirely on such a night.²²⁵ These assertions that Lumryz will have lower rates of adherence than Xyrem and Xywav appear to be based upon speculation,²²⁶ and we are unaware of any scientifically valid evidence to suggest that adherence should be different between the two drugs.²²⁷

Third, Jazz speculates that Lumryz may have higher rates of diversion (i.e., illegally transferring the drug to another person) than Xyrem and Xywav.²²⁸ Jazz suggests without evidence that Lumryz has "greater concealability and ease of transport" compared to Xyrem and Xywav, which would make Lumryz easier to divert.²²⁹ Jazz also suggests without evidence that multiple doses of Lumryz can more easily be combined into a single, more powerful dose than Xyrem and Xywav.²³⁰ Jazz presents no evidence that Lumryz would be easier to conceal, transport, and combine into a large dose than Xyrem and Xywav, and FDA is not aware of any such data.²³¹

Fourth and finally, Jazz argues that Lumryz is less safe than Xyrem and Xywav because the dose of Lumryz cannot be adjusted, whereas the dose of Xyrem and Xywav can be adjusted. Specifically, Lumryz comes in four dosage strengths: 4.5 g, 6 g, 7.5 g, and 9 g,²³² and thus the dose of Lumryz can be adjusted to those four strengths. Xyrem and Xywav are oral solutions, in concentrations of 0.5 g per mL,²³³ and administered using a dosing syringe that measures dosing

²²² DN1 Lumryz Consult, *supra* note 5 at 6.

²²³ Jazz's September 2021 Letter, *supra* note 11, at 14-15.

²²⁴ *Id.* at 14.

²²⁵ *Id.*

²²⁶ We also note that alcohol ingestion is contraindicated for all three medicines.

²²⁷ Jazz also argues: "FT218 patients who do take their medication in these scenarios may also be non-adherent and at greater risk. Patients who take their FT218 with less than 8-10 hours to spend in bed before arising the next morning will be at greater risk of next-day impairment. And patients who do not follow Avadel's recommendation to limit fluid intake for 'several hours before dosing,' or who ingest alcohol, will be at greater risk of enuresis, bed exits, falls, serious respiratory depression, and death." Jazz's September 2021 Letter, *supra* note 11, at 14. The DN1 consult states, and OOPD agrees that: "This is again a speculative argument. There should not be a significant difference in the risks cited between Lumryz and Xywav/Xyrem, if those drugs are used as recommended in labeling." DN1 Lumryz Consult, *supra* note 5, at 6.

²²⁸ Jazz's September 2021 Letter, *supra* note 11, at 15.

²²⁹ *Id.*

²³⁰ *Id.*

²³¹ DN1 Lumryz Consult, *supra* note 5, at 7.

²³² Lumryz labeling, *supra* note 105, at section 3.

²³³ Xyrem 2023 Labeling, *supra* note 86, at section 3; Xywav 2023 Labeling, *supra* note 93, at section 3.

increments of 0.25 g.²³⁴ Jazz argues that the limited ability to dose adjust Lumryz makes it less safe than Xyrem and Xywav for patients who would need to adjust the dose, including patients taking the anti-epileptic medication divalproex, patients taking other central nervous system (“CNS”) depressants, and patients who are hepatically impaired.²³⁵

Regarding patients taking divalproex sodium, no significant pharmacokinetic interaction between Lumryz and divalproex sodium was observed in a drug-drug interaction study conducted by Avadel, so Lumryz’s labeling does not include a specific dose reduction recommendation when Lumryz is co-administered with divalproex sodium.²³⁶ Therefore, a specific dose reduction recommendation, such as that present in Xyrem and Xywav’s labeling related to Xyrem and Xywav patients taking divalproex sodium, is not necessary for Lumryz patients also taking divalproex sodium. Although FDA concluded that a pharmacodynamic interaction between Lumryz and divalproex sodium cannot be ruled out given that both Lumryz and divalproex sodium are CNS depressants, it has determined that the description of the general risks associated with use of CNS depressants in section 5.1 of Lumryz’s labeling is sufficient to inform healthcare prescribers of the risks associated with using Lumryz with other CNS depressants, including divalproex sodium.²³⁷

Regarding patients taking CNS depressants, the labeling for Xyrem, Xywav, and Lumryz have a contraindication for the use of some CNS depressants (i.e., alcohol and sedative hypnotics) with each of those drugs. The labeling for all three drugs contains the same warning that “Use of other CNS depressants may potentiate the CNS-depressant effects of” Xyrem/Xywav/and Lumryz,²³⁸ and a recommendation that “[i]f use of these CNS depressants in combination with” Xyrem/Xywav/Lumryz “is required, dose reduction or discontinuation of one or more CNS depressants” (including Xyrem/Xywav/Lumryz) “should be considered.”²³⁹ Therefore, a patient taking Xyrem or Xywav and another CNS depressant has the option to reduce the dose of Xyrem/Xywav or the other CNS depressant (along with the option to discontinue Xyrem/Xywav or the other CNS depressant). A patient taking Lumryz and another CNS depressant has the option to reduce the dose of Lumryz to one of the set doses below the maximum of 9 g (4.5 g, 6 g, 7.5 g) or reduce the dose of the other CNS depressant (along with the option to discontinue Lumryz or the other CNS depressant). A patient taking Xyrem or Xywav and another CNS depressant may have more options for dose adjustment than a patient taking Lumryz and another CNS depressant, but this does not mean that Lumryz is less safe than Xywav and Xyrem in patients taking another CNS depressant. Lumryz’s labeling mitigates the risk posed by concurrent use of another CNS depressant by providing the same warning in section 5.1 as provided by Xyrem and Xywav. Lumryz patients have the option to reduce the dose of Lumryz to one of the set doses or reduce the dose of the other CNS depressant. Patients who cannot

²³⁴ Xyrem 2023 Labeling, *supra* note 86, at Instructions for Use; Xywav 2023 Labeling, *supra* note 93, at Instructions for use.

²³⁵ Jazz’s September 2021 Letter, *supra* note 11, at 19-20.

²³⁶ DN1 Lumryz Consult, *supra* note 5, at 7.

²³⁷ See Clinical Pharmacology Review, NDA 214755 (October 14, 2021); see Addendum to Clinical Pharmacology Review, NDA 214755 (May 24, 2022).

²³⁸ Xyrem 2023 Labeling, *supra* note 86, at section 7.1; Xywav 2023 Labeling, *supra* note 93, at section 7.1; and Lumryz Labeling, *supra* note 105, at section 7.1.

²³⁹ Xyrem 2023 Labeling, *supra* note 86, at section 5.1; Xywav 2023 Labeling, *supra* note 93, at section 5.1; and Lumryz Labeling, *supra* note 105, at section 5.1.

reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g might not be able to use Lumryz but may be able to use Xyrem and Xywav. This in theory could be a disadvantage of Lumryz for this very particular set of patients (i.e., patients taking oxybate and another CNS depressant who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g), but Jazz has provided no evidence to support and FDA is not aware of any such evidence that this population even exists.²⁴⁰

Finally, regarding patients who are hepatically impaired, Jazz's September 2021 Letter states that "1.8% of U.S. adults have been diagnosed with liver disease," and that "it is reported that diseases of the digestive system (including liver disease) are more frequently reported in patients with narcolepsy compared to the general population."²⁴¹ This statistic does not provide an estimate of the number of narcolepsy patients with hepatic impairment, but according to DN1, patients with narcolepsy have not been reported to have coexisting hepatic impairment.²⁴² Nevertheless, for patients with hepatic impairment, the labeling for Xyrem and Xywav recommends that the starting dose should be reduced by half,²⁴³ whereas the labeling for Lumryz states that Lumryz "should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made with the available dosage strengths."²⁴⁴ However, the labeling also states that "[p]atients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available."²⁴⁵ Therefore, Lumryz is labeled for use by some patients with hepatic impairment, but not all such patients. This does not mean that Lumryz is less safe than Xyrem and Xywav in patients with hepatic impairment because when used as labeled, Lumryz should not be used in patients with hepatic impairment who cannot be switched to Lumryz.

In summary, the limited ability to adjust Lumryz's dosage compared to Xyrem and Xywav does not make Lumryz less safe than Xyrem or Xywav. At most, the increased ability to adjust the dose of Xyrem and Xywav compared to Lumryz provides a minor convenience. For the potential limited number of patients who require a lower or more adjustable dose (i.e., (1) patients taking oxybate and another CNS depressant who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g, and (2) patients with hepatic impairment that cannot be switched to Lumryz), Lumryz may not be the right product for them. Nevertheless, given the paucity of evidence supporting the existence of such population, we still conclude that Lumryz makes a MCTPC over Xyrem and Xywav by providing a once-nightly dosing regimen. As discussed above, MCTPC requires a "global assessment" and there "can not [sic] be an infinite number of

²⁴⁰ Jazz's September 2021 Letter, *supra* note 11, at 19 footnote 104 states, "in the latest Xywav and Xyrem REMS Assessment Report, e.g., 6.2% of patients reported use of benzodiazepines, 4.6% reported use of muscle relaxants, and 4.3% reported use of opioid analgesics and subsequently received a shipment of Xyrem or Xywav." This does not reflect a percentage of patients who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g.

²⁴¹ Jazz's September 2021 Letter, *supra* note 11, at 19 footnote 104.

²⁴² DN1 Lumryz Consult, *supra* note 5, at 8.

²⁴³ Xyrem 2023 Labeling, *supra* note 86, at section 8.6; Xywav 2023 Labeling, *supra* note 93, at section 8.6.

²⁴⁴ Lumryz Labeling, *supra* note 105, at section 8.6.

²⁴⁵ *Id.*

comparison criteria.”²⁴⁶ The advantage of Lumryz’s once-nightly dosing is a significant advantage for patients who can take Lumryz and rises to the level of a MCTPC. What is more, Jazz has not demonstrated any safety concerns regarding Lumryz compared to Xyrem and Xywav, aside from the previously discussed lower sodium of Xywav compared to Lumryz. OOPD has already factored in the safety risk associated with the differences in the content of sodium between Lumryz and Xywav, as discussed above, and concluded that Lumryz makes a MCTPC.

B. MCTPC

Jazz also raised several arguments why Avadel has not met the standard to demonstrate that Lumryz makes a MCTPC over Xyrem and Xywav.

First, Jazz suggests that head-to-head comparative trials should be required for FDA to find that Lumryz makes a MCTPC.²⁴⁷ We do not agree; comparative trials are not required for a demonstration of MCTPC. The definition of “clinically superior” in the regulation states that demonstrating greater effectiveness requires direct comparative clinical trials “in most cases,” and that demonstrating greater safety requires direct comparative clinical trials “in some cases,”²⁴⁸ but similar or comparable language for a MCTPC is absent.²⁴⁹ Consistent with the regulation, FDA does not require direct comparative clinical trials to demonstrate that a drug makes a MCTPC.²⁵⁰ Additionally, the types of factors that FDA considers when determining MCTPC (e.g., convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration)²⁵¹ are not typically studied in a clinical trial for marketing approval.

²⁴⁶ OOPD Rebuttal memo, *supra* note 36, at 3.

²⁴⁷ Jazz’s September 2021 Letter, *supra* note 11, at 15; *see also* Sidley Letter, *supra* note 12, at 9; *see also* Sidley Slides, *supra* note 13, at 31.

²⁴⁸ The clinical superiority findings for BeneFix and Xywav are two examples where FDA found greater safety without direct comparative trials. For BeneFix, FDA concluded that even without direct comparative trials, there was an established epidemiological understanding that certain viruses can be transmitted by plasma-derived coagulation factor IX preparations, and that because those viruses do not exist in the source material for BeneFix, it was reasonable to conclude that the risk of transmitting these viruses is removed for treatment with BeneFix compared to the previously approved drugs. *See* BeneFix memo, *supra* note 163, at 2. Similarly for Xywav, FDA concluded that even without comparative trials, Xywav was clinically superior to Xyrem based on the established scientific knowledge that Xywav’s reduced sodium would be clinically meaningful in reducing cardiovascular morbidity as compared to Xyrem. *See* Xywav Exclusivity Memo, *supra* note 99.

²⁴⁹ 21 CFR § 316.3(b)(3).

²⁵⁰ *See, e.g.,* FDA, *Exclusivity Memorandum DRU-2012-3825, Valtoco (diazepam nasal spray)* (Jan. 10, 2020) (finding an intranasal spray formulation makes a MCTPC over a rectal gel formulation without head-to-head comparative trials, because rectal administration is inherently invasive for the patient and difficult to administer, whereas intranasal administration is inherently more comfortable); Signifor Exclusivity Memo, *supra* note 167 (finding an intramuscular injection dosed once monthly makes a MCTPC over a subcutaneous injection dosed twice daily without head-to-head comparative trials, because of the greatly reduced injections per month); FDA, *Exclusivity Memorandum DRU-2015-5130, Ultomiris (ravulizumab-cwvz)* (Sep. 4, 2020) (finding dosing every eight weeks makes a MCTPC over dosing every two weeks without head-to-head comparative trials, because of the heavy burden associated with each dose); Procybsi Exclusivity Memo, *supra* note 161 (finding dosing every 12 hours makes a MCTPC over dosing every six hours without head-to-head comparative trials, because many patients were unable to follow a strict six-hour-dosing, especially due to the need to awaken from sleep to ensure a timely dose).

²⁵¹ 2013 Final Rule, 78 Fed. Reg. at 35125.

Jazz points to quotations from the regulation preambles to suggest that head-to-head comparative trials should be required for FDA to find that Lumryz makes a MCTPC. Specifically, Jazz cites the 1992 Final Rule, where it states, “While comparative trials are, of course, preferred and will usually be required, it is possible that, in some circumstances, a demonstration of a major contribution to patient care can be made without such trials.”²⁵² Although this comment in the preamble could suggest that findings of MCTPC will usually be supported by comparative trials, the statement makes clear that a demonstration of MCTPC does not require such trials.²⁵³ More importantly, in practice, FDA has not required comparative trials to support findings of MCTPC.²⁵⁴ Jazz also points to the 1992 Final Rule, where it states, “As stated, the kinds of data needed to demonstrate clinical superiority for purposes of the Orphan Drug Act will be the same as the kinds of data required to allow label claims of superiority.”²⁵⁵ In context, this quotation is discussing the final rule, and the words “[a]s stated” mean “as stated in the final rule.”²⁵⁶ As explained above, the final rule requires clinical trials “in most cases” to demonstrate greater efficacy, and “in some cases” to demonstrate greater safety, but does not require clinical trials for a MCTPC.²⁵⁷ Because the quotation is referring to what is stated in the final rule, it cannot be read to superimpose a requirement that there be clinical trials to demonstrate a MCTPC particularly in light of text in the final rule that suggests otherwise.²⁵⁸ Additionally, in context, the quotation is responding to a comment on the proposed rule that suggested FDA require rigorous double-blind, head-to-head comparative clinical trials such as those required to support other comparative safety and efficacy claims.²⁵⁹ The comment only addressed types of studies for safety and efficacy claims. Thus, FDA’s response to the comment only addresses clinical superiority based on greater safety and efficacy. As stated above, in practice, FDA has not required comparative trials to support findings of MCTPC.²⁶⁰ Finally, if comparative trials were required to demonstrate a MCTPC, that would be inconsistent with FDA’s statements that MCTPC is judged on a case-by-case basis and that FDA may take into consideration factors, such as convenient treatment location and patient comfort. Comparative trials are not required to find that Lumryz makes a MCTPC.

Second, Jazz argues that the standard for finding a demonstration of clinical superiority is higher than the standard for finding a plausible hypothesis of clinical superiority and that Avadel has not met that standard for Lumryz. Jazz states that a “mere hypothesis is not enough to support a

²⁵² Jazz’s September 2021 Letter, *supra* note 11, at 15 (quoting 1992 Final Rule, 57 Fed. Reg. at 62079); *see also* Sidley Slides, *supra* note 13, at 31.

²⁵³ To the extent the statement could also be read to be discussing clinical superiority generally, it is simply restating the commonly accepted preference for demonstrating clinical superiority through greater efficacy or greater safety using comparative clinical trials, yet a sponsor can also demonstrate clinical superiority through a MCTPC without such trials.

²⁵⁴ *See supra* note 250.

²⁵⁵ Sidley Letter, *supra* note 12, at 9 (quoting 1992 Final Rule, 57 Fed. Reg. at 62078).

²⁵⁶ *See* 1992 Final Rule, 57 Fed. Reg. at 62078.

²⁵⁷ 21 CFR § 316.3(b)(3).

²⁵⁸ Jazz also cites to 21 CFR § 202.1(e)(6)(ii) regarding the level of evidence required for advertising claims. *See* Sidley Letter, *supra* note 12, at 9. The level of evidence required to make advertising claims comes from a different part of the regulation and is not connected to the level of evidence required to demonstrate clinical superiority for the purposes of the orphan-drug regulations.

²⁵⁹ *See* 1992 Final Rule, 57 Fed. Reg. at 62078.

²⁶⁰ *See supra* note 250.

finding of clinical superiority,”²⁶¹ because the standard for being eligible for ODE is higher than the “plausible hypothesis” standard and the sponsor bears the burden to demonstrate that its drug is in fact clinically superior to the previously approved drug.²⁶²

As a threshold matter, FDA agrees that the standard for clinical superiority for approval and ODE eligibility is higher than the “plausible hypothesis standard” for ODD.²⁶³ Specifically, the condition of clinical superiority for ODE eligibility requires that a sponsor “demonstrate” clinical superiority,²⁶⁴ and “different drug” status for a drug that is otherwise same drug as one with ODE also requires a demonstration of clinical superiority.²⁶⁵ FDA has explained that the difference in standards is meant to meet the intent of the Orphan Drug Act by encouraging “the development of improved versions of existing drugs” by having a lower standard for designation, “while protecting any applicable orphan-drug exclusivity” by requiring an actual demonstration of clinical superiority to overcome such ODE.²⁶⁶

Jazz argues that Avadel’s evidence for clinical superiority is hypothetical and does not meet the demonstration standard.²⁶⁷ Jazz appears to base this argument on an assumption as to what evidence and arguments Avadel has submitted to FDA and what FDA has found compelling in demonstrating clinical superiority. Specifically, Jazz cites public statements from Avadel about market research concerning patient preference for a once-nightly formulation and prescriber surveys that dosing-related challenges are to blame for oxybate-eligible patients not taking oxybate.²⁶⁸ OOPD, however, is not relying on the cited market research and prescriber surveys in its determination that Lumryz makes a MCTPC, and therefore Jazz’s arguments about these sources are moot.

The clinical superiority of Lumryz is not merely hypothetical. As explained above, the science underlying sleep hygiene supports the finding that in the context of oxybate drugs for the treatment of narcolepsy, where the purpose of therapy is to promote sleep consolidation, a drug with once-nightly dosing that avoids disrupting sleep consolidation by avoiding a nocturnal awakening to take a second dose makes a MCTPC over the previously approved drugs for which the patient awakens and disrupts sleep consolidation to take a second dose. Awakening to take a second dose of Xyrem or Xywav fragments sleep and disrupts sleep architecture. If possible, this should be avoided in a narcoleptic patient. Sleep consolidation is the intended purpose of oxybate therapy. Lumryz provides a treatment option that avoids the need to awaken to take a second dose. Thus, based on its scientific expertise and consultation of the literature, FDA has determined that the clinical superiority of Lumryz has been demonstrated.

²⁶¹ Jazz’s September 2021 Letter, *supra* note 11, at 2; *see also* Sidley Slides, *supra* note 13, at 21.

²⁶² Jazz’s September 2021 Letter, *supra* note 11, at 3.

²⁶³ 21 CFR § 316.20(a).

²⁶⁴ Section 527(c)(1) of the FD&C Act.

²⁶⁵ 2013 Final Rule, 78 Fed. Reg. at 35122 (“allowing the subsequent drug to be approved during the pendency of the already approved drug’s exclusivity period (if any) . . . provided that clinical superiority is demonstrated upon approval”).

²⁶⁶ *Id.*

²⁶⁷ Jazz’s September 2021 Letter, *supra* note 11, at 16-18.

²⁶⁸ *Id.* at 16; *see also* Sidley Slides, *supra* note 13, at 31.

The type of evidence on which FDA is basing its finding of Lumryz’s demonstration of clinical superiority over Xywav and Xyrem is quite similar to the type of evidence on which FDA based its finding of Xywav’s demonstration of clinical superiority over Xyrem. FDA found Xywav clinically superior to Xyrem based on greater safety because Xywav provided less sodium than Xyrem, and scientific literature exists that shows reduced dietary sodium generally would be clinically meaningful in reducing cardiovascular morbidity in the general population.²⁶⁹ Jazz did not conduct a head-to-head trial to compare the safety of Xywav and Xyrem.²⁷⁰ Nevertheless, the underlying science supported that “[t]he relationship between daily salt intake and cardiovascular morbidity is widely accepted, as is the need for salt intake to be generally restricted.”²⁷¹ That was sufficient for OOPD to conclude that Xywav was clinically superior to Xyrem, because, as OOPD explained, “although it has never been specifically and adequately investigated whether the sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy, the general base of knowledge about the effects of sodium support that the amount of sodium in Xyrem would increase cardiovascular risks in patients with narcolepsy.”²⁷² By similar logic, for Lumryz, FDA has found that the scientific knowledge of sleep hygiene and the importance of consolidating sleep to treat narcolepsy supports its finding that a drug that avoids a nocturnal awakening to take a second dose provides a significant therapeutic advantage over and above that provided by a drug that necessitates a nocturnal awakening to take a complete nightly dosage.

Third, Jazz argues that Lumryz does not meet the standard for clinical superiority because the change from Xyrem and Xywav’s twice-nightly dosing to Lumryz’s once-nightly dosing does not meet the “high bar” to be considered a MCTPC.²⁷³ Jazz argues that because MCTPC represents a “narrow category”²⁷⁴ of “unusual cases,”²⁷⁵ FDA’s prior MCTPC findings have been based on “much more substantial quantitative and qualitative improvements” than Lumryz’s “50% decrease in dosing frequency relative to Xyrem and Xywav.”²⁷⁶ Jazz cites to two examples where FDA found a MCTPC for a drug going from twice-a-day dosing to once-monthly dosing and a drug going from administration that took one hour to taking one minute.²⁷⁷ FDA does not agree with Jazz’s arguments and finds that Lumryz’s benefit meets the narrow category of MCTPC. All MCTPC determinations are made on a case-by-case basis, and the nature and severity of the disease or condition is a relevant factor.²⁷⁸ More goes into a MCTPC determination than merely a quantitative assessment of the percentage reduction in dosing frequency. For Lumryz, the reduction in the number of doses makes a MCTPC because the dosing eliminates the need to awaken in the middle of sleep to take the second dose. This is relevant in the context of treating narcolepsy with oxybate because the goal of narcolepsy therapy is to enhance sleep consolidation; awakening to take a second dose works directly

²⁶⁹ Xywav Exclusivity Memo, *supra* note 99, at 3.

²⁷⁰ *Id.*

²⁷¹ *Id.* (quoting DN1 2020 Xywav Consult).

²⁷² Xywav Exclusivity Memo, *supra* note 99, at 5.

²⁷³ Jazz’s September 2021 Letter, *supra* note 11, at 15-16.

²⁷⁴ *Id.*, at 15 (quoting 1991 Proposed Rule, 56 Fed. Reg. at 3343).

²⁷⁵ *Id.* (quoting 21 CFR § 316.3(b)(3)).

²⁷⁶ *Id.* at 16.

²⁷⁷ *Id.*

²⁷⁸ 1992 Final Rule, 57 Fed. Reg. at 62078.

against this goal. Furthermore, as noted above, our basis for finding a MCTPC for Lumryz is similar to our basis for FDA’s MCTPC finding for Procysbi.

Fourth, and finally, Jazz argues that FDA should not consider Lumryz to make a MCTPC because FDA did not grant priority review for Lumryz’s marketing application.²⁷⁹ Jazz notes that the standard for priority review is similar to the standard for clinical superiority.²⁸⁰ A review designation type (standard or priority review) for a marketing application is determined on a case-by-case basis at the time that an application is filed based on the information and data available at the time the application is submitted.²⁸¹ As described in the guidance for industry, *Expedited Programs for Serious Conditions – Drug and Biologics* (May 2014), “[a]n application will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.”²⁸² “Significant improvement” may be illustrated by the following examples: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of a serious or life-threatening condition; (2) elimination or substantial reduction of a treatment-limiting adverse reaction; (3) documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or (4) evidence of safety and effectiveness in a new subpopulation.²⁸³

The clinical superiority standard, as described throughout this analysis, includes that “the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care.”²⁸⁴ FDA makes clinical superiority determinations for the purposes of approval and ODE eligibility *after* the agency has conducted a full and substantive review of the relevant marketing application and determined if the drug meets the safety and efficacy requirements for approval; whereas, the priority review designation is made at the time of submission of the marketing application, based upon a “[p]reliminary review.”²⁸⁵ Although the concepts of “clinical superiority” in the orphan-drug context and “significant improvement” in the priority review context may have some practical overlap, the standard for demonstrating clinical superiority differs from the standard for priority review designation; the analyses are conducted at different times in the review of a marketing application and involve different levels of data scrutiny. Given these differences, there are many reasons why FDA could deny priority review for a marketing application for a drug and find clinical superiority for that drug.²⁸⁶ FDA’s decision not to grant priority review for the Lumryz application is not inconsistent with its determination that Lumryz makes a MCTPC over Xyrem and Xywav.

²⁷⁹ Jazz’s September 2021 Letter, *supra* note 11, at 16; *see also* Sidley Slides, *supra* note 13, at 34.

²⁸⁰ Sidley Slides, *supra* note 13, at 34.

²⁸¹ *See* CDER’s Manual of Policies and Procedures 6020.3 Rev. 2, Review Designation Policy: Priority (P) and Standard (S) at 3-4, June 2013, <https://www.fda.gov/media/72723/download>.

²⁸² *Expedited Programs for Serious Conditions – Drug and Biologics* (May 2014) at 2-3 (accessed at <https://www.fda.gov/media/86377/download>).

²⁸³ *Id.*

²⁸⁴ Section 527(c)(2) of the FD&C Act; *see also* 21 CFR § 316.3(b)(3).

²⁸⁵ MAPP 6020.3 Rev. 2, *supra* note 281, at 6.

²⁸⁶ The drug Valtoco (diazepam nasal spray) is another recent example where FDA granted standard review designation for an application but found clinical superiority over a previously approved otherwise same drug for the same indication or use upon approval.

In sum, FDA finds Jazz's arguments about why Lumryz does not make a MCTPC over Xyrem and Xywav unpersuasive.

VI. Conclusion

For the reasons explained above, we have determined that Lumryz, which is dosed once nightly, is clinically superior to Xyrem and Xywav, which are dosed twice nightly. *See* 21 CFR § 316.3(b)(3). Because Lumryz is clinically superior to Xywav and, therefore, not the "same drug" as Xywav under 21 CFR § 316.3(b)(14) and section 527(a) of the FD&C Act, Xywav's unexpired ODE does not block marketing approval of Lumryz. Additionally, because of its clinical superiority to Xyrem and Xywav, Lumryz has met the condition set forth at section 527(c) of the FD&C Act, and Lumryz is eligible for its own term of ODE for the treatment of cataplexy or EDS in adults with narcolepsy under section 527(a) of the FD&C Act.

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