IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	[redacted]
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	[redacted] C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	[redacted] C.A. No. 21-1594-GBW

DEFENDANT'S ANSWERING BRIEF IN OPPOSITION TO
JAZZ'S MOTION FOR AN INJUNCTION OR ONGOING ROYALTY

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Trial Transcript	"Tr."
Declaration of Maggie Lavender in Support of Avadel's Opposition to Jazz's Motion for an Injunction	"Lavender"
Declaration of Dr. Thomas Stern in Support of Avadel's Opposition to a Permanent Injunction	"Stern"
Declaration of Dr. Akinyemi Ajayi in Support of Avadel's Opposition to a Permanent Injunction	"Ajayi"
Declaration of Gregory J. Divis in Support of Avadel's Opposition to Jazz's Motion for a Permanent Injunction	"Divis"
Declaration of Patient 1	"Patient 1"
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Declaration of Patient 3	"Patient 3"
Declaration of Mohan Rao, Ph.D.	"Rao"
Unredacted copy of JTX-0112, FDA U.S. Food & Drug Letter to ProPharma Group regarding FDA's response to Jazz Pharms. Inc. regarding the agency's determination that Xywav's unexpired orphan-drug exclusivity does not block approval of Lumryz (May 1, 2023)	"Ex. 1"
DTX-0762, Messaging guidelines in anticipation of Lumryz sales, dated May 1, 2023	"Ex. 2"
Excerpts of Transcript of Deposition of Richard K. Bogan, M.D., F.C.C.P. (Oct. 25, 2023)	"Ex. 3"
Brief of the Public Interest Patent Law Institute, Professor Robin Feldman, Narcolepsy Patients, and the Niskanen Center as *Amici Curiae* in Support of Defendant-Appellee, *Jazz Pharms. Inc. v. Avadel CNS Pharms. Inc.*, No. 2023-1186, D.I. 43 (Fed. Cir. Jan. 18, 2023)	"Ex. 4"
Statement of Chair Lina M. Khan at the September Open Commission Meeting on Brand Drug Manufacturers' Improper Listing of Patents in the Orange Book Commission File No. P233900 (Sept. 14, 2023)	"Ex. 5"
Jazz Pharms. Form 10-Q (May 2, 2024)	"Ex. 6"
Jazz Pharms. Q1 Earnings Call Transcript (May 1, 2024)	"Ex. 7"
Galderma Labs. L.P. v. Lupin Inc., No. 21-CV-1710 (D. Del. Apr. 11, 2024)	"Ex. 8"
Excerpts of Transcript of Deposition of Mark Rainey, Ph.D. (Nov. 17, 2023)	"Ex. 9"
D.I. 587-1, Jazz Ex. 4, Jazz Pharms. Form 10-K (Feb. 28, 2024)	"Jazz Ex. 4"

[1] All D.I. cites refer to the docket in Case No. 21-cv-00691-GBW.

I. INTRODUCTION

In its motion for a permanent injunction, Jazz asks this Court to prevent thousands of patients from accessing the only oxybate treatment that permits them to receive an uninterrupted night's sleep. That request should be denied. The entry of a permanent injunction is always a matter of equitable discretion, not of right. Each of the equitable factors that governs the issuance of a permanent injunction—that the public interest would not be disserved by an injunction, that the plaintiff has suffered an irreparable injury, that remedies at law are inadequate, and that the balance of hardships favors an injunction—must be satisfied for an injunction to issue.

Jazz establishes none of these factors. The FDA has already declared that Avadel's once-nightly product (Lumryz) is clinically superior to Jazz's twice-nightly products (Xywav and Xyrem), and for good reason: A drug that allows patients with a sleep disorder to get a full, uninterrupted night's sleep is superior to drugs that require them to forcibly awaken in the middle of the night. Jazz criticizes the FDA's expert determination but fails to present ***any*** evidence from patients or health-care providers supporting its position. The evidence at trial showed that Jazz tried for years to create a once-nightly drug, and patients should not suffer because Jazz failed where Avadel succeeded. An injunction taking a clinically superior drug off the market is not in the public interest. Jazz characterizes its request as "limited" because it seeks to deny Lumryz only to new patients, although it does not explain why new patients are any less deserving of access to a life-changing drug. [redacted].

As to irreparable harm, Jazz tells the Court a story of lost market share and price erosion, which it attributes solely to Lumryz. But in its public statements to its shareholders, Jazz tells a different story: It projects continued confidence in the long-term growth of Xywav. And when

Jazz's public statements acknowledge a price-erosion problem, they highlight the effects of ***generic*** competitors, which Jazz itself licensed. Having licensed generic competitors, Jazz cannot pin the blame for the resulting price impacts solely on Lumryz. Furthermore, Jazz failed to establish any causal nexus between the sole remaining patent claim and the irreparable harm of which Jazz complains. Jazz has no evidence that Lumryz's sachet packaging is cutting into its business; the source of its harm is Lumryz's innovative once-nightly dosing. And by Jazz's own admission, claim 24 of the '782 patent is not directed to once-nightly dosing.

The balance of hardships likewise weighs against an injunction. Jazz will continue to sell its branded products in the absence of an injunction. An injunction barring the sale of Lumryz [redacted] Jazz argues that Avadel has itself to blame for betting on Lumryz in the face of potential infringement, but Jazz did not even file an application with the PTO to get claim 24 until several months *after* Avadel had submitted Lumryz for FDA approval. Shutting down the sale of Lumryz on the basis of that eleventh-hour patent claim would be inequitable.

Because Jazz has shown no basis for a permanent injunction here, the only remaining question is the size of an ongoing royalty. The jury has already found that a modest sum compensates Jazz for any harm. Jazz asked the jury for a 27% royalty; the jury rejected that demand and awarded only a small fraction of it. Jazz now asks the Court to ignore that verdict and patient interests. Jazz's motion should be denied, and the Court should enter an ongoing royalty consistent with the jury verdict.

II. JAZZ IS NOT ENTITLED TO AN INJUNCTION

The four-factor *eBay* test governs Jazz's motion. *See* Br. at 3; *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1337 (Fed. Cir. 2012). Jazz bears the burden on each factor. *Conceptus, Inc. v. Hologic, Inc.*, No. C 09-02280 WHA, 2012 WL 44064, at *1 (N.D. Cal.

Jan. 9, 2012). As the Supreme Court has made clear, no general rule entitles patent owners to a permanent injunction. *ActiveVideo Networks, Inc.*, 694 F.3d at 1341. Rather, a "permanent injunction is an extraordinary remedy." *Bianco v. Globus Med., Inc.*, No. 2:12-CV-00147-WCB, 2014 WL 1049067, at *1 (E.D. Tex. Mar. 17, 2014) (Bryson, J.). And courts have generally "refused to permanently enjoin activities" where doing so "would injure the public health." *Cordis Corp. v. Bos. Sci. Corp.*, 99 Fed. App'x 928, 935 (Fed. Cir. 2004). Accordingly, in any case involving the proposed injunction of a medical or pharmaceutical product, the public-interest factor looms large. *See Abbott Cardiovascular Sys., Inc. v. Edwards Lifesciences Corp.*, No. CV 19-149 (MN), 2019 WL 2521305, at *25-26 (D. Del. June 6, 2019) (collecting cases).

A. The Public Interest in Patient Health Weighs Heavily Against an Injunction

As Judge Dyk has observed, where a defendant's medical or pharmaceutical product offers "unique medical benefits [that are] not available from [the plaintiff's] competing products," the "public interest weighs strongly against" an injunction. *Baxalta Inc. v. Genentech, Inc.*, No. CV 17-509-TBD, 2018 WL 3742610, at *12 (D. Del. Aug. 7, 2018). This public-interest principle is deeply rooted, widely recognized, and frequently applied. *See, e.g., Bianco*, 2014 WL 1049067, at *11-12 (collecting cases). It is especially clear that where, as here, the defendant's pharmaceutical product offers patients "a potential sea change in the treatment of their [condition]," a court should abstain from barring those patients' access to the defendant's innovative product. *Baxalta*, 2018 WL 3742610, at *13.

That principle independently disposes of Jazz's motion, as the public interest factor alone can be dispositive. *See Natera Inc. v. ArcherDx, Inc.*, No. 20-CV-125-GBW, 2023 WL 9103876, at *1 (D. Del. Dec. 1, 2023). Lumryz offers a sea change in the treatment of narcolepsy by giving narcolepsy patients—for the first time—the chance to get an undisturbed night's sleep. The FDA's findings and the evidence conclusively establish the clinical importance and superiority of

Lumryz's once-nightly formulation. Jazz offers only attorney argument—not evidence—to the contrary. Jazz has failed to carry its burden.

1. All Narcolepsy Patients Should Have Access to Lumryz

Narcolepsy is a chronic, incurable disease marked by excessive daytime sleepiness and fragmented nighttime sleep; patients typically require a lifetime of medication. Tr. 631:11-632:11. Its symptoms pervasively interfere with a patient's life. Many people go years before a diagnosis. Tr. 632:18-633:6. Oxybate products like Lumryz—or Jazz's competing products, Xyrem and Xywav—are the "most effective treatment for the symptoms of narcolepsy." Tr. 635:1-5. But even though Jazz's oxybate product (Xyrem) was approved in 2002, many patients who might benefit from oxybate still do not receive it. Tr. 635:6-13. As Dr. Corser explained at trial, before Lumryz, patients who wished to take oxybate were forced into a "twice-nightly treatment option; that is, people have to take one dose of oxybate at bedtime and a second dose two and a half to four hours later. So this has not been appealing, either for doctors or for patients." Tr. 635:14-22. Lumryz is better. As Dr. Corser explained, "when we treat narcolepsy, the goal . . . is to allow people to sleep well through the night, sleep uninterrupted. . . . Having to wake up to take a second dose of medication is contrary to what we're trying to achieve." Tr. 636:13-637:2. Accordingly, many patients who refuse a twice-nightly oxybate treatment are expected to try once-nightly Lumryz. Tr. 501:20-23; Tr. 589:17-23; Tr. 602:6-9. These patients—and every other patient for whom Lumryz offers a full night's sleep—would be harmed if Lumryz is enjoined.

a) The FDA determined that Lumryz is clinically superior to Xyrem and Xywav

The FDA is responsible for safeguarding the public health with respect to pharmaceutical

products.[2] In the FDA's judgment, Lumryz is clinically superior to Jazz's existing oxybate products, Xyrem and Xywav.[3] Jazz tried to keep Lumryz off the market by insisting that Jazz's Orphan-Drug Exclusivity ("ODE") blocked the FDA from approving Lumryz. Ex. 1, JTX-112.1-2. But the FDA decided that patients should not have to wait for a better drug. *Id.* Applying its expertise, and with the benefit of submissions by both Jazz and Avadel, the FDA "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***." *Id.* at JTX-112.3.[4] The FDA found significant clinical benefits relative to Jazz's twice-nightly products. As the FDA put it, a "once-nightly dosed oxybate drug will provide a significant therapeutic advantage . . . 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." *Id.* at JTX-112.33; *see also id.* at JTX-112.27-30.

In its motion for a permanent injunction, Jazz all but ignores these findings. Instead, it emphasizes Lumryz's higher sodium content relative to Xywav. But the FDA "acknowledged . . . that Lumryz has a higher sodium content than Xywav and addressed ***why Lumryz is still clinically superior to Xywav***." *Id.* at JTX-112.34. The FDA went on: the FDA "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 [major contribution to patient

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[2] *See* https://www.fda.gov/about-fda/what-we-do#mission.

[3] Jazz mentions in passing (at 15) its suit against the FDA challenging this determination. But that only underscores Jazz's failure of proof: Despite the pending FDA litigation, Jazz offers not one physician declaration here challenging the FDA's medical judgment about Lumryz.

[4] All emphasis added unless otherwise noted.

care]." *Id.* at JTX-112.38. Even with respect to particularly sodium-sensitive patients, the FDA concluded that "the benefit offered by once-nightly dosing would outweigh the risk of increased sodium intake" because disrupted sleep is "antithetical" to the goals of oxybate treatment, and "there are other ways such patients may reduce sodium in their diet." *Id.* at JTX-112.33.

No evidence supports Jazz's assertion (Br. 1) that Lumryz is "less safe." Dr. Corser was clear: "There is no evidence that sodium oxybate increases the risk of cardiovascular disease or hypertension." Tr. 638:5-21. Jazz put in no evidence from any medical doctor to rebut that testimony; instead, it relies on a Jazz lawyer (Mr. Honerkamp) and a damages expert (Dr. Rainey); neither is qualified to render an opinion on that point. And in the real world, Jazz is still selling large volumes of Xyrem, whose sodium content is equivalent to Lumryz's, and it has licensed many generic versions of Xyrem that patients will continue to use for years to come. *See infra* Section II.B.3. This Court should reject Jazz's unsupported argument and instead recognize, as the FDA has, that Lumryz is clinically superior.

Jazz also belittles the FDA's superiority finding because it was based on a major contribution to patient care. But patients are harmed when they are deprived of a differentiated alternative therapy—a therapy that, for example, reduces treatment burdens, increases patient willingness to take a treatment, increases compliance, or otherwise improves patients' lives. *Baxalta*, 2018 WL 3742610, at *13. Taking such a choice away from patients "'militates strongly against an injunction.'" *Abbott*, 2019 WL 2521305, at *26 (quoting *Conceptus*, 2012 WL 44064, at *3-4). In *Baxalta*, the court gave significant weight to the FDA's decision to award a drug Breakthrough-Therapy Designation on the basis that the drug "'***may*** demonstrate a substantial improvement over existing therapies.'" *Baxalta*, 2018 WL 3742610, at *12 (quoting 21 U.S.C. § 356). Here, FDA has determined that Lumryz is in fact clinically superior.

Nor does it matter that some patients might benefit from Xywav. Br. 14. Jazz relies on *Edwards*, but that case was predicated on unique facts. *Edwards Lifesciences AG v. CoreValve, Inc.*, No. CV 08-91 (GMS), 2014 WL 1493187 (D. Del. Apr. 15, 2014).[5] The district court called out "egregious conduct" on Medtronic's part, including a representation to the court that "was false when made." *Id.* at *6, *11 & n.7. No such facts are present here. And while Jazz insists that eliminating "a choice of drugs is not, by itself, sufficient to disserve the public interest" (Br. 14), that argument has no application where, as here, the product proposed to be enjoined "differ[s] in meaningful ways" from existing products on the market. *Baxalta*, 2018 WL 3742610, at *12. This case is not like those in which patients can simply obtain a different form of the enjoined product from another supplier. *See, e.g.*, *Natera*, 2023 WL 9103876, at *5 (concluding that injunction was proper because patients could obtain an "equally" effective product from patentee). Rather, this case is like *Baxalta*, *Abbott*, *Cordis*, *Conceptus*, and others, where the public interest in access to superior therapies precluded an injunction.

b) Patients and providers attest that Lumryz is better

The FDA and Dr. Corser are not alone in recognizing Lumryz's critical benefits. ***Jazz itself*** called the approval of Lumryz "a positive development for patients with narcolepsy." Ex. 2 at 1. And Avadel offers additional evidence from medical providers and patients confirming that Lumryz improves patient lives. *See, e.g., Smith & Nephew, Inc. v. Interlace Med., Inc.*, 955 F. Supp. 2d 69, 80 (D. Mass. 2013) (public interest weighs against injunction where "at least some doctors consider" the infringing product "more effective").

[5] Jazz's other cases likewise do not show injunctions entered under "similar" circumstances. Br. 14. Indeed, Jazz makes no effort to explain how those cases relate to the facts here. Several predate *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 393 (2006), which abrogated categorical patent-case rules providing for the issuance of injunctions as a matter of course.

Nurse Practitioner Maggie Lavender prescribes Xyrem, Xywav, and Lumryz. She emphasizes that "it is not some minor issue that people do not want to have to set an alarm in the middle of the night. Neither Xyrem nor Xywav is an easy treatment. The treatment upends your life." Lavender ¶12. She has seen patients and entire households suffer from twice-nightly dosing, and she has seen patients' lives dramatically improve on Lumryz. *Id.* ¶¶12-17. Several of Ms. Lavender's patients are not yet on Lumryz but will likely start in the future. *Id.* ¶¶15-18. Similarly, Dr. Thomas Stern sees benefits with Lumryz, including better symptom control, decreased anxiety, and better sleep architecture. Stern ¶¶6-11, 13. He confirms that Lumryz is not "less safe" than Xywav. *Id.* ¶¶19-20. He stresses the importance of an option for patients who refuse even to start Xyrem or Xywav. *Id.* ¶12. He thinks Lumryz should be available to all patients, including future patients. *Id.* ¶¶21-22. Dr. Akinyemi Ajayi also treats narcolepsy patients and shares similar views. Ajayi ¶¶13-26. ***Jazz*** itself retained Dr. Richard Bogan and did not tell him that it was seeking an injunction; when Dr. Bogan learned that fact at his deposition, he objected that he "would like to have once-nightly oxybate available." Ex. 3, 116:9-117:17. He currently prescribes Lumryz, and he expects it to be the best choice for more patients in the future. *Id.* at 24:1-9, 31:17-36:10.

Three Lumryz patients have also provided this Court with first-hand accounts of the improvements they have seen on Lumryz.[6] They speak candidly about their struggles with the middle-of-the-night forced awakening required by Xyrem and Xywav, and the awful days that they experienced when those struggles led to missed or skipped doses. *See* Patient 1 ¶6; Patient 2 ¶¶6-7. They speak of the toll of never being able to sleep through the night on Xyrem and Xywav, and they are clear that they do not want to go back to that regimen. *See* Patient 1 ¶11; Patient 2

[6] Additional evidence regarding the burdens on patients of Xyrem's and Xywav's twice-nightly dosing regimen can be found in an *amicus* brief filed earlier in the case. *See* Ex. 4.

¶10; Patient 3 ¶10. These real-world testimonials confirm what the FDA has already found: Lumryz is clinically superior to Xyrem and Xywav.

2. IH Patients Deserve Access to Lumryz for the Same Reasons

Idiopathic hypersomnia (IH) patients are no less deserving of access to Lumryz. Physicians do not consider IH and narcolepsy without cataplexy to be distinct diseases; IH is best thought of as being on a spectrum with narcolepsy. Stern ¶14; Lavender ¶9. Patients with either condition suffer from excessive daytime sleepiness. Diagnostic criteria are similar and imprecise. Lavender ¶9; Stern ¶14. As with narcolepsy, oxybate is a very effective treatment for IH and the vast majority of IH patients take it twice nightly. Stern ¶15-16. Once-nightly Xywav is often not an adequate substitute. *Id.* ¶16-17; Lavender ¶9.

Physicians have thus urged Avadel to seek FDA approval for Lumryz in IH. Tr. 529:13-20; Stern¶18; Lavender ¶19. Avadel is doing so, at great cost. Divis ¶12. Avadel expects that the FDA will approve Lumryz for use with IH patients, and again recognize that Lumryz is clinically superior to Xywav. Divis ¶14. Indeed, Jazz is partly to blame for the fact that IH patients do not yet have access to Lumryz: if Jazz had not improperly delayed Lumryz's approval, Avadel's IH trial would be well underway by now. Divis ¶13.

Jazz is thus wrong that IH patients should be ignored because the FDA has not yet made a clinical superiority finding with respect to Lumryz treatments for IH patients. The key public-interest consideration is whether an injunction would cut off patient access to a differentiated product that offers a "unique" medical benefit, not whether there has been a clinical superiority determination. *See Baxalta*, 2018 WL 3742610, at *12; *Abbott*, 2019 WL 2521305, at *26-27 (finding harm to the public "notwithstanding the lack of clinically proven superiority" based on physician declarations); *Cordis Corp. v. Bos. Sci. Corp.*, 99 Fed. App'x at 935 ("a strong public interest supports a broad choice of drug-eluting stents, even though no published study proves the

superiority of either [accused] stent."); *Smith & Nephew, Inc.*, 955 F. Supp. 2d at 80. The burden remains with the patentee to prove that the product in question "fail[s] to offer any advantage." *Kimberly-Clark Worldwide, Inc. v. Tyco Healthcare Grp. LP*, 635 F. Supp. 2d 870, 882 (E.D. Wis. 2009). Jazz did not carry that burden: Jazz fails to point to ***any*** medical evidence in support of its requested injunction. As with narcolepsy patients, IH patients will gain a significant benefit by having access to Lumryz.

3. Jazz's Proposed "Limited" Injunction Is Not Limited at All

Jazz tries to sidestep all this evidence by saying that it seeks only a "limited" injunction that would allow Avadel to continue marketing to "patients prescribed Lumryz as of the effective date of the injunction" (Br. 16-17), [redacted] There are 16,000 people in the United States on oxybate therapy and a far larger population with narcolepsy (some 200,000 people). Tr. 635:6-10. More patients will be diagnosed in the future. Stern ¶21. Even a "limited" injunction would make Lumryz unavailable "to the vast majority of [narcolepsy] patients in need of [Lumryz] treatment." *Baxalta*, 2018 WL 3742610, at *13.

Furthermore, the purportedly "limited" injunction sought by Jazz [redacted] At current sales levels, Avadel cannot cover its fixed costs and is losing money. Divis ¶7. [redacted].

4. The Injunction that Jazz Requests Does Not Encourage Investment

Finally, Jazz's claim that an injunction will protect ***Jazz's*** investment in new technologies

cannot survive even a cursory review of the facts. As the trial record showed, Jazz failed at developing a once-nightly oxybate. And Jazz offers no evidence that it "attracts investment" based on its allegedly good reputation as a company that develops medicines. Br. 13-14. Quoting cases where that was true of other parties does not make it true for Jazz, which has a different reputation: making money off anticompetitive practices. *See, e.g.* Jazz Ex. 4 p.38 (Jazz 10-K discussing many antitrust suits against Jazz); Ex. 5 at 2 (Stmt. of FTC Chair L. Khan). Nor does *Sanofi* help Jazz; that was an ANDA case enjoining entry of a generic drug that was not the product of innovation and that by definition provided no unique benefits to patients. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006).

B. Jazz Has Not Established Irreparable Harm

Although this Court can and should deny Jazz's request for an injunction solely based on the great harm it will cause the public, Jazz's motion can also be denied for failure to establish irreparable harm. Indeed, Jazz's irreparable-harm showing fails on multiple grounds. First, Jazz has not established any causal nexus between the infringement found at trial and the injuries Jazz will purportedly suffer on account of Lumryz's availability. Second, Jazz's assertions to this Court of market-share loss and price erosion on account of Lumryz are undercut by Jazz's public declarations to its shareholders emphasizing the role of generic competitors and the long-term growth prospects for Xywav sales. Third, and relatedly, Jazz has licensed its Xyrem and Xywav patents to ten different generic competitors, which strongly suggests an absence of irreparable harm necessitating injunctive relief. Finally, Jazz cannot establish any kind of intangible reputational harm that would warrant injunctive relief.

1. Jazz Failed To Establish Causal Nexus

"[T]he purpose of the causal nexus requirement is to show that the patentee is irreparably harmed *by the infringement*." *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1363 (Fed. Cir.

2013) (emphasis in original). "Without a showing of causal nexus, there is no relevant irreparable harm." *Id.* The operative question is "whether there is some connection between [the] patentee's asserted *improvement over the prior art* and the decisions of [purchasers] to choose" the accused product. *Integra Lifesciences Corp. v. Hyperbranch Med. Tech., Inc.*, No. CV 15-819-LPS-CJB, 2016 WL 4770244, at *21 (D. Del. Aug. 12, 2016) (quotation omitted, emphasis in original). And unclaimed features may defeat a nexus argument that relies solely on sales of the full product. Sales of an infringing product prove nexus on their own only where "the infringing product contains no feature relevant to consumers' purchasing decisions other than ***what the patent claims***." *Genband US LLC v. Metaswitch Networks Corp.*, 861 F.3d 1378, 1384 n.2 (Fed. Cir. 2017). Demand for Lumryz does not equate to demand for the patented improvement.

Jazz's theory of irreparable harm does not pass this test. The sole claim at issue claims the sachet packaging used for Lumryz, but Jazz has no evidence that it is losing sales or market share to Avadel because Lumryz is packaged in a sachet. Jazz offers no evidence that any patient has switched because Lumryz is packaged in a sachet (or contains an acid separate from the drug-containing particles). To the contrary, Jazz has consistently acknowledged that patients select Lumryz for its once-nightly dosing. *See, e.g.*, Tr. 581:5-19, 592:20-593:4. And Jazz admits that once-nightly dosing is not even part of the claim: in its MIL No. 1, Jazz argued that claim 24 did not include "any requirement that the modified release particles 'help a patient stay asleep throughout the night.'" MIL No. 1 at 2, D.I. 567-1 at 113. Jazz dropped the method claims including those requirements pre-trial, presumably because even Jazz recognizes it did not invent once-nightly oxybate dosing. Per the Court's order granting Jazz's MIL, once-a-day dosing is an "unclaimed limitation" with respect to claim 24. D.I 540 at 1, 4. Yet Jazz admits that is what drives demand for Lumryz. Br. 10. To the extent that Jazz now tries to argue that Avadel could

not sell a product without using the claimed invention, it is notable that Avadel made investments in developing and seeking regulatory approval for Lumryz before Jazz copied Avadel's claim covering Lumryz. *See infra* Section II.D.; Divis ¶4.

The jury's damages verdict further confirms the lack of nexus. Jazz's damages expert Dr. Rainey ***admitted*** that he never tried to determine the value of the sachet, and instead analyzed the value of Lumryz as a whole—including the once-nightly dosing that Jazz admittedly did not claim—for the purpose of calculating damages. Tr. 605:12-606:17. The jury soundly rejected Dr. Rainey's approach. Now, in pressing for an injunction, Jazz is doing the same thing by asserting "irreparable harm" that has nothing to do with the novel aspects of the claim.

2. Jazz Publicly Contradicts Its Own Allegations of Irreparable Harm

Jazz's irreparable-harm showing also fails because the harms Jazz asserts (including lost market share and price erosion) are at least as attributable to generic competitors as they are to Avadel. This Court need not take Avadel's word for it; Jazz's public statements prove the point.

In its brief, Jazz tries to lay all the blame for lost sales and price erosion on Avadel. Br. 3-7. But Jazz's SEC filings admit that these effects stem at least in part from Jazz's decision to license generic versions of Xyrem. In Jazz's words, generic oxybate sales "have negatively impacted and are expected to continue to negatively impact Xyrem and Xywav sales for patients with narcolepsy," and "a significant percentage of the prescriptions written for Xyrem" will be filled with generic product. Jazz Ex. 4 pp. 17, 36; Ex. 6 at 37; *see also* Rao ¶18, 21-24. Jazz was explicit about this in a recent 10-Q filing, explaining that "generic or AG high-sodium oxybate products or branded high-sodium oxybate entrants in narcolepsy, such as Avadel's Lumryz, have had and may continue to have the effect of changing payor or formulary coverage of Xywav or Xyrem in favor of other products, and indirectly adversely affect sales of Xywav and Xyrem." Ex. 6 at 38; Rao ¶18, 21-23. And generic entry may cause at least some price erosion: "Generic

competition can decrease the net prices at which branded products, such as Xywav and Xyrem are sold." Jazz Ex. 4 p.80; Rao ¶22. As discussed below, Jazz faces such generic competition only because it licensed it. Its effort to remedy those allegedly "irreparable losses" by enjoining its branded competitor, Lumryz, should be rejected.

Moreover, while telling the Court that Lumryz will irreparably harm Xywav sales, *see* Br. 5, Jazz has consistently told its investors it "remain[s] confident in the durability of Xywav and believe that [Jazz is] well-positioned to achieve [its] Vision 2025 goal of $2 billion in sleep revenue." Ex. 7 at 4. Jazz confirmed that it expects "Xywav to remain the oxybate of choice, including the number one treatment for narcolepsy." *Id.* at 3. Those public representations are impossible to square with Jazz's alarmist warnings that Lumryz's presence on the market will "irreparably harm" Jazz's "status" and "reputation" as the "market leader in sleep." Br. 8.

As for IH patients, [redacted]. Divis ¶13. Doctors are free to prescribe off-label, but so far they have done so for [redacted] patients, presumably because IH patients lack insurance coverage for Lumryz. Divis ¶15; Lavender ¶19. Indeed, when asked on a recent earnings call about the "off-label use" of Lumryz to treat IH, Jazz said: "[W]e're not really seeing much, if any, off-label use with Lumryz [to treat IH], given the payer restrictions on these products." Ex. 7 p.18. Jazz's complaints that it is losing its first-mover advantage are overstated. *See Abbott*, 2019 WL 2521305, at *22.

These facts should be taken into account, because "[t]he Federal Circuit has found that lost sales standing alone are insufficient to prove irreparable harm; if they were, irreparable harm would be found in every case involving a manufacturer/patentee, regardless of circumstances." *Waters Corp. v. Agilent Techs. Inc.*, 410 F. Supp. 3d 702, 715 (D. Del. 2019) (quotation omitted). And "courts have routinely decided that market share and price erosion do not amount to

irreparable harm." *Galderma Labs. L.P. v. Lupin Inc.*, No. 21-CV-1710 at 6-7 (D. Del. Apr. 11, 2024) (Ex. 8) (quotation omitted). Jazz has essentially left it to the Court to "piece[] together [Jazz's] assertions regarding irreparable harm," but such a "confusing presentation of the issues presented militates against a finding that Plaintiffs have 'clearly shown' they are likely to suffer irreparable harm in the absence of an injunction." *Abbott*, 2019 WL 2521305, at *19.[7]

3. Jazz Is Willing To License Its Patent Rights

A patentee's "willingness to forego its patent rights for compensation" evidences a lack of irreparable harm. *Advanced Cardiovascular Sys., Inc. v. Medtronic Vascular, Inc.*, 579 F. Supp. 2d 554, 560 (D. Del. 2008). That rule applies here in two ways:

Licensing Its Most Relevant IP: Jazz has willingly licensed its Xyrem and Xywav patents to ten different direct competitors, [redacted]. Ex. 9 at 67:24-68:2; *see also id.* 60:1-64:4. As discussed *supra* Section II.B.2, Jazz expects those generics to take sales and cause price erosion for both Xyrem and Xywav, but it was still "willing, ultimately, to forego its exclusive rights for some manner of compensation. Money damages are rarely inadequate in these circumstances." *Advanced Cardiovascular Sys.*, 579 F. Supp. 2d at 560 (discussing a "selective" licensing program). Those twice-nightly generics did not need a license to the '782 patent, but the point remains that Jazz is willing to license patents protecting its oxybate products and live with the competition that results.

Jazz did not seek or obtain lost profits from Avadel: Pursuing ***and*** securing a jury award of lost profits damages can support a showing of irreparable harm. *f'real Foods, LLC v.*

[7] Nor is that the only flaw in Jazz's analysis. It retained an economist, but it did not ask him to analyze the severity of any alleged irreparable harm, distinguishing this case from Jazz's authority. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (economics expert testimony established price erosion).

Hamilton Beach Brands, Inc., No. CV 16-41-CFC, 2020 WL 4015481, at *4 (D. Del. July 16, 2020). Failing to seek and failing to obtain lost profits implies the opposite. Here, Jazz chose to seek a reasonable royalty—a retroactive license—instead of a lost-profits award. Ex. 9 at 21:11-28:3. The jury then awarded Jazz pennies on the dollar. D.I. 578; Tr. 600:3-8. Just as a lost-profits verdict can support an injunction, the verdict here supports the conclusion that a small royalty is sufficient to mitigate any harm. *Cf. Natera Inc.*, 2023 WL 9103876, at *3 (lost profits award supported irreparable harm).

4. Jazz Has Not Shown Any Actionable Reputational Harm

Finally, Jazz complains (at 7) of "reputational harm" attributable to "Avadel's marketing campaign for its infringing product." But reputational harm weighs in favor of injunctive relief only "where a plaintiff was itself practicing the patented invention and where there was evidence of consumer confusion, a loss of product distinctiveness, or some risk to that plaintiff's status as an innovator." *Baxalta*, 2018 WL 3742610, at *11. Jazz has made none of those showings. It does not practice the '782 patent.[8] Br. at 4. It can point to no risk of consumer confusion. Nor would "the requested injunction . . . stop doctors and patients from associating the innovation of [Lumryz] with [Avadel]." *Baxalta*, 2018 WL 3742610, at *11 (cleaned up). Jazz lost its status as an innovator by failing to develop a once-nightly product, and that will remain true with or without an injunction. *See id.*; *Abbott*, 2019 WL 2521305, at *22. And to the extent Jazz is bothered by Avadel's marketing statements, it should have moved to enjoin ***those statements***, not ***Lumryz***. *See Abbott*, 2019 WL 2521305, at *22 n.22. Jazz has not done so, likely because the statements are

[8] While not itself dispositive, the fact that Jazz does not sell any product that embodies claim 24 likewise militates against a finding of irreparable harm. *See High-Tech Med. Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1556 (Fed. Cir. 1995); *Chestnut Hill Sound, Inc. v. Apple Inc.*, No. 15-261-RGA, 2015 WL 6870037, at *4 (D. Del. Nov. 6, 2015).

true. Jazz's reputation is being harmed, if at all, by its own efforts to take away a clinically superior drug. *See Baxalta*, 2018 WL 3742610, at *11; Stern ¶23; Divis¶16.

C. Jazz Has Not Shown that Monetary Remedies Are Insufficient

This factor, "inadequacy of remedies available at law, is nearly indistinguishable from irreparable injury." *Natera Inc.*, 2023 WL 9103876, at *4. Jazz presents no new arguments or facts, instead referencing its irreparable harm arguments. Br. 10-11. The responses are the same.

D. The Harm to Avadel Greatly Outweighs the Harm to Jazz of Losing Sales

Finally, the balance of hardships clearly weighs against an injunction. Jazz faces no existential risks in the absence of an injunction. Indeed, Jazz expects "Xywav to remain the oxybate of choice." Ex. 7 at 3. But an injunction [redacted] The fact that [redacted] tips the balance of hardships in favor of Avadel. *See Bio-Rad Lab'ys, Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1379 (Fed. Cir. 2020); *Intel Corp. v. ULSI Sys. Tech., Inc.*, 995 F.2d 1566, 1568 (Fed. Cir. 1993).

Jazz (at 13) asks this Court to disregard the parties' relative posture on the ground that Avadel made a "choice" to focus exclusively on Lumryz's development notwithstanding the risk of infringement. But when Avadel made that choice and corresponding investments in 2019, the claim 24 of the '782 patent ***did not exist***. Avadel filed for FDA approval for Lumryz on December 15, 2020, and it was expecting approval on October 15, 2021. Tr. 548:12-13, 552:8-10; Divis ¶4. Jazz did not file the application that led to the '782 patent until March 31, 2021, JTX-6, and kept its prosecution a secret from Avadel. Tr. 547:11-19. The '782 patent issued on October 19, 2021, JTX-6. By that point, the design of Lumryz was locked in—it was not just final, but fully ready for FDA approval. That fact weighs against an injunction. *See Hynix Semiconductor Inc. v. Rambus Inc.*, 609 F. Supp. 2d 951, 985 (N.D. Cal. 2009) (balance of harms "clearly weighs"

against injunction where patentee did not obtain patents-in-suit until after defendant was locked into infringing technology) (distinguishing *Windsurfing*, on which Jazz relies). "[Lumryz] is not a copycat product. It was independently developed and provides important advantages over [Jazz's products] for patients." *Conceptus, Inc.*, 2012 WL 44064, at *3.

III. JAZZ'S REQUESTED RELIEF IS BARRED BY ITS UNCLEAN HANDS

Finally, the Court should reject Jazz's request for equitable relief due to Jazz's unclean hands. *See Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945). Here, Jazz seeks equitable relief (a permanent injunction) after it blocked Avadel's participation in the marketplace through unlawful and improper means (i.e., the improper Orange Book listing of its REMS patent that this Court and the Federal Circuit ordered delisted). Jazz's misconduct has a direct relation to the relief sought, *In re New Valley Corp.*, 181 F.3d 517, 525 (3d Cir. 1999), because Jazz previously excluded Avadel from the marketplace in an unconscionable manner and now seeks to do so through this Court's exercise of its equitable powers. Jazz's hands are unclean. This Court should not reward Jazz's wrongdoing. *See Avid Identification Sys., Inc. v. Phillips Elecs. N. Am. Corp.*, No. 2:04-CV-183, 2008 WL 819962, at *4 (E.D. Tex. Mar. 25, 2008) (patentee's unclean hands with regard to one patent precluded entry of permanent injunction with regard to two other patents despite finding of willful infringement).

IV. AN ONGOING ROYALTY IN LIEU OF AN INJUNCTION IS APPROPRIATE

"Under some circumstances, awarding an ongoing royalty for patent infringement in lieu of an injunction may be appropriate." *Paice LLC v. Toyota Motor Corp.*, 504 F.3d 1293, 1314 (Fed. Cir. 2007); *Innogenetics, N.V. v. Abbott Lab'ys*, 512 F.3d 1363, 1380 (Fed. Cir. 2008) (vacating injunction and remanding for determination of a compulsory license). "Generally, the jury's damages award is a starting point for evaluating ongoing royalties." *Vectura Ltd. v. GlaxoSmithKline LLC*, No. CV 16-638-RGA, 2019 WL 4346502, at *7 (D. Del. Sept. 12, 2019)

(citation omitted). The Court then considers three factors: (1) change in bargaining position; (2) changed economic circumstances; and (3) any post-verdict factors affecting a post-verdict hypothetical negotiation. *Id.* Courts sometimes increase the royalty post-trial, but in all cases the analysis starts with the rate reflected by the jury verdict. *Id.* Here, the jury imposed a royalty of 3.5% on a base reflecting only some sales. It may have determined that royalties should stop after that first payment of $234k. Ongoing royalties are not "automatic[ ]" where an injunction is denied, *Apple, Inc. v. Samsung Elecs. Co., Ltd.*, No. 12-CV-00630, 2014 WL 6687122, at *9 (N.D. Cal. Nov. 25, 2014), and the Court could view the jury award as a fully-paid-up royalty. Alternatively, the Court could treat the award as a determination that Avadel should pay a 3.5% royalty on 20% of Avadel sales.[9]

Jazz asks this Court to base any ongoing royalty on the rate put forward by Dr. Rainey at trial, but the jury unambiguously rejected that rate. The verdict form asked the jury to decide on a royalty rate and then to separately decide the total amount of damages. D.I. 578 at 11. During deliberations, [redacted] D.I. 580 at 7-8. The jury then returned a verdict that Jazz was entitled to only $233,562 in damages. D.I. 578. Jazz presents no argument as to why the Court should entirely reject the jury's determination as to a reasonable royalty. Notably, 3.5% applied to all sales would be a substantial increase relative the jury's verdict.

[9] As Jazz tacitly recognizes (Br. 17 n.3), a jury may engage in apportionment with respect to the royalty base. "[T]he ultimate combination of royalty base and royalty rate must reflect the value attributable to the infringing features of the product, and no more." *Bd. of Regents Univ. of Texas Sys. v. Bos. Sci. Corp.*, 645 F. Supp. 3d 324, 333 (D. Del. 2022) (quotation omitted).

Nor does Jazz offer any persuasive reasons for departing from the rate reflected in the jury verdict. That Dr. Rainey was the only damages expert who testified serves only to emphasize that the jury heard the same arguments that Jazz recycles here and found them unpersuasive. The jury was instructed to evaluate the incremental value of Jazz's invention and apparently found it to be *de minimis*. Jazz suggests that Avadel may be treated as a willful infringer, but Avadel was not even accused of willful infringement in this case, presumably due to Jazz's choice to keep the '782 patent a secret until Jazz sued on it. Tr. 547:11-19. Pre-suit knowledge matters for willfulness, *see Bos. Sci. Corp. v. Nevro Corp.*, 560 F. Supp. 3d 837, 843 (D. Del. 2021), and Avadel had none. This case is thus different from *Joyal Prod., Inc. v. Johnson Elec. N.A.*, in which the defendant ***admitted*** to willful infringement. No. 04-5172, 2009 WL 512156, at *9 (D.N.J. Feb. 27, 2009). And this Court need not (and should not) increase the royalty rate simply because the '782 patent has been found valid and infringed, "given that the jury is required to award a rate negotiated by willing licensors and licensees who considered the patent(s) to be valid and infringed." *Purewick Corp. v. Sage Prod., LLC*, 666 F. Supp. 3d 419, 449 n.23 (D. Del. 2023). Where, as here, the only post-verdict change is the fact of the verdict itself, a higher rate than that adopted by the jury is not warranted. *See id.* at 449-50.

The jury awarded Jazz 3.5% on 20% of sales of Lumryz. The Court could treat that as a lump sum award and decline to award any ongoing royalty. The Court could award Jazz a royalty of 3.5% of some fraction of Lumryz sales. Or the Court could award Jazz a 3.5% royalty on all sales of Lumryz going forward, an award greater than the actual jury verdict by a factor of five. The latter should set a cap on any prospective award.

V. CONCLUSION

In the event the Court believes an ongoing royalty is warranted, the Court should only award Jazz an ongoing royalty, consistent with the jury's award.

Dated: May 13, 2024

MCCARTER & ENGLISH, LLP

/s/ Daniel M. Silver

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EXHIBIT 1

FDA U.S. FOOD & DRUG ADMINISTRATION

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

May 1, 2023

ProPharma Group
1129 20th Street Northwest
Suite 600
Washington, DC 20036

Attention: Marla Scarola, MS
US Agent for Flamel Ireland Limited dba Avadel Ireland
marla.scarola@propharma.com

Dear Ms. Scarola:

Please find enclosed a copy of FDA's response to Sidley Austin LLP on behalf of Jazz Pharmaceuticals, Inc. regarding the agency's determination that Xywav's (NDA 212690) unexpired orphan-drug exclusivity does not block approval of Lumryz (NDA 214755).

Sandra Retzky -S
Digitally signed by Sandra Retzky -S
Date: 2023.05.01 10:00:10 -04'00'

Sandra S. Retzky, D.O., J.D., M.P.H.
Director
Office of Orphan Products Development

Meyer
Exhibit No.:
011
Kiara Miller 2023-11-20

FDA U.S. FOOD & DRUG ADMINISTRATION

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

May 1, 2023

Sidley Austin LLP
Counsel to Jazz Pharmaceuticals, Inc.
1501 K Street, N.W.
Washington, D.C. 20005

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]

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[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]

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[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

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[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 moiety[28] or is clinically superior[29] 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

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[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

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[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 humas 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

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[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

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[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 oxybate[84] 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

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[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

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[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.

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[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, Avadel[106] requested ODD for oxybate[107] 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]

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[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]

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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

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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.

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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

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[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

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[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

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[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

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[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

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[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, Glyceryl 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

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[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

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[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,

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[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

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[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:

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[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"

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[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

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[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

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[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

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[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

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[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

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[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.

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[246] OOPD Rebif 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); Procysbi 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

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[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.

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[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

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[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.

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[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.

Sandra Retzky -S

Digitally signed by Sandra Retzky -S
Date: 2023.05.01 09:58:53 -04'00'

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EXHIBIT 2

REDACTED IN ITS ENTIRETY

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	:	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	:	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	:	C.A. No. 21-1594-GBW

VIDEOTAPED DEPOSITION of RICHARD K. BOGAN, M.D., F.C.C.P., taken by the Defendant, pursuant to Agreement, held at the law offices of Quinn Emmanuel Urquhart & Sullivan, LLP, 51 Madison Avenue, 22nd Floor New York, NY 10010, on October 25, 2023, at 9:33 a.m., before a Notary Public of the State of New York.

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1	Q. Did you prepare this report before Lumryz was	09:59:33
2	allowed to be sold to patients?	09:59:41
3	A. The date on the report was in January.	09:59:45
4	Q. Do you know when Lumryz was first allowed to be	09:59:50
5	sold?	09:59:53
6	A. It was June of this year.	09:59:53
7	Q. And so this report from January was before	09:59:56
8	Lumryz could be given to patients; is that right?	10:00:00
9	A. That's correct.	10:00:02
10	Q. When you prepared this report -- did you have	10:00:03
11	any patients taking Lumryz in connection with any	10:00:12
12	clinical trials?	10:00:16
13	A. I did.	10:00:18
14	Q. As of January 2023, how many patients did you	10:00:18
15	have taking Lumryz as a part of a clinical trial?	10:00:23
16	A. Either two or three. Probably three.	10:00:27
17	Q. Sitting here today, in October of 2023, do you	10:00:31
18	still have any patients taking Lumryz as a part of a	10:00:37
19	clinical trial?	10:00:42
20	A. The reason I hesitate is because we're	10:00:43
21	transitioning that over to a commercial product. I	10:00:47
22	might have one whose pending, because there's an open	10:00:50
23	label extension, and the open label extension is	10:00:56
24	transitioning clinical. So we're close, but that may	10:00:59
25	have already happened within the last month.	10:01:03

Q. Sitting here today in October of 2023, do you have patients taking Lumryz just as regular patients, not in a clinical trial? 10:01:06 10:01:10 10:01:16

A. Yes. 10:01:17

Q. How many patients do you have today, October 25, 2023, taking Lumryz? 10:01:18 10:01:22

A. In the practice? 10:01:25

Q. In the practice. 10:01:26

A. Probably 10. 10:01:28

Q. Are some of the 10 patients of the other four prescribers in your Bogan Sleep Consultants practice? 10:01:29 10:01:35

A. Yes. 10:01:41

Q. Some of those 10 patients were taking Lumryz previously as a part of a clinical trial and some were not; is that right? 10:01:42 10:01:48 10:01:52

A. That's correct. 10:01:53

Q. How many of the approximately 10 patients seeing you specifically as their physician, as opposed to one of the other prescribers in your practice? 10:01:54 10:02:00 10:02:06

A. Five. 10:02:08

Q. In your practice, do patients see the same prescriber every time or do patients sometimes see one of your colleagues instead of you and vice versa? 10:02:09 10:02:12 10:02:16

A. I usually end up seeing my nurse practitioners' patients at some point. It's part of our supervision 10:02:20 10:02:26

process. 10:02:29
Q. Do you expect that for the -- strike that. 10:02:29
Before I ask more questions about patients, I should say at no point in time am I ever asking for patient identifying information. You wouldn't tell me anyways, but I want to be clear, if you think I have asked you about a patient name, I promise I didn't mean it. Please don't tell me any patient identifying information. 10:02:36 10:02:38 10:02:43 10:02:46 10:02:49 10:02:53 10:02:58
A. Understood. 10:02:58
Q. For the patients who are -- strike that. 10:02:58
Do you expect that for the 10 patients currently taking Lumryz, you at some point will see those 10 patients? 10:03:02 10:03:06 10:03:11
A. Of course. 10:03:12
Q. And you also have patients who are taking Xywav, correct? 10:03:12 10:03:25
A. Correct. 10:03:25
Q. And you still have some patients taking Xyrem? 10:03:26
A. That's correct. 10:03:31
Q. Do you have any patients taking the authorized generic version of Xyrem? 10:03:32 10:03:36
A. Probably. And the reason I say probably is I don't necessarily know. 10:03:38 10:03:42
Q. That's something that you expect might happen 10:03:44

to do -- you want me to do the math? 10:09:46

Q. Sure. 10:09:50

A. Okay. Um, it's a small percent, but probably 2 percent. 10:09:52 10:10:01

(Reporter Clarification.) 10:10:10

A. 130. 10:10:12

Q. What percentage of patients who you see in your practice have narcolepsy, roughly? 10:10:13 10:10:15

A. I just stated that. 10:10:19

Q. That's 2 percent of patients have narcolepsy? 10:10:22

A. I think. Might be more than that. 10:10:30

Q. So just thinking of the subset of patients who have narcolepsy, how many of those patients are on Xyrem, Xywav, authorized generic of Xyrem, or Lumryz? 10:10:32 10:10:37 10:10:42

A. About one third. 10:10:47

Q. So you also treat narcolepsy patients -- strike that. 10:10:50 10:10:54

Is there a word that you use to describe the group of drugs that I just referenced? 10:10:54 10:10:57

A. Oxybate. 10:10:59

Q. And so if I refer to oxybate drugs, to your understanding, you will have in mind that that's Xyrem, Xywav, authorized generic version of Xyrem, and Lumryz; is that right? 10:11:01 10:11:09 10:11:14 10:11:20

A. Correct. 10:11:20

Q. Approximately one-third of your narcolepsy patients are taking oxybate; is that right? 10:11:21 10:11:29

A. That's correct. 10:11:31

Q. And two-thirds of your narcolepsy patients then are taking something else? 10:11:32 10:11:36

A. Correct. 10:11:37

Q. You treat patients who have narcolepsy type 1 and type 2; is that right? 10:11:38 10:11:42

A. That's correct. 10:11:43

Q. Narcolepsy type 1 is narcolepsy with cataplexy? 10:11:46

A. That's correct. Or low CSF, hypocretin levels. 10:11:53

Q. How many of your narcolepsy type 1 patients as a percentage are taking an oxybate? 10:11:59 10:12:01

A. The majority. I mean, it would be a guess, but it's the majority. 10:12:03 10:12:16

(Reporter clarification.) 10:12:17

Q. Do you expect to have additional patients beyond the 10 start taking Lumryz? 10:12:17 10:12:55

A. Of course. 10:12:58

Q. Why is that? 10:12:59

A. When I see a patient with narcolepsy, we talk about pathophysiology, and we talk about different therapeutic options in reference to mechanism of action and dosing, et cetera, potential side effects, and so we introduce our narcolepsy patients to all of the therapy. 10:13:00 10:13:07 10:13:12 10:13:17 10:13:22

And then we decide what's best in this particular patient. 10:13:26 10:13:29

Q. Is the decision for what's best for a particular patient a decision that is made with input from the patient? 10:13:29 10:13:32 10:13:37

A. Correct. 10:13:37

Q. For the 10 patients in your practice who are currently taking Lumryz, did you or one of your colleagues have a discussion with those patients about their options for treatment? 10:13:38 10:13:47 10:13:52 10:13:54

A. Correct. 10:13:56

Q. And you said for five of those patients you had seen them yourself so far? 10:13:56 10:14:04

A. Correct. 10:14:07

Q. For the five patients you have who are taking Lumryz that you've seen personally, did you have a conversation with those five patients about their options? 10:14:08 10:14:12 10:14:14 10:14:18

A. Correct. 10:14:18

Q. For those five patients, is -- was there a reason that spans all five that they ended up making the decision in collaboration with you to choose Lumryz? 10:14:19 10:14:24 10:14:30

A. Yes. 10:14:33

Q. And what is that? 10:14:34

A. Well, I think about, in my practice, maybe 10 10:14:36

percent or 15 percent do not want to take twice-nightly dosing. So the once-nightly dose is appealing. 10:14:42 10:14:46

Q. Have you had patients in the past before Lumryz was approved who did not want to take twice-nightly dosing, and so therefore did not take Xyrem or Xywav? 10:14:51 10:14:58 10:15:03

A. A few. 10:15:08

Q. Have you had patients who started Xyrem or Xywav who discontinued treatment because they were unhappy with the twice-nightly dosing? 10:15:09 10:15:15 10:15:19

A. Yes. 10:15:22

Q. For the 10 patients that your practice has that are currently taking Lumryz, are any of those patients who had previously taken an oxybate? 10:15:22 10:15:25 10:15:29

A. Yes. 10:15:34

Q. Do you know what fraction? 10:15:35

A. I'm not certain. It's such a small number. But within the practice, not me personally. 10:15:41 10:15:47

Q. Within the practice? 10:16:04

A. Yeah. Probably 3 new starts, I suspect. 10:16:07

Q. 3 of the 10? 10:16:11

A. 3 to 5, something like that. 10:16:12

Q. 3 to 5 of the 10 Lumryz patients in your overall practice are new starts; is that right? 10:16:15 10:16:23

A. Probably. 10:16:25

Q. And the other 5 to 7 are patients who had 10:16:26

previously tried an oxybate? 10:16:30
A. Correct. Or didn't -- wouldn't take it before, so I guess I should have included those in the new starts. 10:16:32 10:16:36 10:16:40
But yes, we have some patients who have been on the oxybate molecule before and for whatever reason stopped, and then when we restart, they decided to go with Lumryz. 10:16:43 10:16:46 10:16:49 10:16:56
Q. Is it fair to say then that your Lumryz patients fall into three buckets: Patients who had never taken an oxybate, patients who had previously taken an oxybate but discontinued, and then patients who had never taken an oxybate but who you had discussed an oxybate with previously and they didn't want to take it? 10:16:56 10:16:59 10:17:03 10:17:07 10:17:14 10:17:23
A. I'm having trouble separating bucket 1 from bucket 3, because they've both -- they've never taken it. 10:17:25 10:17:31 10:17:35
But there are some patient who decided not to take twice nightly for whatever reason, and of course, decided to take once-nightly. 10:17:36 10:17:39 10:17:44
And then there are patients who, when they considered their options, bucket 1, I'm assuming, new starts. There are some when you give them their choices, they chose the once-nightly. 10:17:47 10:17:51 10:17:56 10:17:59
Q. So among your patients with new starts, new 10:18:01

starts on an oxybate -- strike that. 10:18:04

Among your patients who are new starts for 10:18:05

Lumryz, some of those are patients who had never 10:18:10

considered an oxybate before but some are patients to 10:18:13

whom you have offered an oxybate before, and they didn't 10:18:17

want to take it because it was twice nightly? 10:18:21

A. That's correct. 10:18:24

Q. And then you also had patients on Lumryz who 10:18:25

had previously taken an oxybate and stopped taking an 10:18:28

oxybate? 10:18:34

A. That's correct. 10:18:34

Q. Are you aware of any reason why your patients 10:18:35

who are taking Lumryz who had previously taken an 10:18:38

oxybate, stopped taking the oxybate, other than dislike 10:18:41

of the twice-nightly dosing? 10:18:46

A. Yes. 10:18:48

Q. What are the reasons? 10:18:48

A. It's interesting. The oxybate molecule, when 10:18:50

it works, some patients sort of forget how bad they 10:18:54

were, and they are like, I'm doing okay. I missed doses 10:18:58

and I'm still doing okay. So maybe I don't need it, and 10:19:03

they stopped their medication, and then a few months 10:19:08

later they're back to where they were, so they started 10:19:08

back. 10:19:08

But sometimes it's social, a new baby in the 10:19:15

house or a single mom, or, you know, there are certain circumstances that preclude taking an oxybate molecule, and then when those things change, they may want to restart. There's a lot of chaos in life. 10:19:20 10:19:23 10:19:27 10:19:33

Q. And you've also had patients stop taking an oxybate specifically because it had to be taken twice a night; is that right? 10:19:36 10:19:40 10:19:44

A. That's what I just said, in terms of the social issues, correct. It's more that rather than I don't want to take two doses. 10:19:45 10:19:49 10:19:52

Q. And you mentioned a minute ago you have patients who sometimes miss a dose and think things are okay with a missed dose. Can you elaborate on that? 10:19:53 10:19:59 10:20:02

A. It's very interesting. The molecule is such that one, it takes a while to get an effect, as you know. Based on methods of administration, we titrate the dose until we get a biological effect, and it takes a while for the parents. In fact, the science says, we can see continued improvement two or three months after we reach a stable dose. 10:20:06 10:20:09 10:20:12 10:20:18 10:20:22 10:20:27 10:20:31

And what we've see clinically, and this actually has been reported, that when the patients stop the medication or miss a dose, they continue to do okay for a while, particularly in terms of the cataplexy. 10:20:33 10:20:37 10:20:41 10:20:43

So it may take weeks for the cataplexy to get 10:20:47

back to baseline state. Excessive sleepiness comes back a little quicker, is my opinion, based on clinical experience; but we have patient who skip doses, run out of the medication, don't get it from the pharmacy, travel on vacation and forget it, and they continue to do okay. 10:20:47 10:20:52 10:20:57 10:21:02 10:21:04 10:21:08

Q. And you attribute that to the fact that the drug -- strike that. 10:21:12 10:21:15

Can you say again what you attribute that to? 10:21:18

A. I don't really know. Some -- I mean there's a lot of speculation about some plasticity of the brain. The molecule affects neuronal signalling so these individuals continue to be better despite the absence of the drug. 10:21:22 10:21:26 10:21:31 10:21:37 10:21:40

The drug has a short half life. It's only there four hours, typically. And yet it has this extended biological effect that we don't really understand. We know a lot about mechanism of action, but we don't understand this -- how you relate the short duration of the drug to the biological effect. 10:21:42 10:21:47 10:21:53 10:21:53 10:21:55 10:21:57

Q. Can you turn in Exhibit 1 to your deposition, which is your opening report, to page 8? 10:22:01 10:22:05

A. Okay. I have page 8. 10:22:09

Q. Paragraph 20. And the first sentence: 10:22:13

"As set forth herein, each of the 10:22:17

A. Those are my words. 13:20:45

Q. Did Dr. Courser in his report ever say that he was offering the opinion that Lumryz will necessarily be safer and more convenient? 13:20:47 13:20:55 13:21:01

A. He -- he said, I don't know if he used the word "necessarily," but he did say it was safer and more effective. 13:21:05 13:21:10 13:21:13

Q. Your point of disagreement with Dr. Courser is that you don't think that Lumryz necessarily, in all cases, will be safer and more convenient than the twice-nightly products? 13:21:16 13:21:24 13:21:27 13:21:32

A. I do not believe that. 13:21:33

Q. You have not offered the opinion that Lumryz is never safer or more convenient than a twice-nightly oxybate? 13:21:34 13:21:41 13:21:49

A. I never say never. I have patients -- well -- 13:21:49

Q. Please go ahead and finish. 13:22:01

A. No, that's fine. I never say never. 13:22:03

I'm sure there are going to be patients who prefer once-nightly. 13:22:06 13:22:10

Q. Do you think there will be patients who prefer once-nightly, and if Lumryz is not available, they will not choose to take a twice-nightly product? 13:22:12 13:22:16 13:22:19

A. Yes. 13:22:21

Q. You, in fact, have some patients like that? 13:22:21

A. Yes. 13:22:24
Q. And so for a patient like that, if Lumryz is 13:22:24
not available, the patient won't be able to take an 13:22:27
oxybate for their narcolepsy? 13:22:33
A. They have it available, and they can take it, 13:22:34
and some do take it. Some change their mind, but there 13:22:37
are some patients who say they are not going to take two 13:22:41
doses. There are not many, but there are a few. 13:22:44
Q. Do you think oxybate therapies are the best 13:22:47
treatment available for narcolepsy patients? 13:22:52
A. Yes. As a rule -- I mean. Not for everybody, 13:22:55
but in general. 13:23:02
Q. Do you want Lumryz to be available to patients? 13:23:02
A. Let me put it this way: I think oxybate is a 13:23:11
very effective molecule. It's one of the most effective 13:23:22
that we've seen in the treatment for narcolepsy 13:23:26
patients, and yes, I would like a one-night -- 13:23:30
once-nightly oxybate therapy as an option. 13:23:32
Q. Would you support an effort to prevent Avadel 13:23:39
from selling Lumryz, such that patients could not 13:23:52
receive it? 13:23:57
A. Can I answer it this way: In that I am a 13:23:57
prescriber, and I will prescribe it, so that's not 13:24:06
preventing Avadel from marketing the drug. 13:24:10
Q. Are you aware that Jazz is asking in this 13:24:13

litigation that if it wins, it wants to ask the Court to take Lumryz off the market until the 2030s? 13:24:20 13:24:27

A. Not aware of the specifics. I'm not aware of the implications of this, actually. 13:24:31 13:24:37

Q. So you were not aware that Jazz has asked in its lawsuit for injunctive relief that would stop all Lumryz sales to anyone until the 2030s? 13:24:39 13:24:43 13:24:51

A. No. 13:24:54

Q. As a physician, do you support that request by Jazz? 13:24:55 13:25:14

A. That's sort of out of the scope of what I was asked to do when I was asked to look at the patent and the method of administration and then the reference to the PI. So that's what I was asked to do, and render an opinion on. 13:25:14 13:25:20 13:25:24 13:25:28 13:25:35

As a clinician, I would like to have once-nightly oxybate available. 13:25:36 13:25:40

Q. Can you turn in your report to -- actually stay on page 1, paragraph 3. 13:25:41 13:26:04

A. Okay. 13:26:09

Q. The second sentence begins "and while." Do you see that? 13:26:09 13:26:21

A. Yes. 13:26:21

Q. In your report you state: 13:26:22

"And while there may be a perceived 13:26:23

benefit in Lumryz, based on convenience, there is no clear evidence in clinical or research use of an advantage or enhanced efficacy in Lumryz over Jazz's twice-nightly oxybate products." Do you see that? 13:26:26 13:26:29 13:26:31 13:26:35 13:26:38 13:26:39

A. I see that. 13:26:39

Q. Now, you're not opining that there never could be evidence in the future that Lumryz has an advantage over Jazz's twice-nightly oxybate products; is that right? 13:26:40 13:26:43 13:26:50 13:26:56

A. That's correct. I'm not testifying there's going to be more disadvantage either. It's talking about the current state of the art. 13:26:56 13:26:59 13:27:05

(Reporter Clarification.) 13:27:09

THE WITNESS: Art. 13:27:10

Q. Can you turn in your report to page 3 and 4. 13:27:10

This is a section starting on 3. It says, "A response to Dr. Courser's overview of narcolepsy." Do you see that? 13:27:34 13:27:38 13:27:42

A. I do. 13:27:42

Q. And then I want to ask you about paragraph 11 on page 4. 13:27:43 13:27:48

Paragraph 11, you reference an article by R.H. Ben-Joseph. Do you see that? 13:27:52 13:27:59

C E R T I F I C A T E

STATE OF NEW YORK)

) ss.:

COUNTY OF QUEENS)

I, BROOKE E. PERRY, a Notary Public within and for the State of New York, do hereby certify:

That RICHARD K. BOGAN, M.D. FCCP, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage; and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 25th day of October, 2023.

Brooke E. Perry

BROOKE E. PERRY

EXHIBIT 4

No. 2023-1186

In the

United States Court of Appeals for the Federal Circuit

JAZZ PHARMACEUTICALS, INC.,

Plaintiff-Appellant,

v.

AVADEL CNS PHARMACEUTICALS LLC,

Defendant-Appellee.

Appeal from the United States District Court
for the District of Delaware, Gregory B. Williams, J.

BRIEF OF THE PUBLIC INTEREST PATENT LAW INSTITUTE, PROFESSOR ROBIN FELDMAN, NARCOLEPSY PATIENTS, AND THE NISKANEN CENTER AS *AMICI CURIAE* IN SUPPORT OF DEFENDANT-APPELLEE

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CERTIFICATE OF INTEREST

Pursuant to Rules 29(a) and 47.4 of the Federal Circuit Rules of Practice, counsel certifies as follows:

(1) The full name of every party or amicus represented by me is **the Public Interest Patent Law Institute, Professor Robin Feldman, Eliana Bookbinder, Brian Mahn, and the Niskanen Center**.

(2) The above-identified parties are the real parties in interest.

(3) The corporate disclosure statement of Rule 26.1 of the Federal Rules of Appellate Procedure is as follows: There is no parent corporation to or any corporation that owns 10% or more of stock in the above-identified parties.

(4) The names of all law firms and the partners and associates that have appeared for the party in the lower tribunal or are expected to appear for the party in this court, not including those who have entered or are expected to enter an appearance before this court, are: **None**.

(5) The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal are: **None other than that identified in Appellee's brief**.

(6) All information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees): **None**.

Dated: January 18, 2023

/s/ David Bookbinder
David Bookbinder
Counsel for Amici Curiae

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INTEREST OF *AMICI CURIAE*[1]

The Public Interest Patent Law Institute ("PIPLI") is a nonprofit organization dedicated to ensuring the patent system promotes innovation and access for the public's benefit. PIPLI conducts research on patent policy issues, represents the public's interest in courts and agencies deciding issues of patent law, and advocates for transparency, integrity, and accountability throughout the patent system.

Professor Robin Feldman is the Arthur J. Goldberg Distinguished Professor of Law, Albert Abramson '54 Distinguished Professor of Law Chair, and Director of the Center for Innovation at UC College of the Law, San Francisco.[2]

Eliana Bookbinder and Brian Mahn are patients with narcolepsy who take Xyrem or Xywav.[3] They have benefited from the existence of these drugs and are happy that a treatment for their condition is available. However, they are personally familiar with the logistical difficulties associated with taking Xyrem and Xywav and support the entry of new products.

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[1]Pursuant to Federal Rule of Appellate Procedure 29(a), all parties received appropriate notice of and consented to the filing of this brief. Pursuant to Rule 29(c)(5), no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of the brief. No person or entity, other than *amici*, their members, or their counsel, made a monetary contribution to the preparation or submission of this brief.

[2]Affiliations are included for identification purposes only.

[3]Jazz recently introduced Xywav, a low-sodium formulation of Xyrem; this brief refers to them collectively as Xyrem.

The Niskanen Center is a nonprofit, nonpartisan 501(c)(3) public policy think tank and advocacy organization working to protect private property rights, economic liberty, well-functioning markets, and to roll back regressive regulations which restrict freedom of exchange and increase inequality. The Niskanen Center believes that the patent system should be a force for progress and should not be used in a manner that prevents free entry and innovation and that U.S. food and drug regulations are not used as a tool to block competition, innovation, patient choice, and better health outcomes for those dealing with narcolepsy.

SUMMARY OF ARGUMENT

Delisting of U.S. Patent No. 8,731,963 ("the '963 patent") from the Orange Book, as the district court ordered, is in the interest of the balance built into the patent system, the intent of the Hatch–Waxman Act, and patients who suffer from narcolepsy. Appellant Jazz Pharmaceuticals makes a useful product, Xyrem, that helps people with narcolepsy and other serious sleep disorders. Appellee Avadel Pharmaceuticals developed a different drug, Lumryz, that improves on Xyrem by addressing some of the drawbacks associated with taking Xyrem.

Xyrem must be taken twice a night: an initial dose at bedtime, and then a second two to four hours later. Ironically, Xyrem requires patients with sleep disorders to wake in the middle of the night, while still under the influence of the first dose. Once-nightly Lumryz eliminates patients' need to rouse themselves from a drug-induced sleep in order to take a second dose. This brief includes the first-hand experiences of Xyrem patients, showing the pressing and immediate need for this improved treatment to be available on the market.

The '963 patent that Jazz asserts to block introduction of Lumryz is directed not to the drug itself, but to a computer system for safe dispensation of a drug.[4] The Food and Drug Administration ("FDA") mandated use of such a safe dispensation

[4] *See generally Risk Evaluation and Mitigation Strategies (REMS)*, U.S. Food & Drug Admin. (last updated Dec. 17, 2021), *available online*. Locations of authorities available online are shown in the Table of Authorities.

system under its Risk Evaluation and Mitigation Strategies ("REMS") authority, because the active ingredient in both Xyrem and Lumryz is sodium oxybate, a controlled substance.[5] Such patent assertions exploiting the regulatory system are uniquely problematic, as they upend traditional expectations of how patents work, give rise to strong market power, and undermine the very innovation incentives that patents are supposed to create.

Jazz maintains that the '963 patent entitles the company to a stay on the approval of Lumryz under the Drug Price Competition and Patent Term Restoration Act ("Hatch–Waxman") as amended. And yet that statute, primarily designed to facilitate the marketing of generic pharmaceuticals rather than to impede novel and improved products, is improperly used here. To achieve the twin goals of patent protection and competition, the statute provides what is effectively a 30-month preliminary injunction for a limited class of patents on active ingredients, drug formulations, and methods of use—none of which characterizes the '963 patent. Allowing patent holders like Jazz—who have not created the kinds of inventions Hatch–Waxman was designed to encourage—to use this remedy undermines the purposes of both Hatch–Waxman and the patent system overall.

[5]The Drug Enforcement Administration lists sodium oxybate as a Schedule I controlled substance, and Xyrem as a Schedule III substance. Drug Enf't Admin., U.S. Dep't of Justice, *Drug Fact Sheet* (Apr. 2020), *available online*.

ARGUMENT

I. Jazz Harms Patients by Blocking a Useful Improvement to Their Treatment

By using the '963 patent to prevent Lumryz's introduction, Jazz harms those it has in the past helped: the 135,000 to 200,000 Americans suffering from narcolepsy and other serious sleep disorders.[6] Xyrem's twice-nightly regimen means users take a sleep-inducing drug that requires them to wake up in the middle of the night in order to take a second dose designed to give them a full night's sleep. Xyrem users are grateful for an often effective narcolepsy treatment, but Xyrem's 2-dose regimen causes serious disruptions in their lives that Lumryz will hopefully eliminate.

To assess the real-world effects for patients, *amici* spoke with several of them about their experiences with Xyrem, and also researched existing online commentary by narcolepsy patients.[7]

A. Xyrem's Double-Dose Schedule Creates Significant Problems for Patients

Taking Xyrem's second dose around four hours after taking the first one means having to wake up while still under the influence of the first dose. The most obvious

[6]Office of Commc'ns & Pub. Liaison, Nat'l Insts. of Health, *Narcolepsy Fact Sheet* (last reviewed Sept. 27, 2022) [hereinafter Narcolepsy Fact Sheet], *available online*.

[7]To maintain the privacy of their specific medical conditions, patients are discussed only anonymously or in the aggregate below.

problem is that having been knocked out by the first dose, patients are often unable to wake for their alarms; patients reported setting multiple blaring alarms, often unsuccessfully, and relying on spouses and family members to wake them up. One patient reported that even after two years of using Xyrem, they miss their second dose about once a week.

If a patient does not wake up for the second dose, they may then wake up after about five or six hours of sleep. This creates a dilemma for patients. The patient can skip their second dose and suffer the symptoms of narcolepsy resulting from lack of sleep. Missing the second dose means, in the words of one patient "wak[ing] up tired, achey, [and in a] bad mood." Missing the second dose can also lead to rapid-onset drowsiness and cataplexy attacks—the sudden onset of "weakness and a loss of voluntary muscle control".[8]

Alternatively, patients who have not woken up on schedule can take their second dose late, forcing them to oversleep. Whether or not the patient successfully wakes up and times their dosage correctly, a second problem emerges: patients are often groggy and disoriented—in no condition to measure out a precise volume of the liquid Xyrem formulation—meaning that the second-dose routine must be carefully orchestrated in advance. One patient measured out the second dose before bed but feared that the family pets might knock over the container; another

[8] Narcolepsy Fact Sheet, *supra* note 6.

reported receiving a concussion from falling over in the process of taking the second dose. Another patient reported falling asleep in the bathroom when going to take the second dose.

Even worse is when a patient wakes up early, as can happen when the first dose is not titrated precisely or the patient's daytime activities cause a change in sleep patterns. Ideally, the patient realizes the error and is subjected to staying awake for hours until it is the right time to take the second dose. But being half-asleep in the middle of the night, some patients reported not realizing what time it was and taking the second dose early, effectively overdosing on Xyrem. One patient recalled realizing they had taken the second dose early, and panickedly tried to monitor for overdose symptoms by staying awake while on the double-dose of sleep medication. Adding to the complexity of mistiming the second administration of Xyrem is the fact that these decisions are made under the influence of the first dose of Xyrem in the wee hours of the morning.[9]

B. The Drug's Complexity Has Caused Personal and Professional Losses

Structuring one's life around a twice-nightly drug and fearing dosage errors, unsurprisingly, exacts a toll. One patient compared the lifestyle changes required to take Xyrem to those associated with being diabetic. The patients *amici* spoke

[9] *See also Overdose? Profuse Sweating on Xyrem*, Reddit r/Narcolepsy (July 25, 2021), *available online*.

to discussed how Xyrem's complicated dosing regimen had cost them personally and professionally.

Families of patients bear an immense burden. One patient relied on their parents to wake them up for their second dose (alarms did not work for them); the patient said they were immensely thankful to have family around to help but felt bad for making them wake up every night. Marriages have ended in divorce and students could not find roommates, we were told, because of the disruptive nightly second-dose routine. One patient wondered how a Xyrem patient could ever have children, as the drug's strict schedule regimen would seem incompatible with the unpredictable midnight needs of infants and toddlers.

Patients' careers and education also often suffered. Xyrem patients face more than the general inconveniences associated with oversleeping: if they are still experiencing the effects of Xyrem when they wake up it is unsafe to drive a car to get to work or school. Delayed second doses made patients late for school or work. One patient we talked to was a college student at the time they started taking Xyrem and reported not being able to enroll in morning courses because they might miss class due to a delayed second dose. One patient lost their job, another contemplated dropping out of school, and third could barely find time to do homework.

C. Patients Often Feel Unheard

The opportunity to take a once-nightly formulation excited the patients *amici* spoke to, given their longstanding difficulties with the twice-nightly Xyrem formulation. These patients anticipated that Avadel's once-nightly formulation would tremendously improve their quality of life beyond the benefits they already receive from having a drug, Xyrem, to treat their narcolepsy. One patient mentioned the simple joy of having mornings where they can have breakfast after a predictable night of sleep. Others anticipated relieving burdens on their families, being able to work, traveling freely, and thinking of children and pets as companions rather than as risks to the medication regimen.

Given these tremendous benefits for patients, one would think that Jazz would have had strong incentives to develop its products to satisfy demand. And yet many of the patients intimated (or said outright) that Jazz insufficiently prioritized patient welfare. One complained that Jazz's distribution restrictions had become more burdensome over time, making it increasingly difficult for them to receive treatment. Surprisingly, one patient, attending a national narcolepsy conference, found no Jazz representatives delegated to meet with patients there.

Patients also reported difficulties with another aspect of Xyrem: the complex delivery and distribution process required under the REMS program. Patients had to stay home from work to sign for shipments of their medications, and had

difficulty finding providers and pharmacies authorized to prescribe and dispense Xyrem. Jazz distributes Xyrem using FedEx, and requires receipt by someone over the age of 21. This is inconvenient for those who either live alone, with someone who is out during the day, or who have trouble receiving such sensitive packages via their apartment, workplace, or dormitory mail room. One of the patients found a workaround to this system by asking FedEx to hold the package at their facility. This way, they could pick up Xyrem in the same way they would go to a pharmacy to pick up a drug. But Jazz does not offer that option to patients: instead, they must use FedEx's system to ask for the package to be held.

The patients we talked to were clear that they did not think Xyrem was a bad product: many of them used it successfully or knew of others who did so. One gave it a ringing endorsement when they described it as "amazingly effective" in the treatment of narcolepsy. What was ultimately of concern to them was patient choice. Narcolepsy affected each of them differently, and the lifestyle choices imposed by Xyrem worked for some patients and not others, we were told. Having new and different sodium oxybate products on the market, especially ones that addressed patient difficulties such as twice-nightly dosing, was the ultimate outcome that patients hoped would be achieved.

Patients desire an alternative to Xyrem that can also treat their narcolepsy without the side effects of their current medication. The practical benefits of improved

choice in and access to medication should inform this Court's decision to affirm the district court's order.

II. A Healthy Drug Patent System Relies on Judicial Oversight of Orange Book Listings

A. An Improperly Listed Orange Book Patent Interferes with the Development and Utilization of Medicines

Bringing a new drug to market is no mean feat, especially if that drug can be abused and requires the FDA to approve a REMS for it. Avadel sought FDA's approval for Lumryz, including the development of a REMS. Avadel worked with the FDA to develop a REMS modeled after one previously approved for Jazz, and Lumryz was tentatively approved pending certification that Lumryz did not infringe on any patents in the Orange Book.

After receiving a complaint for infringement of the '963 patent (and four others), Avadel filed a counterclaim seeking, among other forms of relief, a requirement by the district court for Jazz to delist the '963 patent from the Orange Book as the '963 patent "only includes claims to a 'computer-implemented system for treatment of a narcoleptic patient with a prescription drug,' which are neither method claims nor claims to a drug product or drug substance." Answer to Complaint for Patent Infringement, Defenses and Counterclaims at 41, *Jazz Pharm., Inc. v. Avadel CNS Pharm., LLC*, No. 1:21-cv-691 (D. Del. Nov. 18, June 3, 2021) (Doc. No. 11).

The question presented to the Court is whether or not to uphold the Delaware District Court's order for Jazz Pharmaceuticals to delist its patent covering a required REMS because the patent covers neither a "drug substance (active ingredient) . . . a drug product (formulation composition) [or a] method of using such drug." Federal Food, Drug, and Cosmetic Act (FFDCA) § 505(b)(1)(A)(viii), 21 U.S.C. § 355. The district court found that the '963 patent "does not belong in the Orange Book." Given the unambiguous finding by the district court and the harm of granting Jazz what is effectively a 30-month preliminary injunction, this Court should affirm the district court's order.

Instead of covering an invention that can be statutorily submitted to the Orange Book, the '963 patent covers the use of a REMS. Because Avadel's product at issue here uses the same active ingredient as Jazz's product, sodium oxybate, the FDA requires a REMS for the drug. The '963 patent is described as a "sensitive drug distribution system and method" claiming, "A *computer-implemented* system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising prescriptions for a sensitive drug." A drug, active ingredient, formulation, composition, or method of using the drug are not mentioned. *See id.*

The erroneous listing of the '963 patent in the Orange Book creates a unique problem for those like Avadel that want to develop novel therapies that compete

with Xyrem by offering a product, Lumryz, that is an improvement over Jazz's. Lumryz represents a significant step forward in treating narcolepsy and the innovation offers greater choice to patients who suffer from it.

An automatic 30-month delay goes well beyond the normal injunctive relief available to those claiming patent infringement. Avadel developed a new product to address a real need by patients and took all the necessary steps to ensure the product is available safely. This is what a well-functioning pharmaceutical industry looks like. The Court should not allow Jazz to interrupt this process by using the special rights granted to it by a patent that is incorrectly placed in the Orange Book.

B. Keeping the '963 Patent in the Orange Book Undermines the Balance Created in the Hatch-Waxman Act

The patent system exists to "promote the Progress of . . . useful Arts," by authorizing the grant of exclusive rights over new inventions. U.S. Const. art. I, § 8, cl. 8. These inventions include pharmaceutical products, an industry that relies heavily on the patent system. Pharmaceutical innovations rely on Hatch–Waxman.[10] The law "established several practices intended to facilitate the marketing of generic

[10]Drug Price Competition and Patent Term Restoration Act (Hatch–Waxman), Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at FFDCA § 505). Throughout this brief, "Hatch–Waxman" will refer to the statutory framework as subsequently amended. *See* Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066; Orange Book Transparency Act of 2020, Pub. L. No. 116-290, 134 Stat. 4889.

drugs while permitting brand name companies to recover a portion of their intellectual property rights lost during the pharmaceutical approval process."[11] Among these practices intended to strike a balance between new drug entry and protecting intellectual property rights is a special process for treating patents associated with improved pharmaceuticals, documented in what is commonly called the "Orange Book."[12]

Despite granting a temporary period of exclusivity in exchange for the development and disclosure of an invention, the Patent Act and the larger body of patent law contain provisions to facilitate competition through the provision of injunctive relief not automatically, but "in accordance with the general principles of equity." 35 U.S.C. § 283. Following this requirement of equitable considerations, this Court has repeatedly held that "[a] plaintiff seeking a preliminary injunction must establish [1] that he is likely to succeed on the merits, [2] that he is likely to suffer irreparable harm in the absence of preliminary relief, [3] that the balance of equities tips in his favor, and [4] that an injunction is in the public interest." *See Takeda Pharm. USA v. Mylan Pharm. Inc.*, 967 F.3d 1339, 1345 (Fed. Cir. 2020) (citing *Winter v. Nat. Res. Def. Council, Inc.*, 129 S. Ct. 365, 20 (2008)); *Titan Tire*

[11] Wendy H. Schacht & John R. Thomas, *The Hatch-Waxman Act: A Quarter Century Later* 1 (Cong. Research Serv., Report No. R41114, Mar. 13, 2012), *available online*.

[12] *See* Food & Drug Admin., *Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book)* (42d ed. 2022), *available online*.

Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1375–76 (Fed. Cir. 2009); *Apple, Inc. v. Samsung Elecs. Co.*, 678 F.3d 1314 (Fed. Cir. 2012). The Federal Circuit has also acknowledged the importance of deference to district court in determining whether or not to provide injunctive relief. *See Apple*, 678 F.3d at 1323 ("The decision to grant or deny a preliminary injunction lies within the sound discretion of the district court, and we will not reverse its judgment absent an abuse of that discretion.") (citing *Titan Tire*, 566 F.3d at 1375).

The 30-month stay made available under Hatch–Waxman is a departure from this generally equitable approach. The rights afforded to those with a patent in the Orange Book are, by design, a tool to protect the exclusive rights granted to patent holders by allowing them to block entry by would-be competitors beyond those normally available in other cases of alleged infringement. Such rights were conferred as part of a general program designed to speed new drug entry and is part of the tradeoffs built into that system. But as a tradeoff, it was not designed merely as a way to beef up injunctive relief. Hatch–Waxman restricts patents eligible to receive this protection to patents on "a drug substance (active ingredient)[,] a drug product (formulation or composition)[,] or a method of using such a drug." FFDCA § 505(b)(1)(A)(viii).

The FDA's role in the administration of the Orange Book is "ministerial"[13]

[13] Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36675, 36683 (Food & Drug Admin. June 18, 2003).

and "does not have the expertise or the desire to become involved in issues concerning patent law and sufficiency of notice."[14] It is then left to the judiciary to ensure that patents listed in the Orange Book belong there. Hatch–Waxman tolerates this hands-off approach from the FDA by building in a mechanism to resolve improperly listed Orange Book patents. In 2003 Congress passed the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. *See* Pub. L. No. 108-173, 117 Stat. 2066. This updated the Hatch–Waxman framework by creating the opportunity for an applicant to file a counterclaim and receive an order from a district court for the patent holder to "correct or delete the patent information submitted by the holder [if] that patent does not claim either . . . the drug for which the application was approved [or] an approved method of approving the drug." FFDCA § 505(c)(3)(D)(ii)(I).

This balance was carefully crafted to help patients by making it possible for drugs like Lumryz to enter the market. The responsibility to prevent outcomes contrary to the intent of Hatch–Waxman falls to the district court, a responsibility it fulfilled. Reversing the district court's delisting order would undermine the balance built into the framework of Hatch–Waxman.

[14] Abbreviated New Drug Application Regulations, 59 Fed. Reg. 50338, 50350 (Food & Drug Admin. Oct. 3, 1994).

III. Jazz's Unusual Patent Here Undermines Innovation Rather Than Advancing It

The question presented to this Court has significant ramifications for the interaction between the United States' patent and regulatory systems. Jazz's patent exploits the regulatory system in a well-known but distinct manner, giving rise to actual monopoly power and the innovation disincentives that arise therefrom. The district court's finding that the '963 patent does not belong in the Orange Book should be sufficient to uphold the district court's order. Yet this case has broader implications that the Court should take into consideration in its ruling.

A. Jazz's Patent Exploits the Regulatory System, Creating a "Mandatory Infringement" Situation

To understand why the '963 patent is uniquely problematic to innovation, competition, and patients, it is first necessary to observe that it is no ordinary patent. Instead, it is a patent designed to exploit regulatory and public safety systems in a way that, unlike the mine-run of patents, confers extraordinary monopoly power at the expense of public health and welfare.

Scholars have characterized patents that overlap with the regulatory system as "regulatory gaming" or, because competitors must infringe the patent to comply with the regulation, "mandatory infringement." *See* Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 Tex. L. Rev. 685 (2008–2009); Charles Duan, *Mandatory Infringement*, 75 Fla. L. Rev. (forthcoming 2023), *avail-*

able online. Typically, the government mandate has little to do with innovation policy, generally being designed to promote public safety or societal welfare. Mandatory infringement involves the collision of patent policy with other, siloed, governmental policies that each pursue a separate public interest goal. This Court should take into consideration this complicated dynamic and the impossible situation companies like Avadel find themselves in when trying to navigate both the regulatory state and the patent system.

B. Exploiting the Regulatory System Lets Jazz Engage in Anticompetitive Behavior

The mandatory-infringement nature of the '963 patent is critical because it radically alters the usual relationship between patents, competition, and innovation. The basic observation in an extensive literature is that the holder of a patent on a regulatory mandate goes from a mere advantaged competitor in a larger market to a full-blown monopolist. *See, e.g.,* Dogan & Lemley, *supra*, at 687–88; Michael A. Gollin, *Using Intellectual Property to Improve Environmental Protection*, 4 Harv. J.L. & Tech. 193, 219 n.128 (1991) (describing such patents as a "supermonopoly"); *see also* Robert H. Bork, *The Antitrust Paradox* 159 (1978) ("predation by abuse of governmental procedure"); Susan A. Creighton et al., *Cheap Exclusion*, 72 Antitrust L.J. 975, 990–92 (2005). This increase in market power happens because the regulatory mandate constrains the competitive market space

to the scope of the patent, precluding design-around competition and giving the patent holder true market power. *See* Duan, *supra*, at 30–36.[15]

Contrast this with the dynamic that usually exists in markets where innovation—and thus patenting—is extensive. Usually, "[t]he opportunity to charge monopoly prices—at least for a short period—is what attracts 'business acumen' in the first place; it induces risk taking that produces innovation and economic growth." *Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP*, 540 U.S. 398, 407 (2004). But once such a position has been achieved, that incentive no longer exists because those returns can already be counted on, and further investment would not achieve greater returns. *See* Thomas J. Holmes et al., *Monopoly and the Incentive to Innovate When Adoption Involves Switchover Disruptions*, 4 Am. Econ. J.: Microeconomics 1, 3 (2012) ("a firm with a lucrative monopoly may decide not to adopt a technology that, in the short run, disturbs its lucrative position."). The ability to legally block any competition from rivals also enables nonresponsiveness to the needs of consumers.

[15]The overlap with regulation thus distinguishes mandatory-infringement patents from ordinary patents that typically do not confer market power, because ordinarily competitors are not constrained by regulation and so can design around patents to satisfy consumer demand. *See* U.S. Dep't of Justice & Fed. Trade Comm'n, *Antitrust Guidelines for the Licensing of Intellectual Property* 4 (1995), *available online*, *quoted in Ill. Tool Works Inc. v. Indep. Ink, Inc.*, 547 U.S. 28, 45 (2006).

The context of this case provides some evidence to support these observations about competition and market power. In the case of Xyrem, the only substantial innovation since the introduction of the drug came in the form of a low-sodium formulation Xywav—an improvement to be sure, especially for those who have cardiac issues and must watch their sodium intake. But this improvement is one that allowed Jazz to expand on the *extensive* margins and sell to patients who couldn't take something with a high sodium content without addressing the concerns of patients for whom sodium content was not a primary issue.

Patients' comments demonstrate some of the nonresponsiveness to patient needs associated with a firm holding an unchallenged market position. Improvements to the drug itself to change the dosage from twice- to once-nightly were both possible and a clear area for improvement: yet Jazz forwent the opportunity to invest in such improvements. The inconveniences patients face when actually acquiring lawfully prescribed Xyrem and the lack of responsiveness from Jazz to make it easier for patients to obtain their medication is an example of business conduct disinterested in improving customer service. While some of the frustrations expressed by patients in their dealings with Jazz in section I.C of this brief are unavoidable due to the REMS requirement, this does not mean that every feature is essential or Jazz has no opportunities to improve its customer service.

Taken together, this creates a situation where patients must do without improved treatment options for reasons immaterial to the technical or material realities of innovation. It is one entirely created by anticompetitive abuse of the Orange Book system by Jazz. Even a thirty-month stay is a serious hindrance, as the Federal Trade Commission made clear in its *amicus* brief before the district court:

> An improper listing harms competition and consumers: By listing a patent in the Orange Book and then filing an infringement suit, a brand can block competition for up to two-and-a-half years regardless of the scope or validity of the patent and regardless of whether it meets the statutory listing criteria . . . Consumers suffer both because they are forced to continue paying non-competitive prices and because they are deprived of the ability to choose between products . . . [I]f the '963 patent is improperly listed, it appears to be causing significant harm to competition.

Federal Trade Commission's Brief as *Amicus Curiae* at 14–15, *Jazz Pharm.*, No. 1:21-cv-691 (Nov. 15, 2022) (Doc. No. 227).

This case is not the first time that processes related to REMS compliance have been patented and subsequently used to block free entry of competitors. *See* Ameet Sarpatwari et al., *Using a Drug-Safety Tool to Prevent Competition*, 370 New Eng. J. Med. 1476 (2014). This has been identified as a hindrance to generic entry in the context of shared REMS programs and non-Orange Book patents. While initial development of a REMS is not a simple task, it only involves complying with FDA guidelines and regulations. Subsequent entrants who are required to use the same REMS program, by contrast, face "issues such as cost-sharing, confidential-

ity, product liability concerns, antitrust concerns, and access to a license for elements protected by a patent, and generic drug companies have reported difficulty in trying to develop a single, shared system with brand companies."[16]

The stakes here are higher. Rather than delaying generic competition with an existing drug, abuse of REMS via patent law is stopping a new product. And rather than using the ordinary remedies available to the owners of allegedly infringed patents, the remedy is an automatic 30-month stay of approval. A system that allows what is effectively an automatic preliminary injunction to stop new drugs is one that disserves both patients and the progress of medical science.

C. Blocking Patents Discourage Investment in the Development of Related Products

If Jazz only held patents to a "drug substance (active ingredient) . . . , a drug product (formulation composition) [or a] method of using such drug" as required for listing in the Orange Book, then there would still be opportunities for entry and competition by inducing competitors to "invent around" the new patent by inventing, for example, a new and distinct formulation of sodium oxybate. *See* FFDCA § 505(b)(1)(A)(viii).[17] But, as is the case here, if Jazz holds the exclusive

[16] *See* Agata Dabrowska, Cong. Research Serv., *Report No. R44810*, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development* 11 (Mar. 16, 2018).

[17] The active ingredient has been known since the 1950s and is plainly unpatentable now.

right to the use of a method required for entry *at all* into the market for sodium oxybate formulations, then all entry into the market is prevented.

What would-be competitor would invest resources in the development of a drug that they could not even sell due to a competitor's patent on the only way to comply with regulations necessary for participation in the market? The promise of a slice of the supranormal profits created by a dominant position encourages investment and entry by competitors who offer a product that is either of superior quality to that consumer or at a lower price. If there is no opportunity to access such profits, then there will not be investment in further development. It is unreasonable to expect a non-infringing competitor to incur the "collateral injury the Hatch-Waxman Act's 30-month stay invariably inflicts." *FTC v. AbbVie Inc.*, 976 F.3d 327, 361 (3d Cir. 2020).

* * *

Lumryz is a story of successful pharmaceutical innovation made possible by the rules established under Hatch–Waxman. Avadel identified a market of patients who have had their lives improved by a drug to treat their condition but dealt with negative side effects from their medication. They stepped in and developed a new product to both treat narcolepsy and address the shortcomings of the previous system.

Had the '963 patent not been listed in the Orange Book, then Avadel would be able to obtain approval of its once-nightly product, enabling patients to enjoy its benefits earlier so long as Avadel accepts the risk of retrospective infringement damages. *See* FFDCA § 505(c)(1). Yet by listing it, Jazz has forced Avadel to wait until the completion of litigation for approval, for up to 30 months. *See id.* § 505(c)(3)(C). The improper use of the statutory stay contravenes the principles of balance in patent law and harms narcolepsy patients. The district court's order to delist the patent should be affirmed.

CONCLUSION

For the foregoing reasons, the decision of the district court should be affirmed.

Respectfully submitted,

Dated: January 18, 2023

/s/ David Bookbinder

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CERTIFICATE OF COMPLIANCE

This document complies with the type-volume limitation of the Federal Rules of Appellate Procedure and the Circuit Rules. The document contains **5,479** words, excluding the parts of the document exempted by Federal Rule of Appellate Procedure 32(f).

This document complies with the typeface and type style requirements of the Federal Rules. The document has been prepared in a proportionally spaced typeface using the *xelatex* typesetting system, in the font Times New Roman.

Dated: January 18, 2023

/s/ David Bookbinder
David Bookbinder
Counsel for Amici Curiae

EXHIBIT 5

UNITED STATES OF AMERICA
Federal Trade Commission
WASHINGTON, D.C. 20580

Office of the Chair

Statement of Chair Lina M. Khan at the
September Open Commission Meeting on
Brand Drug Manufacturers' Improper Listing of Patents in the Orange Book
Commission File No. P233900

September 14, 2023

Drug prices are sky high. Americans pay more for medicines that any other country in the world. A striking number of people now report having to ration their medicines or skip them altogether because they are too expensive.[1] Many factors contribute to this unaffordability crisis—including unlawful business practices. We at the FTC are committed to using all of our tools to combat corporate conduct that unlawfully inflates drug prices.

That is why the Commission today is considering a policy statement on how the FTC will scrutinize improper "Orange Book" patent listings. The Orange Book is where brand manufacturers list their patents for FDA-approved drug products. A brand pharmaceutical company can obtain a presumptive 30-month stay of the FDA approving competitors merely by listing a patent in the Orange Book and filing a lawsuit against a generic manufacturer, regardless of whether the patent it listed is actually valid or infringed by the competing generic product. In this way, a pharmaceutical company can weaponize the Orange Book to protect monopoly rights to a medical product—even if those monopoly rights are invalid. This practice can delay or block generic and innovative drugs from entering the market, keeping prices higher for American patients.

Experience shows that we have good reason to be concerned about improperly listed patents in the Orange Book. Last year the FTC filed an amicus brief in a lawsuit that highlighted the stakes.[2] Avadel, a specialty pharmaceutical company, had developed an extended-release version of a narcolepsy drug that allowed patients to avoid having to wake up in the middle of the night to take a second dose. The FDA tentatively approved Avadel's extended-release version in 2022, but by that time, Jazz, another pharma company, had sued Avadel for infringing

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[1] MUNIRA Z. GUNJA, ET AL., U.S. HEALTH CARE FROM A GLOBAL PERSPECTIVE, 2022: ACCELERATING SPENDING, WORSENING OUTCOMES, THE COMMONWEALTH FUND (2023), https://www.commonwealthfund.org/publications/issue-briefs/2023/jan/us-health-care-global-perspective-2022; Katie Adams, *Rising Costs Force 39% of Americans to Skip Ration Meds, Survey Says*, BECKER'S HOSP. REV. (Mar. 22, 2021), https://www.beckershospitalreview.com/pharmacy/rising-costs-force-39-of-americans-to-skip-ration-meds-survey-says.html; Dan Witters, *In U.S., An Estimated 18 Million Can't Pay for Needed Drugs*, GALLUP (Sept. 21, 2021), https://news.gallup.com/poll/ 354833/estimated-million-pay-needed-drugs.aspx; Ken Alltucker, *More than 1.3M Americans Ration Life-Saving Insulin Due to Cost. That's 'Very Worrisome' to Doctors.*, USA TODAY (Oct. 17, 2022), https://www.usatoday.com/story/news/health/2022/10/17/high-cost-insulin-prompts-1-3- million-americans-ration-drug/10498626002/.

[2] Fed. Trade Comm'n's Brief as Amicus Curiae, *Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC*, C.A. No. 21-691-GBW (D. Del. Nov. 10, 2022).

Jazz's "Risk Evaluation and Mitigation Strategies" ("REMS") patent—a patent that had nothing to do with the drug itself or an approved method of using the drug. Jazz cited the Orange Book to automatically trigger the 30-month stay, blocking Avadel from the market. The Federal Circuit court eventually held that the patent was improperly listed in the Orange Book and ordered it to be delisted.[3] Following this order, the FDA granted final approval of Avadel's new drug—nearly ten months after the original tentative approval. In that intervening period, Jazz continued to rake in monopoly profits and patients were deprived of a potentially superior formulation of a critical narcolepsy drug.[4]

Concerns over improper Orange Book listings have also been raised in the context of device patents. For example, in late 2016 direct purchasers of the insulin Lantus brought an antitrust lawsuit claiming that certain device patents were improperly listed in the Orange Book, resulting in delay of entry of competing insulin products. That case made its way to the First Circuit, which agreed with the plaintiffs that device patents that do not claim the drug itself are not properly listed in the Orange Book as a matter of law.[5] The same concern has been raised with regard to brand inhalers for asthma and chronic obstructive pulmonary disease. Even though inhalers have been on the market for decades, they have faced relatively limited generic competition in recent years.[6]

Our laws—and even the Constitution[7]—enshrine an important role for patents in promoting innovation and creativity. But abuse of patent rights can deprive Americans of access to more affordable drugs and medical products, and the FTC has a long history of challenging these practices when they violate the antitrust laws.[8]

The policy statement we're considering today builds on this important work. This statement explains that patents that are improperly listed in the Orange Book can unlawfully harm patients, competition, and innovation, and notes that these practices may be an unfair method of competition and violate the FTC Act.

The soaring price of drugs, including essential life-saving medicines, is a real crisis in our country, and we at the FTC have an obligation to use all our tools and authorities to combat any illegal business practices that may be contributing to the crisis.

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[3] *Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC*, 60 F.4th 1373, 1380 (Fed. Cir. 2023).
[4] *See* Rebecca Robbins, *A Drug Company Exploited a Safety Requirement to Make Money*, N.Y. TIMES (Feb. 28, 2023), https://www.nytimes.com/2023/02/28/business/jazz-narcolepsy-avadel-patents.html (noting that Jazz's narcolepsy drug "generat[ed] more than $13 billion in revenue since Jazz acquired it in 2005").
[5] *In re Lantus Direct Purchaser Antitrust Litig.*, 950 F.3d 1 (1st Cir. 2020).
[6] *See* Brandon J. Demkowicz, et al., *Patenting Strategies on Inhaler Delivery Devices*, 164 CHEST 450 (2023); William B. Feldman, et al., *Manufacturer Revenue on Inhalers After Expiration of Primary Patents, 2000-2021*, 329 JAMA 87 (2023).
[7] U.S. CONST. art. I, § 8, cl. 8.
[8] *See, e.g.*, FED. TRADE COMM'N, OVERVIEW OF FTC ACTIONS IN PHARMACEUTICAL PRODUCTS AND DISTRIBUTION (2022); *FTC v. Actavis, Inc.*, 570 U.S. 136 (2013) (holding that pay-for-delay settlements can violate antitrust laws); *FTC v. Shkreli*, 581 F. Supp. 3d 579, 590 (S.D.N.Y. 2022) (banning Martin Shkreli from the pharmaceutical industry); *In re Bristol-Myers Squibb Co.*, FTC File No. 0110046 (May 25, 2004) (settling charges that, among other things, respondent purposely made wrongful listings in the Orange Book); *Biovail Corp.*, FTC File No. 0110094 (Oct. 2, 2002) (same).

I am eager for us to continue approaching this work with the enormous urgency that it deserves, and I am grateful to the FTC teams whose talent and commitment will allow us to do so. Many thanks to the Office of Policy Planning for giving us the opportunity to consider this policy statement, including Hillary Green, Sarah Mackey, Anu Sawkar, Marc Lanoue, David Barclay, and Brad Vettraino.

***

EXHIBIT 6

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-Q

(Mark One)

☒ **Quarterly report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

For the quarterly period ended March 31, 2024

or

☐ **Transition report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

For the transition period from to

Commission File Number: 001-33500

JAZZ PHARMACEUTICALS PUBLIC LIMITED COMPANY

(Exact name of registrant as specified in its charter)

Ireland	**98-1032470**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

Fifth Floor, Waterloo Exchange,
Waterloo Road, Dublin 4, Ireland D04 E5W7
011-353-1-634-7800
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value $0.0001 per share	JAZZ	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of April 25, 2024, 63,039,618 ordinary shares of the registrant, nominal value $0.0001 per share, were outstanding.

JAZZ PHARMACEUTICALS PLC
QUARTERLY REPORT ON FORM 10-Q FOR THE QUARTER ENDED MARCH 31, 2024

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We own or have rights to various copyrights, trademarks, and trade names used in our business in the U.S. and/or other countries, including the following: Jazz Pharmaceuticals®, Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, Xyrem® (sodium oxybate) oral solution, Epidiolex® (cannabidiol) oral solution, Epidyolex® (the trade name in Europe and other countries outside the U.S. for Epidiolex), Rylaze® (asparaginase erwinia chrysanthemi (recombinant)-rywn), Enrylaze® (the trade name in Europe and other countries outside the U.S. and Canada for Rylaze), Zepzelca® (lurbinectedin), Defitelio® (defibrotide sodium), Defitelio® (defibrotide), Vyxeos® (daunorubicin and cytarabine) liposome for injection, Vyxeos® liposomal 44 mg/100 mg powder for concentrate for solution for infusion, CombiPlex® and Sativex® (nabiximols) oral solution. This Quarterly Report on Form 10-Q also includes trademarks, service marks and trade names of other companies. Trademarks, service marks and trade names appearing in this Quarterly Report on Form 10-Q are the property of their respective owners.

PART I – FINANCIAL INFORMATION

Item 1. Financial Statements

JAZZ PHARMACEUTICALS PLC
CONDENSED CONSOLIDATED BALANCE SHEETS
(In thousands)
(Unaudited)

	March 31, 2024	December 31, 2023
ASSETS		
Current assets:		
Cash and cash equivalents	$ 1,443,385	$ 1,506,310
Investments	375,000	120,000
Accounts receivable, net of allowances	707,095	705,794
Inventories	577,321	597,039
Prepaid expenses	122,562	185,476
Other current assets	314,535	320,809
Total current assets	3,539,898	3,435,428
Property, plant and equipment, net	166,236	169,646
Operating lease assets	61,637	65,340
Intangible assets, net	5,235,496	5,418,039
Goodwill	1,739,495	1,753,130
Deferred tax assets, net	507,749	477,834
Deferred financing costs	5,784	6,478
Other non-current assets	70,780	67,464
Total assets	$ 11,327,075	$ 11,393,359
LIABILITIES AND SHAREHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 80,976	$ 102,750
Accrued liabilities	826,530	793,914
Current portion of long-term debt	605,375	604,954
Income taxes payable	49,325	35,074
Total current liabilities	1,562,206	1,536,692
Long-term debt, less current portion	5,105,111	5,107,988
Operating lease liabilities, less current portion	56,158	59,225
Deferred tax liabilities, net	809,714	847,706
Other non-current liabilities	97,425	104,751
Commitments and contingencies (Note 9)		
Shareholders' equity:		
Ordinary shares	6	6
Non-voting euro deferred shares	55	55
Capital redemption reserve	473	473
Additional paid-in capital	3,714,283	3,699,954
Accumulated other comprehensive loss	(882,394)	(842,147)
Retained earnings	864,038	878,656
Total shareholders' equity	3,696,461	3,736,997
Total liabilities and shareholders' equity	$ 11,327,075	$ 11,393,359

The accompanying notes are an integral part of these condensed consolidated financial statements.

JAZZ PHARMACEUTICALS PLC
CONDENSED CONSOLIDATED STATEMENTS OF INCOME (LOSS)
(In thousands, except per share amounts)
(Unaudited)

	Three Months Ended March 31,	
	2024	2023
Revenues:		
Product sales, net	$ 842,102	$ 884,219
Royalties and contract revenues	59,881	8,593
Total revenues	901,983	892,812
Operating expenses:		
Cost of product sales (excluding amortization of acquired developed technologies)	95,487	128,644
Selling, general and administrative	351,712	297,917
Research and development	222,847	189,410
Intangible asset amortization	155,730	149,786
Acquired in-process research and development	10,000	1,000
Total operating expenses	835,776	766,757
Income from operations	66,207	126,055
Interest expense, net	(66,116)	(74,147)
Foreign exchange gain (loss)	(1,693)	3,193
Income (loss) before income tax expense (benefit) and equity in loss of investees	(1,602)	55,101
Income tax expense (benefit)	11,669	(15,324)
Equity in loss of investees	1,347	1,005
Net income (loss)	$ (14,618)	$ 69,420
Net income (loss) per ordinary share:		
Basic	$ (0.23)	$ 1.09
Diluted	$ (0.23)	$ 1.04
Weighted-average ordinary shares used in per share calculations - basic	62,537	63,494
Weighted-average ordinary shares used in per share calculations - diluted	62,537	73,771

The accompanying notes are an integral part of these condensed consolidated financial statements.

JAZZ PHARMACEUTICALS PLC
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(In thousands)
(Unaudited)

	Three Months Ended March 31,	
	2024	2023
Net income (loss)	$ (14,618)	$ 69,420
Other comprehensive income (loss):		
Foreign currency translation adjustments	(44,068)	145,279
Unrealized gain on cash flow hedging activities, net of income tax expense of $1,720 and $—, respectively	5,177	—
Gain on cash flow hedging activities reclassified from accumulated other comprehensive income (loss) to interest expense, net of income tax expense of $451 and $—, respectively	(1,356)	—
Other comprehensive income (loss)	(40,247)	145,279
Total comprehensive income (loss)	$ (54,865)	$ 214,699

The accompanying notes are an integral part of these condensed consolidated financial statements.

JAZZ PHARMACEUTICALS PLC
CONDENSED CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
(In thousands)
(Unaudited)

	Ordinary Shares		Non-voting Euro Deferred		Capital Redemption Reserve	Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Retained Earnings	Total Equity
	Shares	Amount	Shares	Amount					
Balance at December 31, 2023	62,255	$ 6	4,000	$ 55	$ 473	$ 3,699,954	$ (842,147)	$ 878,656	$ 3,736,997
Issuance of ordinary shares in conjunction with exercise of share options	7	—	—	—	—	494	—	—	494
Issuance of ordinary shares in conjunction with vesting of restricted stock units	686	—	—	—	—	—	—	—	—
Issuance of ordinary shares in conjunction with vesting of performance-based restricted stock units	80	—	—	—	—	—	—	—	—
Shares withheld for payment of employee's withholding tax liability	—	—	—	—	—	(49,296)	—	—	(49,296)
Share-based compensation	—	—	—	—	—	63,131	—	—	63,131
Other comprehensive loss	—	—	—	—	—	—	(40,247)	—	(40,247)
Net loss	—	—	—	—	—	—	—	(14,618)	(14,618)
Balance at March 31, 2024	63,028	$ 6	4,000	$ 55	$ 473	$ 3,714,283	$ (882,394)	$ 864,038	$ 3,696,461

	Ordinary Shares		Non-voting Euro Deferred		Capital Redemption Reserve	Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Retained Earnings	Total Equity
	Shares	Amount	Shares	Amount					
Balance at December 31, 2022	63,214	$ 6	4,000	$ 55	$ 472	$ 3,477,124	$ (1,125,509)	$ 733,586	$ 3,085,734
Issuance of ordinary shares in conjunction with exercise of share options	188	—	—	—	—	21,228	—	—	21,228
Issuance of ordinary shares in conjunction with vesting of restricted stock units	585	—	—	—	—	—	—	—	—
Shares withheld for payment of employee's withholding tax liability	—	—	—	—	—	(43,266)	—	—	(43,266)
Share-based compensation	—	—	—	—	—	56,646	—	—	56,646
Other comprehensive income	—	—	—	—	—	—	145,279	—	145,279
Net income	—	—	—	—	—	—	—	69,420	69,420
Balance at March 31, 2023	63,987	$ 6	4,000	$ 55	$ 472	$ 3,511,732	$ (980,230)	$ 803,006	$ 3,335,041

The accompanying notes are an integral part of these condensed consolidated financial statements.

JAZZ PHARMACEUTICALS PLC
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)
(Unaudited)

	Three Months Ended March 31,	
	2024	**2023**
Operating activities		
Net income (loss)	$ (14,618)	$ 69,420
Adjustments to reconcile net income (loss) to net cash provided by operating activities:		
Intangible asset amortization	155,730	149,786
Share-based compensation	61,441	56,352
Acquisition accounting inventory fair value step-up adjustment	28,943	60,458
Acquired in-process research and development	10,000	1,000
Depreciation	7,653	7,574
Provision for losses on accounts receivable and inventory	7,403	2,316
Non-cash interest expense	5,988	4,766
Deferred tax benefit	(66,385)	(66,061)
Other non-cash transactions	14,674	16,773
Changes in assets and liabilities:		
Accounts receivable	(8,443)	28,460
Inventories	(12,844)	(6,266)
Prepaid expenses and other current assets	54,947	42,032
Operating lease assets	3,703	4,508
Other non-current assets	(4,090)	(9,541)
Accounts payable	(19,597)	34,286
Accrued liabilities	34,677	(96,985)
Income taxes payable	14,858	25,413
Deferred revenue	—	(459)
Operating lease liabilities, less current portion	(2,980)	(4,959)
Other non-current liabilities	(3,831)	1,835
Net cash provided by operating activities	267,229	320,708
Investing activities		
Acquisition of investments	(375,000)	—
Acquired in-process research and development	(10,000)	(1,000)
Purchases of property, plant and equipment	(6,904)	(3,822)
Proceeds from maturity of investments	120,000	—
Net cash used in investing activities	(271,904)	(4,822)
Financing activities		
Payment of employee withholding taxes related to share-based awards	(49,296)	(43,266)
Repayments of long-term debt	(7,750)	(7,750)
Proceeds from employee equity incentive and purchase plans	494	21,228
Net cash used in financing activities	(56,552)	(29,788)
Effect of exchange rates on cash and cash equivalents	(1,698)	331
Net increase (decrease) in cash and cash equivalents	(62,925)	286,429
Cash and cash equivalents, at beginning of period	1,506,310	881,482
Cash and cash equivalents, at end of period	$ 1,443,385	$ 1,167,911

The accompanying notes are an integral part of these condensed consolidated financial statements.

JAZZ PHARMACEUTICALS PLC
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
(Unaudited)

1. The Company and Summary of Significant Accounting Policies

Jazz Pharmaceuticals plc is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases - often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines, including leading therapies for sleep disorders and epilepsy, and a growing portfolio of cancer treatments. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics in oncology and neuroscience.

Our lead marketed products, listed below, are approved in countries around the world to improve patient care.

Neuroscience

- **Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution**, a product approved by the U.S. Food and Drug Administration, or FDA, in July 2020, and launched in the U.S. in November 2020 for the treatment of cataplexy or excessive daytime sleepiness, or EDS, in patients seven years of age and older with narcolepsy, and also approved by FDA in August 2021 for the treatment of idiopathic hypersomnia, or IH, in adults and launched in the U.S. in November 2021. Xywav contains 92% less sodium than Xyrem®. Xywav is also approved in Canada for the treatment of cataplexy in patients with narcolepsy;
- **Xyrem (sodium oxybate) oral solution**, a product approved by FDA and distributed in the U.S. for the treatment of cataplexy or EDS in patients seven years of age or older with narcolepsy; Jazz also markets Xyrem in Canada for the treatment of cataplexy in patients with narcolepsy. Xyrem is also approved and distributed in the European Union, or EU (EU market authorizations include Northern Ireland), Great Britain and other markets through a licensing agreement; and
- **Epidiolex® (cannabidiol) oral solution**, a product approved by FDA and launched in the U.S. in 2018 by GW Pharmaceuticals plc, or GW, and currently indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, or LGS, Dravet syndrome, or DS, or tuberous sclerosis complex, or TSC, in patients one year of age or older; in the EU and Great Britain (where it is marketed as Epidyolex®) and other markets, it is approved for adjunctive treatment of seizures associated with LGS or DS, in conjunction with clobazam (EU and Great Britain only), in patients 2 years of age and older and for adjunctive treatment of seizures associated with TSC in patients 2 years of age and older.

Oncology

- **Rylaze® (asparaginase erwinia chrysanthemi (recombinant)-rywn)**, a product approved by FDA in June 2021 and launched in the U.S. in July 2021 for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia or lymphoblastic lymphoma in adults and pediatric patients aged one month or older who have developed hypersensitivity to *E. coli*-derived asparaginase. In September 2023, the European Commission granted marketing authorization for this therapy under the trade name Enrylaze; and
- **Zepzelca® (lurbinectedin)**, a product approved by FDA in June 2020 under FDA's accelerated approval pathway and launched in the U.S. in July 2020 for the treatment of adult patients with metastatic small cell lung cancer, or SCLC, with disease progression on or after platinum-based chemotherapy; in Canada, Zepzelca received conditional approval in September 2021 for the treatment of adults with Stage III or metastatic SCLC, who have progressed on or after platinum-containing therapy.

Throughout this Quarterly Report on Form 10-Q, unless otherwise indicated or the context otherwise requires, all references to “Jazz Pharmaceuticals,” “the registrant,” "the Company", “we,” “us,” and “our” refer to Jazz Pharmaceuticals plc and its consolidated subsidiaries. Throughout this Quarterly Report on Form 10-Q, all references to “ordinary shares” refer to Jazz Pharmaceuticals plc’s ordinary shares.

Basis of Presentation

These unaudited condensed consolidated financial statements have been prepared following the requirements of the U.S. Securities and Exchange Commission for interim reporting. As permitted under those rules, certain footnotes and other financial information that are normally required by U.S. generally accepted accounting principles, or U.S. GAAP, can be condensed or omitted. The information included in this Quarterly Report on Form 10-Q should be read in conjunction with our

annual audited consolidated financial statements and accompanying notes included in our Annual Report on Form 10-K for the year ended December 31, 2023.

In the opinion of management, these condensed consolidated financial statements have been prepared on the same basis as the annual audited consolidated financial statements and include all adjustments, consisting only of normal recurring adjustments, considered necessary for the fair presentation of our financial position and operating results. The results for the three months ended March 31, 2024, are not necessarily indicative of the results to be expected for the year ending December 31, 2024, for any other interim period or for any future period.

Our significant accounting policies have not changed substantially from those previously described in our Annual Report on Form 10-K for the year ended December 31, 2023.

These condensed consolidated financial statements include the accounts of Jazz Pharmaceuticals plc and our subsidiaries, and intercompany transactions and balances have been eliminated.

Our operating segment is reported in a manner consistent with the internal reporting provided to the chief operating decision maker, or CODM. Our CODM has been identified as our chief executive officer. We have determined that we operate in one business segment, which is the identification, development and commercialization of meaningful pharmaceutical products that address unmet medical needs.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues and expenses, and related disclosures in the condensed consolidated financial statements and accompanying notes. Management bases its estimates on historical experience and on assumptions believed to be reasonable under the circumstances. Actual results could differ materially from those estimates.

Adoption of New Accounting Standards

In November 2023, the Financial Accounting Standards Board, or FASB, issued ASU 2023-07, “Segment Reporting (Topic 280) - Improvements to Reportable Segment Disclosures”, which requires enhanced disclosures about significant segment expenses. The amendments are effective retrospectively to all prior periods presented in the financial statements, for fiscal years beginning after December 15, 2023. The new guidance is not expected to have a material impact on our financial statement disclosures.

Significant Risks and Uncertainties

Historically, our business was substantially dependent on Xyrem and while we expect that our business will continue to meaningfully depend on oxybate revenues from both Xywav and Xyrem, there is no guarantee that oxybate revenues will remain at current levels. In this regard, our ability to maintain oxybate revenues and realize the anticipated benefits from our investment in Xywav are subject to a number of risks and uncertainties including, without limitation, those related to the launch of Xywav for the treatment of IH in adults and adoption in that indication; competition from the introduction of two authorized generic, or AG, versions of high-sodium oxybate and a branded fixed-dose, high-sodium oxybate, Avadel’s Lumryz, for treatment of cataplexy and/or EDS in narcolepsy in the U.S. market, as well as potential future competition from additional AG versions of high-sodium oxybate and from generic versions of high-sodium oxybate and from other competitors; increased pricing pressure from, changes in policies by, or restrictions on reimbursement imposed by, third party payors, including our ability to maintain adequate coverage and reimbursement for Xywav and Xyrem; increased rebates required to maintain access to our products; challenges to our intellectual property around Xywav and/or Xyrem, including from pending antitrust and intellectual property litigation; and continued acceptance of Xywav and Xyrem by physicians and patients. A significant decline in oxybate revenues could cause us to reduce our operating expenses or seek to raise additional funds, which would have a material adverse effect on our business, financial condition, results of operations and growth prospects, including on our ability to acquire, in-license or develop new products to grow our business.

In addition to risks related specifically to Xywav and Xyrem, we are subject to other challenges and risks related to successfully commercializing a portfolio of oncology products and other neuroscience products, and other risks specific to our business and our ability to execute on our strategy, as well as risks and uncertainties common to companies in the pharmaceutical industry with development and commercial operations, including, without limitation, risks and uncertainties associated with: ongoing clinical research activity and related outcomes, obtaining regulatory approval of our late-stage product candidates; effectively commercializing our approved or acquired products such as Epidiolex, Rylaze and Zepzelca; obtaining and maintaining adequate coverage and reimbursement for our products; contracting and rebates to pharmacy benefit managers and similar organizations that reduce our net revenue; increasing scrutiny of pharmaceutical product pricing and resulting

changes in healthcare laws and policy; market acceptance; regulatory concerns with controlled substances generally and the potential for abuse; future legislation, action by the U.S. Federal Government authorizing the sale, distribution, use, and insurance reimbursement of non-FDA approved cannabinoid products; delays or problems in the supply of our products, loss of single source suppliers or failure to comply with manufacturing regulations; delays or problems with third parties that are part of our manufacturing and supply chain; identifying, acquiring or in-licensing additional products or product candidates; our ability to realize the anticipated benefits of acquired or in-licensed products or product candidates, such as Epidiolex and zanidatamab, at the expected levels, with the expected costs and within the expected timeframe; pharmaceutical product development and the inherent uncertainty of clinical success; the challenges of protecting and enhancing our intellectual property rights; complying with applicable regulatory requirements; and possible restrictions on our ability and flexibility to pursue certain future opportunities as a result of our substantial outstanding debt obligations.

Concentrations of Risk

Financial instruments that potentially subject us to concentrations of credit risk consist of cash, cash equivalents, investments and derivative contracts. Our investment policy permits investments in U.S. federal government and federal agency securities, corporate bonds or commercial paper issued by U.S. corporations, money market instruments, certain qualifying money market mutual funds, certain repurchase agreements, and tax-exempt obligations of U.S. states, agencies and municipalities and places restrictions on credit ratings, maturities, and concentration by type and issuer. We are exposed to credit risk in the event of a default by the financial institutions holding our cash, cash equivalents and investments to the extent recorded on the balance sheet.

We manage our foreign currency transaction risk and interest rate risk within specified guidelines through the use of derivatives. All of our derivative instruments are utilized for risk management purposes, and we do not use derivatives for speculative trading purposes. As of March 31, 2024, we had foreign exchange forward contracts with notional amounts totaling $537.1 million. As of March 31, 2024, the outstanding foreign exchange forward contracts had a net asset fair value of $0.4 million. As of March 31, 2024, we had interest rate swap contracts with notional amounts totaling $500.0 million. These outstanding interest rate swap contracts had an asset fair value of $5.5 million as of March 31, 2024. The counterparties to these contracts are large multinational commercial banks, and we believe the risk of nonperformance is not significant.

We are also subject to credit risk from our accounts receivable related to our product sales. We monitor our exposure within accounts receivable and record a reserve against uncollectible accounts receivable as necessary. We extend credit to pharmaceutical wholesale distributors and specialty pharmaceutical distribution companies, primarily in the U.S., and to other international distributors and hospitals. Customer creditworthiness is monitored and collateral is not required. We monitor economic conditions in certain European countries which may result in variability of the timing of cash receipts and an increase in the average length of time that it takes to collect accounts receivable outstanding. Historically, we have not experienced significant credit losses on our accounts receivable and, as of March 31, 2024 and December 31, 2023, allowances on receivables were not material. As of March 31, 2024, five customers accounted for 78% of gross accounts receivable, including Express Scripts Specialty Distribution Services, Inc. and its affiliates, or ESSDS, which accounted for 41% of gross accounts receivable, McKesson Corporation and affiliates, or McKesson, which accounted for 12% of gross accounts receivable and ASD Specialty Healthcare LLC, or ASD, which accounted for 12% of gross accounts receivable. As of December 31, 2023, five customers accounted for 79% of gross accounts receivable, including ESSDS, which accounted for 41% of gross accounts receivable, ASD, which accounted for 13% of gross accounts receivable and McKesson, which accounted for 11% of gross accounts receivable.

We depend on single source suppliers for most of our products, product candidates and their active pharmaceutical ingredients, or APIs. With respect to our oxybate products, the API is manufactured for us by a single source supplier and the finished products are manufactured both by us in our facility in Athlone, Ireland and by our U.S.-based supplier.

Recent Accounting Pronouncements

In December 2023, the FASB issued ASU 2023-09, “Income Taxes (Topic 740) - Improvements to Income Tax Disclosures”, which requires additional enhanced tax disclosures. The amendments are effective on a prospective basis, with the option to apply it retrospectively, for fiscal years beginning after December 15, 2024. We are currently evaluating the impact of adopting this new accounting guidance.

2. Cash and Available-for-Sale Securities

Cash, cash equivalents and investments consisted of the following (in thousands):

	March 31, 2024					
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Cash and Cash Equivalents	Investments
Cash	$ 444,140	$ —	$ —	$ 444,140	$ 444,140	$ —
Time deposits	585,000	—	—	585,000	210,000	375,000
Money market funds	789,245	—	—	789,245	789,245	—
Totals	$ 1,818,385	$ —	$ —	$ 1,818,385	$ 1,443,385	$ 375,000

	December 31, 2023					
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Cash and Cash Equivalents	Investments
Cash	$ 437,724	$ —	$ —	$ 437,724	$ 437,724	$ —
Time deposits	420,000	—	—	420,000	300,000	120,000
Money market funds	768,586	—	—	768,586	768,586	—
Totals	$ 1,626,310	$ —	$ —	$ 1,626,310	$ 1,506,310	$ 120,000

Cash equivalents and investments are considered available-for-sale securities. We use the specific-identification method for calculating realized gains and losses on securities sold and include them in interest expense, net in the condensed consolidated statements of income (loss). Our investment balances represent time deposits with original maturities of greater than three months and less than one year. Interest income from available-for-sale securities was $23.3 million and $10.6 million in the three months ended March 31, 2024 and 2023, respectively.

3. Fair Value Measurement

The following table summarizes, by major security type, our available-for-sale securities and derivative contracts as of March 31, 2024 and December 31, 2023, that were measured at fair value on a recurring basis and were categorized using the fair value hierarchy (in thousands):

	March 31, 2024			December 31, 2023		
	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Total Estimated Fair Value	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Total Estimated Fair Value
Assets:						
Available-for-sale securities:						
Money market funds	$ 789,245	$ —	$ 789,245	$ 768,586	$ —	$ 768,586
Time deposits	—	585,000	585,000	—	420,000	420,000
Interest rate contracts	—	5,464	5,464	—	3,784	3,784
Foreign exchange forward contracts	—	708	708	—	18,035	18,035
Totals	$ 789,245	$ 591,172	$ 1,380,417	$ 768,586	$ 441,819	$ 1,210,405
Liabilities:						
Interest rate contracts	$ —	$ —	$ —	$ —	$ 3,410	$ 3,410
Foreign exchange forward contracts	—	357	357	—	681	681
Totals	$ —	$ 357	$ 357	$ —	$ 4,091	$ 4,091

As of March 31, 2024, our available-for-sale securities included money market funds and time deposits and their carrying values were approximately equal to their fair values. Money market funds were measured using quoted prices in active markets, which represent Level 1 inputs and time deposits were measured at fair value using Level 2 inputs. Level 2 inputs are obtained from various third party data providers and represent quoted prices for similar assets in active markets, or these inputs were derived from observable market data, or if not directly observable, were derived from or corroborated by other observable market data.

Our derivative assets and liabilities include interest rate and foreign exchange derivatives that are measured at fair value using observable market inputs such as forward rates, interest rates, our own credit risk as well as an evaluation of our counterparties' credit risks. Based on these inputs, the derivative assets and liabilities are classified within Level 2 of the fair value hierarchy.

There were no transfers between the different levels of the fair value hierarchy in 2024 or 2023.

As of March 31, 2024 and December 31, 2023, the carrying amount of investments measured using the measurement alternative for equity investments without a readily determinable fair value was $4.3 million. The carrying amount, which is recorded within other non-current assets, is based on the latest observable transaction price.

As of March 31, 2024, the estimated fair values of the 1.50% exchangeable senior notes due 2024, or 2024 Notes, the 2.00% exchangeable senior notes due 2026, or 2026 Notes, which we refer to collectively as the Exchangeable Senior Notes, the 4.375% senior secured notes, due 2029, or the Secured Notes, and the seven-year $3.1 billion term loan B facility, or the Dollar Term Loan were approximately $566 million, $1.0 billion, $1.4 billion and $2.7 billion respectively. The fair values of each of these debt facilities was estimated using quoted market prices obtained from brokers (Level 2).

4. Derivative Instruments and Hedging Activities

We are exposed to certain risks arising from operating internationally, including fluctuations in foreign exchange rates primarily related to the translation of sterling and euro-denominated net monetary liabilities, including intercompany balances, held by subsidiaries with a U.S. dollar functional currency and fluctuations in interest rates on our outstanding term loan borrowings. We manage these exposures within specified guidelines through the use of derivatives. All of our derivative instruments are utilized for risk management purposes, and we do not use derivatives for speculative trading purposes.

We enter into foreign exchange forward contracts, with durations of up to 12 months, designed to limit the exposure to fluctuations in foreign exchange rates related to the translation of certain non-U.S. dollar denominated liabilities, including intercompany balances. Hedge accounting is not applied to these derivative instruments as gains and losses on these hedge transactions are designed to offset gains and losses on underlying balance sheet exposures. As of March 31, 2024 and December 31, 2023, the notional amount of foreign exchange contracts where hedge accounting is not applied was $537.1 million and $511.7 million, respectively.

The foreign exchange gain (loss) in our condensed consolidated statements of income (loss) included the following gain (losses) associated with foreign exchange contracts not designated as hedging instruments (in thousands):

	Three Months Ended March 31,	
Foreign Exchange Forward Contracts:	**2024**	**2023**
Gain (loss) recognized in foreign exchange gain (loss)	$ (4,086)	$ 4,275

To achieve a desired mix of floating and fixed interest rates on our variable rate debt, we entered into interest rate swap agreements in April 2023, which are effective until April 2026. These agreements hedge contractual term loan interest rates. As of March 31, 2024, the interest rate swap agreements had a notional amount of $500.0 million. As a result of these agreements, the interest rate on a portion of our term loan borrowings is fixed at 3.9086%, plus the borrowing spread, until April 30, 2026.

The impact on accumulated other comprehensive income (loss) and earnings from derivative instruments that qualified as cash flow hedges for the three months ended March 31, 2024 was as follows (in thousands):

Interest Rate Contracts:	Three Months Ended March 31, 2024
Gain recognized in accumulated other comprehensive income (loss), net of tax	$ 5,177
Gain reclassified from accumulated other comprehensive income (loss) to interest expense, net of tax	(1,356)

Assuming no change in the U.S dollar Secured Overnight Financing Rate, or Term SOFR, based interest rates from market rates as of March 31, 2024, $3.7 million of gains, net of tax, recognized in accumulated other comprehensive income (loss) will be reclassified to earnings over the next 12 months.

The cash flow effects of our derivative contracts for the three months ended March 31, 2024 and 2023 are included within net cash provided by operating activities in the condensed consolidated statements of cash flows.

The following tables summarize the fair value of outstanding derivatives (in thousands):

	Classification	March 31, 2024	December 31, 2023
Assets			
Derivatives designated as hedging instruments:			
Interest rate contracts	Other current assets	$ 5,041	$ 3,784
	Other non-current assets	423	—
Derivatives not designated as hedging instruments:			
Foreign exchange forward contracts	Other current assets	708	18,035
Total fair value of derivative asset instruments		$ 6,172	$ 21,819
Liabilities			
Derivatives designated as hedging instruments:			
Interest rate contracts	Other non-current liabilities	$ —	$ 3,410
Derivatives not designated as hedging instruments:			
Foreign exchange forward contracts	Accrued liabilities	357	681
Total fair value of derivative liability instruments		$ 357	$ 4,091

Although we do not offset derivative assets and liabilities within our condensed consolidated balance sheets, our International Swap and Derivatives Association agreements provide for net settlement of transactions that are due to or from the same counterparty upon early termination of the agreement due to an event of default or other termination event. The following table summarizes the potential effect on our condensed consolidated balance sheets of offsetting our interest rate and foreign exchange forward contracts subject to such provisions (in thousands):

	March 31, 2024					
				Gross Amounts Not Offset in the Consolidated Balance Sheet		
Description	Gross Amounts of Recognized Assets/ Liabilities	Gross Amounts Offset in the Consolidated Balance Sheet	Net Amounts of Assets/ Liabilities Presented in the Consolidated Balance Sheet	Derivative Financial Instruments	Cash Collateral Received (Pledged)	Net Amount
Derivative assets	$ 6,172	$ —	$ 6,172	$ (250)	$ —	$ 5,922
Derivative liabilities	(357)	—	(357)	250	—	(107)

	December 31, 2023					
				Gross Amounts Not Offset in the Consolidated Balance Sheet		
Description	Gross Amounts of Recognized Assets/ Liabilities	Gross Amounts Offset in the Consolidated Balance Sheet	Net Amounts of Assets/ Liabilities Presented in the Consolidated Balance Sheet	Derivative Financial Instruments	Cash Collateral Received (Pledged)	Net Amount
Derivative assets	$ 21,819	$ —	$ 21,819	$ (4,091)	$ —	$ 17,728
Derivative liabilities	(4,091)	—	(4,091)	4,091	—	—

5. Inventories

Inventories consisted of the following (in thousands):

	March 31, 2024	December 31, 2023
Raw materials	$ 17,769	$ 25,595
Work in process	390,882	431,732
Finished goods	168,670	139,712
Total inventories	$ 577,321	$ 597,039

As of March 31, 2024 and December 31, 2023 inventories included $297.3 million and $328.0 million, respectively, related to the purchase accounting inventory fair value step-up on inventory acquired as part of our acquisition of GW, which we refer to as the GW Acquisition.

6. Goodwill and Intangible Assets

The gross carrying amount of goodwill was as follows (in thousands):

Balance at December 31, 2023	$ 1,753,130
Foreign exchange	(13,635)
Balance at March 31, 2024	$ 1,739,495

The gross carrying amounts and net book values of our intangible assets were as follows (in thousands):

	March 31, 2024				December 31, 2023		
	Remaining Weighted-Average Useful Life (In years)	Gross Carrying Amount	Accumulated Amortization	Net Book Value	Gross Carrying Amount	Accumulated Amortization	Net Book Value
Acquired developed technologies	8.5	$ 7,743,422	$ (2,507,926)	$ 5,235,496	$ 7,785,495	$ (2,367,456)	$ 5,418,039
Manufacturing contracts	—	11,572	(11,572)	—	11,828	(11,828)	—
Trademarks	—	2,879	(2,879)	—	2,886	(2,886)	—
Total finite-lived intangible assets		$ 7,757,873	$ (2,522,377)	$ 5,235,496	$ 7,800,209	$ (2,382,170)	$ 5,418,039

The decrease in the gross carrying amount of intangible assets as of March 31, 2024 compared to December 31, 2023 relates to the negative impact of foreign currency translation adjustments primarily due to the weakening of sterling against the U.S. dollar.

The assumptions and estimates used to determine future cash flows and remaining useful lives of our intangible and other long-lived assets are complex and subjective. They can be affected by various factors, including external factors, such as industry and economic trends, and internal factors such as changes in our business strategy and our forecasts for specific product lines.

Based on finite-lived intangible assets recorded as of March 31, 2024, and assuming the underlying assets will not be impaired and that we will not change the expected lives of the assets, future amortization expenses were estimated as follows (in thousands):

Year Ending December 31,	Estimated Amortization Expense
2024 (remainder)	$ 466,008
2025	621,344
2026	621,344
2027	621,344
2028	620,012
Thereafter	2,285,444
Total	$ 5,235,496

7. Certain Balance Sheet Items

Property, plant and equipment consisted of the following (in thousands):

	March 31, 2024	December 31, 2023
Manufacturing equipment and machinery	$ 85,717	$ 82,897
Land and buildings	69,750	70,912
Leasehold improvements	69,600	67,722
Computer software	38,159	38,134
Construction-in-progress	17,274	18,661
Computer equipment	16,704	15,398
Furniture and fixtures	9,297	9,273
Subtotal	306,501	302,997
Less accumulated depreciation and amortization	(140,265)	(133,351)
Property, plant and equipment, net	$ 166,236	$ 169,646

Other current assets consisted of the following (in thousands):

	March 31, 2024	December 31, 2023
Deferred charge for income taxes on intercompany profit	$ 178,684	$ 171,507
Other	135,851	149,302
Total other current assets	$ 314,535	$ 320,809

Accrued liabilities consisted of the following (in thousands):

	March 31, 2024	December 31, 2023
Rebates and other sales deductions	$ 369,301	$ 325,711
Employee compensation and benefits	118,966	121,209
Consulting and professional services	39,539	19,538
Clinical trial accruals	38,406	44,757
Accrued royalties	29,236	30,706
Selling and marketing accruals	25,890	14,743
Accrued collaboration expenses	24,626	10,158
Accrued interest	23,392	36,443
Sales return reserve	22,137	20,435
Current portion of lease liabilities	18,357	19,447
Inventory-related accruals	15,902	13,977
Accrued construction-in-progress	7,055	5,141
Accrued facilities expenses	5,333	55,455
Derivative instrument liabilities	357	681
Other	88,033	75,513
Total accrued liabilities	$ 826,530	$ 793,914

8. Debt

The following table summarizes the carrying amount of our indebtedness (in thousands):

	March 31, 2024	December 31, 2023
2024 Notes	$ 575,000	$ 575,000
Unamortized - debt issuance costs	(624)	(1,046)
2024 Notes, net	574,376	573,954
2026 Notes	1,000,000	1,000,000
Unamortized - debt issuance costs	(5,782)	(6,400)
2026 Notes, net	994,218	993,600
Secured Notes	1,481,011	1,480,214
Term Loan	2,660,881	2,665,174
Total debt	5,710,486	5,712,942
Less current portion	605,375	604,954
Total long-term debt	$ 5,105,111	$ 5,107,988

Credit Agreement

On May 5, 2021, the Company, Jazz Financing Lux S.à.r.l., or Jazz Lux, and certain of our other subsidiaries, as borrowers, or, collectively with the Company and Jazz Lux, the "Borrowers", entered into the Credit Agreement by and among the Borrowers, the lenders and issuing banks from time to time party thereto, Bank of America, N.A., as administrative agent and U.S. Bank Trust Company, National Association, as collateral trustee, or the Credit Agreement, that provided for (i) the Dollar Term Loan which was drawn by Jazz Lux on the Closing Date in U.S. dollars (ii) the Euro Term Loan which was drawn by Jazz Lux on the Closing Date in Euros and (iii) the Revolving Credit Facility.

In January 2024, Jazz Lux entered into an amendment, or Repricing Amendment, to the Credit Agreement. Upon entry into the Repricing Amendment, certain existing lenders converted outstanding Dollar Term Loans into a new tranche of U.S. dollar term loans, or the Tranche B-1 Dollar Term Loans, and Jazz Lux borrowed $201.9 million aggregate principal amount of additional Tranche B-1 Dollar Term Loans, the proceeds of which were used to repay the outstanding Dollar Term Loans that were not converted. The Tranche B-1 Dollar Term Loans are a separate class of term loans under the Credit Agreement with the same material terms (including with respect to maturity, prepayment, security, covenants and events of default) as the previously outstanding Dollar Term Loans, with the interest rate amended as described below. The principal amount of Dollar Term Loans outstanding immediately prior to the Repricing Amendment and the outstanding principal amount of Tranche B-1 Dollar Term Loans immediately following the Repricing Amendment, each totaled $2.723 billion. The Tranche B-1 Dollar Term Loans bear interest at a rate equal to either (a) Term SOFR, or (b) the prime lending rate, in each case, plus an applicable margin. The applicable margin for the Tranche B-1 Dollar Term Loans is 3.00% (in the case of Term SOFR borrowings) and 2.00% (in the case of borrowings at the prime lending rate), a decrease of 50 basis points from the applicable margin on the Initial Dollar Term Loans. The Tranche B-1 Dollar Term Loans are subject to a Term SOFR floor of 0.50%. The applicable margin for the Revolving Credit Facility ranges from 3.25% to 2.75% (in the case of Term SOFR borrowings) and 2.25% to 1.75% (in the case of borrowings at the prime lending rate), depending on our first lien secured net leverage ratio level. The Tranche B-1 Dollar Term Loan is subject to a Term SOFR floor of 0.50% and loans under the Revolving Credit Facility are not subject to a floor. The Revolving Credit Facility has a commitment fee payable on the undrawn amount ranging from 0.50% to 0.40% per annum based upon our first lien secured net leverage ratio. As of March 31, 2024, the interest rate and effective interest rate on the Tranche B-1 Dollar Term Loans were 8.44% and 9.04%, respectively. As of March 31, 2024, we had an undrawn Revolving Credit Facility totaling $500.0 million.

Exchangeable Senior Notes

The Exchangeable Senior Notes were issued by Jazz Investments I Limited, or the Issuer, a 100%-owned finance subsidiary of Jazz Pharmaceuticals plc. The Exchangeable Senior Notes are senior unsecured obligations of the Issuer and are fully and unconditionally guaranteed on a senior unsecured basis by Jazz Pharmaceuticals plc. No subsidiary of Jazz Pharmaceuticals plc guaranteed the Exchangeable Senior Notes. Subject to certain local law restrictions on payment of dividends, among other things, and potential negative tax consequences, we are not aware of any significant restrictions on the ability of Jazz Pharmaceuticals plc to obtain funds from the Issuer or Jazz Pharmaceuticals plc's other subsidiaries by dividend or loan, or any legal or economic restrictions on the ability of the Issuer or Jazz Pharmaceuticals plc's other subsidiaries to transfer funds to Jazz Pharmaceuticals plc in the form of cash dividends, loans or advances. There is no assurance that in the future such restrictions will not be adopted.

The total liability of the 2026 Notes is reflected net of issuance costs of $15.3 million which will be amortized over the term of the 2026 Notes. The effective interest rate of the 2026 Notes is 2.26%. During the three months ended March 31, 2024 and 2023, we recognized interest expense of $5.5 million, of which $5.0 million related to the contractual coupon rate and $0.5 million related to the amortization of debt issuance costs, respectively.

The total liability of the 2024 Notes is reflected net of issuance costs of $11.4 million which will be amortized over the term of the 2024 Notes. The effective interest rate of the 2024 Notes is 1.79%. During the three months ended March 31, 2024 and 2023, we recognized interest expense of $2.5 million, of which $2.1 million related to the contractual coupon rate and $0.4 million related to the amortization of debt issuance costs, respectively.

Maturities

Scheduled maturities with respect to our long-term debt principal balances outstanding as of March 31, 2024 were as follows (in thousands):

Year Ending December 31,	Scheduled Long-Term Debt Maturities
2024 (remainder)	$ 598,250
2025	31,000
2026	1,031,000
2027	31,000
2028	2,598,500
Thereafter	1,500,000
Total	$ 5,789,750

9. Commitments and Contingencies

Indemnification

In the normal course of business, we enter into agreements that contain a variety of representations and warranties and provide for general indemnification, including indemnification associated with product liability or infringement of intellectual property rights. Our exposure under these agreements is unknown because it involves future claims that may be made but have not yet been made against us. To date, we have not paid any claims or been required to defend any action related to these indemnification obligations.

We have agreed to indemnify our executive officers, directors and certain other employees for losses and costs incurred in connection with certain events or occurrences, including advancing money to cover certain costs, subject to certain limitations. The maximum potential amount of future payments we could be required to make under the indemnification obligations is unlimited; however, we maintain insurance policies that may limit our exposure and may enable us to recover a portion of any future amounts paid. Assuming the applicability of coverage, the willingness of the insurer to assume coverage, and subject to certain retention, loss limits and other policy provisions, we believe the fair value of these indemnification obligations is not significant. Accordingly, we did not recognize any liabilities relating to these obligations as of March 31, 2024 and December 31, 2023. No assurances can be given that the covering insurers will not attempt to dispute the validity, applicability, or amount of coverage without expensive litigation against these insurers, in which case we may incur substantial liabilities as a result of these indemnification obligations.

Legal Proceedings

We are involved in legal proceedings, including the following matters:

Xyrem Antitrust Litigation

From June 2020 to May 2022, a number of lawsuits were filed on behalf of purported direct and indirect Xyrem purchasers, alleging that the patent litigation settlement agreements we entered with generic drug manufacturers who had filed Abbreviated New Drug Applications, or ANDA, violate state and federal antitrust and consumer protection laws, as follows:

On June 17, 2020, a class action lawsuit was filed in the United States District Court for the Northern District of Illinois by Blue Cross and Blue Shield Association, or BCBS, against Jazz Pharmaceuticals plc, Jazz Pharmaceuticals, Inc., and Jazz Pharmaceuticals Ireland Limited, or, collectively, the Company Defendants (hereinafter referred to as the BCBS Lawsuit). The BCBS Lawsuit also names Roxane Laboratories, Inc., Hikma Pharmaceuticals USA Inc., Eurohealth (USA), Inc., Hikma Pharmaceuticals plc, Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals Inc., and Lupin Inc., or, collectively, the BCBS Defendants.

On June 18 and June 23, 2020, respectively, two additional class action lawsuits were filed against the Company Defendants and the BCBS Defendants: one by the New York State Teamsters Council Health and Hospital Fund in the United States District Court for the Northern District of California, and another by the Government Employees Health Association Inc. in the United States District Court for the Northern District of Illinois (hereinafter referred to as the GEHA Lawsuit).

On June 18, 2020, a class action lawsuit was filed in the United States District Court for the Northern District of California by the City of Providence, Rhode Island, on behalf of itself and all others similarly situated, against Jazz Pharmaceuticals plc, and Roxane Laboratories, Inc., West-Ward Pharmaceuticals Corp., Hikma Labs Inc., Hikma Pharmaceuticals USA Inc., and Hikma Pharmaceuticals plc, or, collectively, the City of Providence Defendants.

On June 30, 2020, a class action lawsuit was filed in the United States District Court for the Northern District of Illinois by UFCW Local 1500 Welfare Fund on behalf of itself and all others similarly situated, against Jazz Pharmaceuticals Ireland Ltd., Jazz Pharmaceuticals, Inc., Roxane Laboratories, Inc., Hikma Pharmaceuticals plc, Eurohealth (USA), Inc. and West-Ward Pharmaceuticals Corp., or collectively the UFCW Defendants (hereinafter referred to as the UFCW Lawsuit).

On July 13, 2020, the plaintiffs in the BCBS Lawsuit and the GEHA Lawsuit dismissed their complaints in the United States District Court for the Northern District of Illinois and refiled their respective lawsuits in the United States District Court for the Northern District of California. On July 14, 2020, the plaintiffs in the UFCW Lawsuit dismissed their complaint in the United States District Court for the Northern District of Illinois and on July 15, 2020, refiled their lawsuit in the United States District Court for the Northern District of California.

On July 31, 2020, a class action lawsuit was filed in the United States District Court for the Southern District of New York by the A.F. of L.-A.G.C. Building Trades Welfare Plan on behalf of itself and all others similarly situated, against Jazz Pharmaceuticals plc (hereinafter referred to as the AFL Plan Lawsuit). The AFL Plan Lawsuit also names Roxane Laboratories Inc., West-Ward Pharmaceuticals Corp., Hikma Labs Inc., Hikma Pharmaceuticals plc, Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc.

On August 14, 2020, an additional class action lawsuit was filed in the United States District Court for the Southern District of New York by the Self-Insured Schools of California on behalf of itself and all others similarly situated, against the Company Defendants, as well as Hikma Pharmaceuticals plc, Eurohealth (USA) Inc., Hikma Pharmaceuticals USA, Inc., West-Ward Pharmaceuticals Corp., Roxane Laboratories, Inc., Amneal Pharmaceuticals LLC, Endo International, plc, Endo Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals Inc., Lupin Inc., Sun Pharmaceutical Industries Ltd., Sun Pharmaceutical Holdings USA, Inc., Sun Pharmaceutical Industries, Inc., Ranbaxy Laboratories Ltd., Teva Pharmaceutical Industries Ltd., Watson Laboratories, Inc., Wockhardt Ltd., Morton Grove Pharmaceuticals, Inc., Wockhardt USA LLC, Mallinckrodt plc, and Mallinckrodt LLC (hereinafter referred to as the Self-Insured Schools Lawsuit).

On September 16, 2020, an additional class action lawsuit was filed in the United States District Court for the Northern District of California, by Ruth Hollman on behalf of herself and all others similarly situated, against the same defendants named in the Self-Insured Schools Lawsuit.

In December 2020, the above cases were centralized and transferred to the United States District Court for the Northern District of California, where the multidistrict litigation will proceed for the purpose of discovery and pre-trial proceedings.

On March 18, 2021, United Healthcare Services, Inc. filed a lawsuit in the United States District Court for the District of Minnesota against the Company Defendants, Hikma Pharmaceuticals plc, Roxane Laboratories, Inc., Hikma Pharmaceuticals USA Inc., Eurohealth (USA) Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., and Lupin Pharmaceuticals, Inc., raising similar allegations, or the UHS Lawsuit. On March 24, 2021, the U.S. Judicial Panel on Multidistrict Litigation conditionally transferred the UHS Lawsuit to the United States District Court for the Northern District of California, where it was consolidated for discovery and pre-trial proceedings with the other cases.

On August 13, 2021, the United States District Court for the Northern District of California granted in part and denied in part the Company Defendants' motion to dismiss the complaints in the cases referenced above.

On October 8, 2021, Humana Inc. filed a lawsuit in the United States District Court for the Northern District of California against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations.

On October 8, 2021, Molina Healthcare Inc. filed a lawsuit in the United States District Court for the Northern District of California against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations.

On February 17, 2022, Health Care Service Corporation filed a lawsuit in the United States District Court for the Northern District of California against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations.

On April 19, 2023, the Court held a hearing on class certification in the consolidated multi-district litigation referenced above. On May 12, 2023, the Court granted the plaintiffs' motion and preliminarily certified classes of Xyrem purchasers seeking monetary and injunctive relief. The Court excluded Xywav purchasers from the classes. On April 26, 2024, we, Hikma, and the plaintiffs filed motions for summary judgment. The Court scheduled a hearing for these motions on July 19, 2024. Trial in this matter is scheduled for October 28, 2024.

On January 13, 2023, Amneal Pharmaceuticals LLC, Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, notified the Court that they had reached a settlement-in-principle with the class action plaintiffs. On April 19, 2023, the Court held a hearing on a motion for preliminary approval of this proposed settlement. On May 12, 2023, the Court granted the motion for preliminary approval of the proposed settlement. On January 11, 2024, the Court held a hearing on the motion for final approval of the proposed settlement. The Court deferred ruling and scheduled a further hearing for final approval of the proposed settlement on April 17, 2024. During February and March 2024, the parties notified the Court of settlements between certain non-class action plaintiffs and each of Amneal and Lupin, and the Court dismissed those plaintiffs' claims against the applicable parties. On April 17, 2024, the Court issued an order granting the motion for final approval of the settlement between the class action plaintiffs, Amneal, and Lupin.

On December 11, 2023, Blue Cross and Blue Shield of Florida, Inc. and Health Options, Inc. filed a lawsuit in the United States District Court for the Middle District of Florida against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., and Eurohealth (USA), Inc., raising similar allegations. On January 23, 2024, the Blue Cross Florida case was transferred to the United States District Court for the Northern District of California and consolidated with the above referenced multidistrict litigation for pretrial purposes.

On May 9, 2022, Aetna Inc., or Aetna, filed a lawsuit in the Superior Court of California for the County of Alameda against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations. On December 27, 2022, the Court granted in part and denied in part our motion to dismiss Aetna's complaint. As a result of that ruling, the generic defendants have been dismissed from the case, and certain of Aetna's claims against Jazz have been dismissed. On January 27, 2023, Aetna filed an amended complaint against Jazz. On March 22, 2023, we filed motions to dismiss and to strike portions of the amended complaint. On June 26, 2023, the Court granted our motions, and granted Aetna leave to further amend its complaint. On November 17, 2023, Aetna filed its second amended complaint. On February 2, 2024, we filed our answer to the second amended complaint and Hikma filed a motion to quash service. That motion remains pending.

The plaintiffs in certain of these lawsuits are seeking to represent a class of direct purchasers of Xyrem, and the plaintiffs in the remaining lawsuits are seeking to represent a class of indirect purchasers of Xyrem. Each of the lawsuits generally alleges violations of U.S. federal and state antitrust, consumer protection, and unfair competition laws in connection with the Company Defendants' conduct related to Xyrem, including actions leading up to, and entering into, patent litigation settlement agreements with each of the other named defendants. Each of the lawsuits seeks monetary damages, exemplary damages, equitable relief against the alleged unlawful conduct, including disgorgement of profits and restitution, and injunctive relief. It is possible that additional lawsuits will be filed against the Company Defendants making similar or related allegations. If the plaintiffs were to be successful in their claims, they may be entitled to injunctive relief or we may be required to pay significant monetary damages, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

GW Acquisition Litigation

On March 15, 2021, GW filed a definitive proxy statement, or Proxy Statement, with the Securities and Exchange Commission in connection with the GW Acquisition.

Since the filing of the Proxy Statement, Jazz Pharmaceuticals plc has been named in two lawsuits filed in state and federal courts in New York on March 17, 2021 by purported GW shareholders in connection with the GW Acquisition. The first was filed in the United States District Court for the Southern District of New York by James Farrell (hereinafter referred to as the Farrell Lawsuit) and an additional suit was filed in New York state court by Brian Levy (hereinafter referred to as the Levy Lawsuit). In addition to Jazz Pharmaceuticals plc, Jazz Pharmaceuticals U.K. Holdings Ltd., GW Pharmaceuticals plc, and the GW board of directors are named as defendants in the Farrell Lawsuit. In the Levy Lawsuit, GW Pharmaceuticals plc, the GW board of directors, Centerview Partners LLC, and Goldman Sachs & Co. LLC are named as defendants. In addition to the Farrell Lawsuit and the Levy Lawsuit, ten additional suits have been filed in New York, California, and Pennsylvania federal courts by purported GW shareholders against GW Pharmaceuticals plc and its board of directors, but which do not name any Jazz Pharmaceuticals parties (hereinafter referred to as the GW Litigation, and collectively with the Farrell Lawsuit and the Levy Lawsuit, as the Transaction Litigation). In the Transaction Litigation, the plaintiffs allege that the Proxy Statement omitted material information and contained misrepresentations, and that the individual members of the GW board of directors breached their fiduciary duties, in violation of state and federal laws, including the Securities Exchange Act of 1934. The plaintiffs in the Transaction Litigation sought various remedies, including injunctive relief to prevent the consummation of the GW Acquisition unless certain allegedly material information was disclosed, or in the alternative, rescission or damages.

On April 14, 2021, GW filed a Form 8-K containing supplemental disclosures related to the GW Acquisition. Pursuant to a memorandum of understanding between the parties, the Levy Lawsuit was dismissed on April 14, 2021.

On May 27, 2021, a class action lawsuit was filed in the United States District Court for the Southern District of California by plaintiff Kurt Ziegler against GW and its former Directors asserting claims under Sections 14(a) and 20(a) of the Securities Exchange Act of 1934, referred to as the Ziegler Lawsuit. The allegations in the Ziegler Lawsuit are similar to those in the previously dismissed Transaction Litigation.

On June 3, 2022, we filed a motion to dismiss the Ziegler Lawsuit. While the motion to dismiss was pending, in December 2022, the parties participated in a mediation and reached a tentative settlement, which remains subject to court approval. On March 20, 2023, the plaintiffs in the Ziegler Lawsuit filed a motion for preliminary approval of the settlement. On July 28, 2023, the Court granted the motion for preliminary approval, which conditionally certified a class for settlement purposes. On December 11, 2023, the Court held a hearing regarding final approval of the proposed settlement and took the matter under advisement. On March 25, 2024, the Court issued an order finally approving the settlement and a judgment dismissing the case. On April 4, 2024, the Court issued amended versions of the order and judgment.

Patent Infringement Litigation

Avadel Litigation

On May 13, 2021, we filed a patent infringement suit against Avadel Pharmaceuticals plc, or Avadel, and several of its corporate affiliates in the United States District Court for the District of Delaware. The suit alleges that Avadel's Lumryz will infringe five of our patents related to controlled release formulations of oxybate and the safe and effective distribution of oxybate. The suit seeks an injunction to prevent Avadel from launching a product that would infringe these patents, and an award of monetary damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product will not infringe our patents. Avadel filed a motion for partial judgment on the pleadings on its counterclaim that one of our patents should be delisted from the Orange Book. On November 18, 2022, the Court issued an order that we delist the patent from the Orange Book. On November 22, 2022, we filed a notice of appeal to the United States Court of Appeals for the Federal Circuit. The Federal Circuit temporarily stayed the District Court's delisting order. On February 24, 2023, the Federal Circuit affirmed the District Court's delisting order, lifted the temporary stay, and gave Jazz 14 days to request that FDA delist the patent from the Orange Book. Jazz complied with the Federal Circuit's order and requested delisting on February 28, 2023. On March 3, 2023, we and Avadel stipulated to the dismissal without prejudice of the claims and counterclaims related to infringement and validity of the delisted patent in both this suit and a later-filed suit described below related to the same patent.

On August 4, 2021, we filed an additional patent infringement suit against Avadel in the United States District Court for the District of Delaware. The second suit alleges that Avadel's Lumryz will infringe a newly-issued patent related to sustained-release formulations of oxybate. The suit seeks an injunction to prevent Avadel from launching a product that would infringe this patent, and an award of monetary damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product will not infringe our patents.

On November 10, 2021, we filed an additional patent infringement suit against Avadel in the United States District Court for the District of Delaware. The third suit alleges that Avadel's Lumryz will infringe a newly-issued patent related to sustained-release formulations of oxybate. The suit seeks an injunction to prevent Avadel from launching a product that would infringe this patent, and an award of monetary damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product will not infringe our patents.

On April 14, 2022, Avadel sued us in the United States District Court for the District of Delaware. Avadel's new suit alleges that we misappropriated trade secrets related to Avadel's once-nightly sodium oxybate development program and breached certain contracts between the parties. Avadel seeks monetary damages, an injunction preventing us from using Avadel's confidential information, and an order directing the United States Patent and Trademark Office to modify the inventorship of one of our oxybate patents. On July 8, 2022, we filed a motion for judgment on the pleadings, which the Court denied on July 18, 2023. The denial is not a ruling that Jazz misappropriated Avadel's trade secrets or breached any contract. The case will go forward in discovery and the Court instructed the parties to submit a proposed scheduling order.

On June 7, 2022, we received notice from Avadel that it had filed a "paragraph IV certification" regarding one patent listed in the Orange Book for Xyrem. A paragraph IV certification is a certification by a generic applicant that alleges that patents covering the branded product are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the generic product. On July 15, 2022, we filed an additional lawsuit against Avadel asserting infringement of that patent. The suit alleges that the filing of Avadel's application for approval of FT218 is an act of infringement, and that Avadel's product would infringe the patent if launched. The suit seeks an injunction to prevent Avadel from launching a product that would infringe the patent, and an award of damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patent is invalid, that its product would not infringe, and that by listing the patent in the Orange Book, we engaged in unlawful monopolization in violation of the Sherman Act. On December 9, 2022, we filed a motion to dismiss Avadel's counterclaims. On June 29, 2023, we filed a motion seeking leave to supplement our motion to dismiss, as well as a motion to stay discovery pending resolution of the motion to dismiss. The Court has not yet ruled on these motions. As noted above, on March 3, 2023, we and Avadel stipulated to the dismissal without prejudice of the claims and counterclaims related to infringement and validity of the delisted patent.

On November 1, 2023, the Court held a claim construction hearing relating to disputed terms in the asserted patents. On December 15, 2023, the Court issued a written opinion and order resolving the parties' remaining claim construction disputes. On November 20, 2023, we and Avadel each filed motions for summary judgment. On February 14, 2024, the Court issued a written opinion and order denying both parties' motions for summary judgment.

Trial regarding our patent infringement claims against Avadel began on February 26, 2024 and concluded on March 4, 2024, with the jury finding both of our asserted patents valid, and awarding us damages for infringement for Avadel's

past sales of Lumryz. On April 12, 2024, we filed a motion for a permanent injunction and ongoing royalties. The Court scheduled a hearing on that motion for June 4, 2024.

The Court scheduled a trial regarding Avadel's counterclaims for unlawful monopolization for November 3, 2025 and a trial regarding Avadel's trade secret misappropriation claims for December 15, 2025. On March 13, 2024 and March 19, 2024, we filed motions to stay Avadel's unlawful monopolization counterclaim and trade secret claims, respectively, pending resolution of post-trial motions and potential appeals in the patent infringement suit. Both motions to stay remain pending.

On July 21, 2022, Avadel filed a lawsuit against FDA in the United States District Court for the District of Columbia, challenging FDA's determination that Avadel was required to file a paragraph IV certification regarding one of our Orange Book listed patents. Avadel filed a motion for preliminary injunction, or in the alternative, summary judgment, seeking relief including a declaration that FDA's decision requiring patent certification was unlawful, an order setting aside that decision, an injunction prohibiting FDA from requiring such certification as a precondition to approval of its application for FT218, and an order requiring FDA to take final action on Avadel's application for approval of FT218 within 14 days of the Court's ruling. On July 27, 2022, we filed a motion to intervene in that case, which the Court granted. The Court held a hearing on the parties' respective motions for summary judgment on October 7, 2022. On November 3, 2022, the Court granted our and FDA's motions for summary judgment and denied Avadel's motion.

Xywav Patent Litigation

In June 2021, we received notice from Lupin Inc., or Lupin, that it has filed with FDA an ANDA, for a generic version of Xywav. The notice from Lupin included a paragraph IV certification with respect to ten of our patents listed in FDA's Orange Book for Xywav on the date of our receipt of the notice. The asserted patents relate generally to the composition and method of use of Xywav, and methods of treatment when Xywav is administered concomitantly with certain other medications.

In July 2021, we filed a patent infringement suit against Lupin in the United States District Court for the District of New Jersey. The complaint alleges that by filing its ANDA, Lupin has infringed ten of our Orange Book listed patents. We are seeking a permanent injunction to prevent Lupin from introducing a generic version of Xywav that would infringe our patents. As a result of this lawsuit, we expect that a stay of approval of up to 30 months will be imposed by FDA on Lupin's ANDA. In June 2021, FDA recognized seven years of Orphan Drug Exclusivity for Xywav through July 21, 2027. On October 4, 2021, Lupin filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

In April 2022, we received notice from Lupin that it had filed a paragraph IV certification regarding a newly-issued patent listed in the Orange Book for Xywav. On May 11, 2022, we filed an additional lawsuit against Lupin in the United States District Court for the District of New Jersey alleging that by filing its ANDA, Lupin infringed the newly-issued patent related to a method of treatment when Xywav is administered concomitantly with certain other medications. The suit seeks a permanent injunction to prevent Lupin from introducing a generic version of Xywav that would infringe our patent. On June 22, 2022, the Court consolidated the two lawsuits we filed against Lupin.

In November 2022, we received notice from Lupin that it had filed a paragraph IV certification regarding a newly-issued patent listed in the Orange Book for Xywav. On January 19, 2023, we filed an additional lawsuit against Lupin in the United States District Court for the District of New Jersey alleging that by filing its ANDA, Lupin infringed the newly-issued patent referenced in its November 2022 paragraph IV certification, as well as another patent that issued in January 2023. The suit seeks a permanent injunction to prevent Lupin from introducing a generic version of Xywav that would infringe the two patents in suit. On February 15, 2023, the Court consolidated the new lawsuit with the two suits we previously filed against Lupin. No trial date has been set in the consolidated case against Lupin.

In February 2023, we received notice from Teva Pharmaceuticals, Inc., or Teva, that it had filed with FDA an ANDA for a generic version of Xywav. The notice from Teva included a paragraph IV certification with respect to thirteen of our patents listed in FDA's Orange Book for Xywav on the date of the receipt of the notice. The asserted patents relate generally to the composition and method of use of Xywav, and methods of treatment when Xywav is administered concomitantly with certain other medications.

In March 2023, we filed a patent infringement suit against Teva in the United States District Court for the District of New Jersey. The complaint alleges that by filing its ANDA, Teva has infringed thirteen of our Orange Book listed patents. We are seeking a permanent injunction to prevent Teva from introducing a generic version of Xywav that would infringe our patents. As a result of this lawsuit, we expect that a stay of approval of up to 30 months will be imposed by FDA on Teva's ANDA. On May 23, 2023, Teva filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

On December 15, 2023, based on a stipulation between all parties, the Court consolidated the Lupin lawsuits and the Teva lawsuit for all purposes. No trial date has been set in the consolidated case.

Alkem Patent Litigation

In April 2023, we received notice from Alkem Laboratories Ltd., or Alkem, that it has filed with FDA an ANDA, for a generic version of Xyrem. The notice from Alkem included a paragraph IV certification with respect to six of our patents listed in FDA's Orange Book for Xyrem on the date of our receipt of the notice. The asserted patents relate generally to methods of treatment when Xyrem is administered concomitantly with certain other medications.

In June 2023, we filed a patent infringement suit against Alkem in the United States District Court for the District of New Jersey. The complaint alleges that by filing its ANDA, Alkem has infringed six of our Orange Book listed patents. We are seeking a permanent injunction to prevent Alkem from introducing a generic version of Xyrem that would infringe our patents. As a result of this lawsuit, we expect that a stay of approval of up to 30 months will be imposed by FDA on Alkem's ANDA.

On October 4, 2023, we entered into a settlement agreement with Alkem that resolves our patent litigation. Under the settlement agreement, we granted Alkem a license to manufacture, market, and sell its generic version of Xyrem on or after December 31, 2025, or earlier under certain circumstances, including circumstances where Hikma launches its own generic sodium oxybate product.

Epidiolex Patent Litigation

In November and December 2022, we received notices from Teva Pharmaceuticals, Inc.; Padagis US LLC; Apotex Inc.; API Pharma Tech LLC and InvaGen Pharmaceuticals, Inc.; Lupin Limited; Taro Pharmaceutical Industries Ltd.; Zenara Pharma Private Limited and Biophore Pharma, Inc.; MSN Laboratories Pvt. Ltd. and MSN Pharmaceuticals, Inc.; Alkem Laboratories Ltd.; and Ascent Pharmaceuticals, Inc. (hereinafter referred to as the "Epidiolex ANDA Filers"), that they have each filed with FDA an ANDA for a generic version of Epidiolex (cannabidiol) oral solution. As of the date of this filing, we are not aware of other ANDA filers. The notices from the Epidiolex ANDA Filers each included a "paragraph IV certification" with respect to certain of our patents listed in FDA's Orange Book for Epidiolex on the date of the receipt of the notice. The listed patents relate generally to the composition and method of use of Epidiolex, and methods of treatment using Epidiolex. A paragraph IV certification is a certification by a generic applicant that alleges that patents covering the branded product are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the generic product.

On January 3, 2023, we filed a patent infringement suit against the Epidiolex ANDA Filers in the United States District Court for the District of New Jersey. The complaint alleges that by filing their ANDAs, the Epidiolex ANDA Filers have infringed certain of our Orange Book listed patents, and seeks an order that the effective date of FDA approval of the ANDAs shall be a date no earlier than the expiration of the last to expire of the asserted patents. As a result of this lawsuit, we expect that a stay of approval of up to 30 months will be imposed by FDA on the Epidiolex ANDA Filers' ANDAs.

From March 2023 through May 2023, we received the Epidiolex ANDA Filers' answers to the complaint. The answers include defenses and counterclaims asserting that the Epidiolex ANDA Filers' products, if launched, would not infringe our patents, that our patents are invalid and, in one instance, counterclaims related to allegations of inequitable conduct and improper listing of patents in the Orange Book. On May 25, 2023, we filed a motion to dismiss certain of the counterclaims. On January 11, 2024, the Court issued an order granting in part and denying in part our motion to dismiss.

The Court in the Epidiolex Patent Litigation scheduled trial for September 2025.

In June and July 2023, we received notice from certain of the Epidiolex ANDA Filers that they had each filed a paragraph IV certification regarding a newly-issued patent listed in the Orange Book for Epidiolex. On July 21, 2023, we filed an additional lawsuit against all of the Epidiolex ANDA Filers in the United States District Court for the District of New Jersey alleging that, by filing its ANDA, each Epidiolex ANDA Filer infringed the newly-issued patent related to a method of treatment using Epidiolex. The suit seeks an order that the effective date of FDA approval of each Epidiolex ANDA Filer's application shall be a date no earlier than the expiration of the newly-issued patent.

On October 24, 2023, we entered into a settlement agreement with Padagis US LLC, or Padagis, that resolved our patent litigation with Padagis related to Epidiolex. Under the settlement agreement, we granted Padagis a license to manufacture, market, and sell its generic version of Epidiolex on a date that depends on the occurrence of certain other events. The specific terms of the Padagis settlement agreement are confidential.

On November 20, 2023, we entered into a settlement agreement with Teva Pharmaceuticals, Inc., or Teva, that resolved our patent litigation with Teva related to Epidiolex. Under the settlement agreement, we granted Teva a license to manufacture, market and sell its generic version of Epidiolex on a date which remains confidential. The specific terms of the Teva settlement agreement are confidential.

On December 4, 2023, we entered into a settlement agreement with Alkem Laboratories Ltd., or Alkem, that resolved our patent litigation with Alkem related to Epidiolex. Under the settlement agreement, we granted Alkem a license to manufacture, market, and sell its generic version of Epidiolex on a date which remains confidential. The specific terms of the Alkem settlement are confidential.

The settlements with Padagis, Teva and Alkem do not resolve the litigation against the other seven Epidiolex ANDA Filers, which is ongoing. We cannot predict the specific timing or outcome of events in these matters with respect to the remaining defendants or the impact of developments involving any specific parties or patents on other ongoing proceedings with any specific Epidiolex ANDA Filer.

In September and October 2023, we received notice from certain of the Epidiolex ANDA filers that they had each filed a paragraph IV certification regarding one or more newly-issued patents listed in the Orange Book for Epidiolex. On December 15, 2023, we filed an additional lawsuit against seven of the original Epidiolex ANDA Filers with whom we have not previously settled. We filed this lawsuit in the United States District Court for the District of New Jersey alleging that, by filing its ANDA, each Epidiolex ANDA Filer infringed the newly-issued patents related to methods of treatment using Epidiolex. The suit seeks an order that the effective date of FDA approval of each Epidiolex ANDA Filer's application shall be a date no earlier than the expiration of the newly-issued patents.

Epidiolex also has orphan drug exclusivity, or ODE, for the treatment of seizures associated with LGS or DS in patients 2 years of age and older through September 28, 2025, and for the treatment of seizures associated with LGS or DS in patients between 1 and 2 years of age and for the treatment of seizures associated with TSC through July 31, 2027.

The Company vigorously enforces its intellectual property rights but cannot predict the outcome of these matters.

MSP Litigation

On April 3, 2023, MSP Recovery Claims, Series LLC, or MSP, filed a class action lawsuit on behalf itself and others similarly situated against Jazz Pharmaceuticals plc, Jazz Pharmaceuticals, Inc., and Jazz Pharmaceuticals Ireland Limited, (collectively, the Company Defendants), Express Scripts, Inc., Express Scripts Holding Company, Express Scripts Specialty Distribution Services, Inc., Curascript, Inc. d/b/a Curascript, S.D., Priority Healthcare Distribution, Inc. d/b/a Curascript SD and Curascript Specialty Distribution SD, Caring Voice Coalition, and Adira Foundation (collectively with the Company Defendants, referred to as the Defendants) in the United States District Court for the Northern District of California. The MSP complaint alleges that the Defendants conspired to increase the price and quantity dispensed of Xyrem and Prialt, in violation of the Racketeer Influenced and Corrupt Organizations Act and several state laws. The allegations relate generally to the conduct at issue in the investigation conducted by the United States Department of Justice from 2016-2019, involving the Company's contributions to certain charitable foundations. MSP seeks monetary damages, restitution, disgorgement, and a declaration that the conduct alleged is unlawful.

On July 25, 2023, we and certain other defendants filed motions to dismiss MSP's complaint, which the Court granted on December 12, 2023. On January 5, 2024, the MSP filed an amended complaint. On February 20, 2024, we filed a motion to dismiss MSP's amended complaint. The Court scheduled a hearing on the motion for June 13, 2024. No trial date has been set for this matter.

FDA Litigation

On June 22, 2023, we filed a complaint in the United States District Court for the District of Columbia seeking a declaration that FDA's approval on May 1, 2023 of the New Drug Application, or NDA, for Avadel's Lumryz was unlawful. In the complaint, we allege that FDA acted outside its authority under the Orphan Drug Act, when, despite ODE protecting Jazz's low-sodium oxybate product Xywav, FDA approved the Lumryz NDA and granted Lumryz ODE based on FDA's finding that Lumryz makes a major contribution to patient care and is therefore clinically superior to Xywav and Xyrem. Jazz further alleges that in doing so, FDA failed to follow its own regulations, failed to follow established agency policy without providing a reasoned explanation for the departure, reversed prior decisions by its own staff and experts without a reasoned explanation, and disregarded the relevant scientific literature and data. The complaint, filed pursuant to the Administrative Procedure Act, seeks to have the Court vacate and set aside FDA's approval of the Lumryz NDA and seeks a declaration that FDA's approval of the Lumryz NDA was arbitrary, capricious, an abuse of discretion and otherwise not in accordance with law; and that approval of the Lumryz NDA was in excess of FDA's statutory authority and was made without observance of procedure required by law.

On September 15, 2023, we filed a motion for summary judgment. On October 20, 2023, Avadel and FDA filed cross motions for summary judgment. Oral argument on these motions is currently scheduled for May 10, 2024.

From time to time we are involved in legal proceedings arising in the ordinary course of business. We believe there is no other litigation pending that could have, individually or in the aggregate, a material adverse effect on our results of operations or financial condition.

10. Shareholders' Equity

Share Repurchase Program

In November 2016, our board of directors authorized a share repurchase program and, as of March 31, 2024, had authorized the repurchase of ordinary shares having an aggregate purchase price of up to $1.5 billion, exclusive of any brokerage commissions. Under this program, which has no expiration date, we may repurchase ordinary shares from time to time on the open market. The timing and amount of repurchases will depend on a variety of factors, including the price of our ordinary shares, alternative investment opportunities, restrictions under the May 2021 credit agreement, corporate and regulatory requirements and market conditions. The share repurchase program may be modified, suspended or discontinued at any time without prior notice. During the three months ended March 31, 2024, no shares were repurchased. As of March 31, 2024, the remaining amount authorized under the share repurchase program was $161.4 million, exclusive of any brokerage commissions.

Accumulated Other Comprehensive Loss

The components of accumulated other comprehensive loss as of March 31, 2024 and December 31, 2023 were as follows (in thousands):

	Net Unrealized Gain From Hedging Activities	Foreign Currency Translation Adjustments	Total Accumulated Other Comprehensive Loss
Balance at December 31, 2023	$ 235	$ (842,382)	$ (842,147)
Other comprehensive income (loss) before reclassifications	5,177	(44,068)	(38,891)
Amounts reclassified from accumulated other comprehensive income (loss)	(1,356)	—	(1,356)
Other comprehensive income (loss), net	3,821	(44,068)	(40,247)
Balance at March 31, 2024	$ 4,056	$ (886,450)	$ (882,394)

During the three months ended March 31, 2024, other comprehensive income (loss) primarily reflects foreign currency translation adjustments, primarily due to the weakening of sterling and the euro against the U.S. dollar.

11. Net Income (Loss) per Ordinary Share

Basic net income (loss) per ordinary share is based on the weighted-average number of ordinary shares outstanding. Diluted net income (loss) per ordinary share is based on the weighted-average number of ordinary shares outstanding and potentially dilutive ordinary shares outstanding.

Basic and diluted net income (loss) per ordinary share were computed as follows (in thousands, except per share amounts):

	Three Months Ended March 31,	
	2024	2023
Numerator:		
Net income (loss)	$ (14,618)	$ 69,420
Effect of interest on assumed conversions of Exchangeable Senior Notes, net of tax	—	6,963
Net income (loss) for dilutive net income (loss) per ordinary share	$ (14,618)	$ 76,383
Denominator:		
Weighted-average ordinary shares used in per share calculations - basic	62,537	63,494
Dilutive effect of Exchangeable Senior Notes	—	9,044
Dilutive effect of employee equity incentive and purchase plans	—	1,233
Weighted-average ordinary shares used in per share calculations - diluted	62,537	73,771
Net income (loss) per ordinary share:		
Basic	$ (0.23)	$ 1.09
Diluted	$ (0.23)	$ 1.04

Potentially dilutive ordinary shares from our employee equity incentive and purchase plans are determined by applying the treasury stock method to the assumed vesting of outstanding restricted stock units, or RSUs, and performance-based restricted stock units, or PRSUs, the assumed exercise of share options and the assumed issuance of ordinary shares under our employee stock purchase plan, or ESPP. Potentially dilutive ordinary shares from the Exchangeable Senior Notes are determined by applying the if-converted method to the assumed issuance of ordinary shares upon exchange of the Exchangeable Senior Notes. In August 2023, we made an irrevocable election to fix the settlement method for exchanges of the 2024 Notes to a combination of cash and ordinary shares of the Company with a specified cash amount per $1,000 principal amount of the 2024 Notes of $1,000. As a result, the assumed issuance of ordinary shares upon exchange of the 2024 Notes has only been included in the calculation of diluted net income per ordinary share in the three months ended March 31, 2023. The potential issue of ordinary shares upon exchange of the 2026 Notes was anti-dilutive and had no impact on diluted net loss per ordinary share for the three months ended March 31, 2024.

The following table represents the weighted-average ordinary shares that were excluded from the calculation of diluted net income (loss) per ordinary share for the periods presented because including them would have an anti-dilutive effect (in thousands):

	Three Months Ended March 31,	
	2024	2023
Exchangeable Senior Notes	6,418	—
Employee equity incentive and purchase plans	3,500	1,072

12. Revenues

The following table presents a summary of total revenues (in thousands):

	Three Months Ended March 31,	
	2024	2023
Xywav	$ 315,300	$ 277,761
Xyrem	64,232	178,130
Epidiolex/Epidyolex	198,716	188,909
Sativex	2,735	7,098
Total Neuroscience	580,983	651,898
Rylaze/Enrylaze	102,750	85,927
Zepzelca	75,100	67,181
Defitelio/defibrotide	47,676	39,079
Vyxeos	32,023	36,700
Total Oncology	257,549	228,887
Other	3,570	3,434
Product sales, net	842,102	884,219
High-sodium oxybate AG royalty revenue	49,947	2,096
Other royalty and contract revenues	9,934	6,497
Total revenues	$ 901,983	$ 892,812

The following table presents a summary of total revenues attributed to geographic sources (in thousands):

	Three Months Ended March 31,	
	2024	2023
United States	$ 808,214	$ 810,116
Europe	71,355	65,900
All other	22,414	16,796
Total revenues	$ 901,983	$ 892,812

The following table presents a summary of the percentage of total revenues from customers that represented more than 10% of our total revenues:

	Three Months Ended March 31,	
	2024	2023
ESSDS	42 %	51 %
McKesson	12 %	12 %
Cardinal Health, Inc.	8 %	10 %

Financing and payment

Our payment terms vary by the type and location of our customer but payment is generally required in a term ranging from 30 to 65 days.

13. Share-Based Compensation

Share-based compensation expense related to RSUs, PRSUs, grants under our ESPP and share options was as follows (in thousands):

	Three Months Ended March 31,	
	2024	2023
Selling, general and administrative	$ 40,213	$ 37,402
Research and development	18,831	15,492
Cost of product sales	2,397	3,458
Total share-based compensation expense, pre-tax	61,441	56,352
Income tax benefit from share-based compensation expense	(3,399)	(8,619)
Total share-based compensation expense, net of tax	$ 58,042	$ 47,733

Restricted Stock Units

The table below shows the number of RSUs granted covering an equal number of our ordinary shares and the weighted-average grant date fair value of RSUs granted:

	Three Months Ended March 31,	
	2024	2023
RSUs granted (in thousands)	1,955	1,571
Grant date fair value	$ 118.89	$ 146.20

The fair value of RSUs is determined on the date of grant based on the market price of our ordinary shares on that date. The fair value of RSUs is expensed ratably over the vesting period, generally over four years.

Performance-Based Restricted Stock Units

The Compensation & Management Development Committee of our board of directors and, in the case of our Chief Executive Officer, the independent members of our board of directors, approved awards of PRSUs to certain employees of the Company, subject to vesting on the achievement of certain commercial and pipeline performance criteria to be assessed over a performance period from the date of the grant to December 31, 2024, December 31, 2025 and December 31, 2026, respectively. The number of shares that will be awarded is determined based on the Company's achievement with respect to the performance criteria. For PRSUs granted prior to 2024, the amount of shares awarded will be subject to adjustment based on the application of a relative total shareholder return, or TSR, modifier. For PRSUs granted in 2024, the relative TSR represents one of the performance metrics. In both cases, the number of shares that may be earned ranges between 0% and 200% of the target number of PRSUs granted.

The table below shows the number of PRSUs granted covering an equal number of our ordinary shares and the weighted-average grant date fair value of PRSUs granted:

	Three Months Ended March 31,	
	2024	2023
PRSUs granted (in thousands)	297	252
Grant date fair value	$ 136.19	$ 158.13

As the PRSUs granted in each year are subject to a market condition, the grant date fair value for such PRSUs was based on a Monte Carlo simulation model. The Company evaluated the performance targets in the context of its current long-range financial plan and its product candidate development pipeline and recognized expense based on the probable number of awards that will ultimately vest.

As of March 31, 2024, compensation cost not yet recognized related to unvested RSUs, PRSUs, ESPP and share options was $435.9 million, $51.5 million, $8.3 million and $0.3 million, respectively, which is expected to be recognized over a weighted-average period of 3.0 years, 1.8 years, 1.1 years and 0.5 years, respectively.

14. Income Taxes

Our income tax expense was $11.7 million for the three months ended March 31, 2024, resulting primarily from tax deficiencies from share based compensation. Our income tax benefit was $15.3 million for the same period in 2023, relating to tax arising on income or losses in Ireland, the U.K., the U.S. and certain other foreign jurisdictions, offset by deductions on subsidiary equity, foreign derived intangible income, or FDII, and patent box benefits.

Our net deferred tax liability is primarily related to acquired intangible assets, and is net of deferred tax assets related to U.S. federal and state tax credits, U.S. federal and state and foreign net operating loss carryforwards and other temporary differences. We maintain a valuation allowance against certain deferred tax assets. Each reporting period, we evaluate the need for a valuation allowance on our deferred tax assets by jurisdiction and adjust our estimates as more information becomes available.

We are required to recognize the financial statement effects of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. As a result, we have recorded an unrecognized tax benefit for certain tax benefits which we judge may not be sustained upon examination. We file income tax returns in multiple tax jurisdictions, the most significant of which are Ireland, the U.K. and the U.S. (both at the federal level and in various state jurisdictions). For Ireland, we are no longer subject to income tax examinations by taxing authorities for the years prior to 2019. For the U.K., we are no longer subject to income tax examinations by taxing authorities for the years prior to 2016. The U.S. jurisdictions generally have statute of limitations three to four years from the later of the return due date or the date when the return was filed. However, in the U.S. (at the federal level and in most states), carryforwards that were generated in 2019 and earlier may still be adjusted upon examination by the taxing authorities. One of our subsidiaries is currently under examination by the Luxembourg taxing authorities for the years ended December 31, 2017, 2018 and 2019. In October 2022 and in January 2023, we received tax assessment notices from the Luxembourg taxing authorities for all years under examination relating to certain transfer pricing and other adjustments. The notices propose additional Luxembourg income tax of approximately $24.2 million, translated at the foreign exchange rate as March 31, 2024. We disagree with the proposed assessments and are contesting them vigorously.

The Government of Ireland, the jurisdiction in which Jazz Pharmaceuticals Plc is incorporated, transposed the Global Minimum Tax Pillar Two rules into domestic legislation as part of the Finance (No. 2) Act 2023 (the "Finance Act"). The Finance Act closely follows the EU Minimum Tax Directive and OECD Guidance released to date. The Company is within the scope of these rules, which took effect from January 1, 2024. Under the new legislation, we are liable to pay a top-up tax for the difference between the Pillar Two effective tax rate per jurisdiction and the 15% minimum rate. The rules on how to calculate the 15% effective tax rate are detailed and highly complex and specific adjustments envisaged in the Pillar Two legislation can give rise to different effective tax rates compared to those calculated for accounting purposes. We will account for it as a current tax when it is incurred. We expect to be subject to the top-up tax in relation to our operations in Ireland, where the trading statutory tax rate is 12.5%, though the impact in 2024 is not significant. The proportion of our profit before tax which is subject to the top-up tax and our exposure to Pillar Two income taxes in future years will depend on factors such as future revenues, costs and foreign currency exchange rates. We will continue to monitor changes in law and guidance in relation to Pillar Two.

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion of our financial condition and results of operations should be read in conjunction with the condensed consolidated financial statements and the notes to condensed consolidated financial statements included elsewhere in this Quarterly Report on Form 10-Q. This discussion contains forward-looking statements that involve risks and uncertainties. When reviewing the discussion below, you should keep in mind the substantial risks and uncertainties that could impact our business. In particular, we encourage you to review the risks and uncertainties described in "Risk Factors" in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023, as supplemented by the risks and uncertainties described in "Risk Factors" Item 1A. Risk Factors in Part II of this Quarterly Report on Form 10-Q. These risks and uncertainties could cause actual results to differ materially from those projected in forward-looking statements contained in this report or implied by past results and trends. Forward-looking statements are statements that attempt to forecast or anticipate future developments in our business, financial condition or results of operations. See the "Cautionary Note Regarding Forward-Looking Statements" that appears at the end of this discussion. These statements, like all statements in this report, speak only as of the date of this Quarterly Report on Form 10-Q (unless another date is indicated), and we undertake no obligation to update or revise these statements in light of future developments.

Overview

Jazz Pharmaceuticals plc is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases - often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines, including leading therapies for sleep disorders and epilepsy, and a growing portfolio of cancer treatments. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics in oncology and neuroscience.

Our strategy for growth is rooted in executing commercial launches and ongoing commercialization initiatives, advancing robust research and development, or R&D, programs and delivering impactful clinical results, effectively deploying capital to strengthen the prospects of achieving our short- and long-term goals through strategic corporate development, and delivering strong financial performance. We focus on patient populations with high unmet needs. We identify and develop differentiated therapies for these patients that we expect will be long-lived assets and that we can support with an efficient commercialization model. In addition, we leverage our efficient, scalable operating model and integrated capabilities across our global infrastructure to effectively reach patients around the world.

In January 2022, we announced our Vision 2025, which aims to deliver sustainable growth and enhanced value, driving our continued transformation to an innovative, high-growth global pharmaceutical leader. The three core components of our Vision 2025 focus on commercial execution, pipeline productivity and operational excellence.

Our strategy to deliver sustainable growth and enhanced value is focused on:

- Strong commercial execution to drive diversified revenue growth and address unmet medical needs of our patients across our product portfolio, which focuses on neuroscience and oncology medicines;
- Expanding and advancing our pipeline to achieve a valuable portfolio of durable, highly differentiated products;
- Continuing to build a flexible, efficient and productive development engine for targeted therapeutic areas to identify and progress early-, mid- and late-stage assets;
- Identifying and acquiring novel product candidates and approved therapies to complement our existing pipeline and commercial portfolio;
- Investing in an efficient, scalable operating model and differentiated capabilities to enable growth; and
- Unlocking further value through indication expansion and entry into global markets.

In 2024, consistent with our strategy, we are continuing to focus on research and development activities within our neuroscience and oncology therapeutic areas.

Our lead marketed products, listed below, are approved in countries around the world to improve patient care.

Product	Indications	Initial Approval Date	Markets
NEUROSCIENCE			
Xywav® (calcium, magnesium, potassium, and sodium oxybates)	Treatment of cataplexy or excessive daytime sleepiness, or EDS, in patients seven years of age and older with narcolepsy.	July 2020	U.S.
	Treatment of idiopathic hypersomnia, or IH, in adults.	August 2021	U.S.
	Treatment of cataplexy in patients with narcolepsy.	May 2023	Canada
Xyrem® (sodium oxybate)	Treatment of cataplexy or EDS in patients seven years of age and older with narcolepsy.	July 2002	U.S.
	Treatment of cataplexy in patients with narcolepsy.	August 2005	Canada
	Treatment of narcolepsy with cataplexy in adult patients, adolescents and children from age of 7 years.	October 2005	European Union, or EU, Great Britain, other markets (through licensing agreement)
Epidiolex® (cannabidiol)	Treatment of seizures associated with Lennox-Gastaut syndrome, or LGS, Dravet syndrome, or DS, or tuberous sclerosis complex, or TSC, in patients 1 year of age and older.	June 2018	U.S.
Epidyolex® (cannabidiol)	For adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients 2 years of age and older.[1]	September 2019	EU, Great Britain, EEA[2], Israel, Switzerland, Australia and New Zealand
	For adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.	April 2021	EU, Great Britain, Israel and Switzerland
Epidiolex® (cannabidiol)	For adjunctive therapy of seizures associated with LGS, DS or TSC for patients 2 years of age and older.	November 2023	Canada
ONCOLOGY			
Rylaze® (asparaginase erwinia chrysanthemi (recombinant)-rywn)	A component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia, or ALL, and lymphoblastic lymphoma, or LBL, in adult and pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase.	June 2021	U.S.
Rylaze® (crisantaspase recombinant)	A component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL, in adults and pediatric patients 1 year or older who have developed hypersensitivity to E. coli-derived asparaginase.	September 2022	Canada

Product	Indications	Initial Approval Date	Markets
Enrylaze® (recombinant crisantaspase)	A component of a multi-agent chemotherapeutic regimen for the treatment of ALL and LBL in adult and pediatric patients (1 month and older) who have developed hypersensitivity or silent inactivation to E. coli-derived asparaginase.	September 2023	EU, Great Britain
Zepzelca® (lurbinectedin)	Treatment of adult patients with metastatic small cell lung cancer, or SCLC, with disease progression on or after platinum-based chemotherapy.	June 2020	U.S. (licensed from Pharma Mar S.A., or PharmaMar)[3]
	Treatment of adults with Stage III or metastatic SCLC who have progressed on or after platinum-containing therapy.	September 2021	Canada (licensed from PharmaMar)[4]
Defitelio® (defibrotide)	Treatment of severe hepatic veno-occlusive disease, or VOD, also known as sinusoidal obstruction syndrome, or SOS, following hematopoietic stem cell transplantation, or HSCT, therapy.	October 2013	EU, Great Britain, EEA[2], Switzerland, Israel, Australia, South Korea, Saudi Arabia
Defitelio® (defibrotide sodium)	Treatment of adult and pediatric patients with hepatic VOD, also known as SOS, with renal or pulmonary dysfunction following HSCT.	March 2016	U.S.
Defitelio® (defibrotide sodium)	Treatment of severe hepatic VOD, also known as SOS, following HSCT therapy.	July 2017	Canada, Brazil
Defitelio® (defibrotide)	Treatment of hepatic SOS (hepatic VOD).	June 2019	Japan
Vyxeos® (daunorubicin and cytarabine) liposome for injection	Treatment of newly-diagnosed therapy-related acute myeloid leukemia, or t-AML, or AML with myelodysplasia-related changes, or AML-MRC, in adults and pediatric patients one year and older.	August 2017	U.S.
Vyxeos® liposomal 44 mg/100 mg powder for concentrate for solution for infusion	Treatment of adults with newly-diagnosed t-AML or AML-MRC.	August 2018	EU, Great Britain, Switzerland, Israel, Australia, South Korea, Saudi Arabia
Vyxeos® Daunorubicin and cytarabine liposome for injection Powder, 44 mg daunorubicin and 100 mg cytarabine per vial, intravenous, or IV, infusion	Treatment of adults with newly diagnosed therapy-related t-AML or AML with AML-MRC.	April 2021	Canada
Vyxeos® Combination for I.V. Injection	High-risk AML	March 2024	Japan (through licensing agreement)[5]

[1] The clobazam restriction limited to EU and Great Britain

[2] European Economic Area

[3] Accelerated approval received from U.S. Food and Drug Administration, or FDA

[4] Conditional approval received from Health Canada

[5] Development and commercialization rights held by Nippon Shinyaku Co. Ltd. in Japan

Neuroscience

We are the global leader in the development and commercialization of oxybate therapy for patients with sleep disorders. Xyrem was approved by FDA in 2002 for treatment of cataplexy and in 2005 for treatment of EDS in narcolepsy. In 2020, we received FDA approval for Xywav for the treatment of cataplexy or EDS, in patients seven years of age and older with narcolepsy. In August 2021, Xywav became the first and only therapy approved by FDA for the treatment of IH in adults. Xywav is an oxybate therapy that contains 92% less sodium than Xyrem. Xywav has become a standard of care for patients with narcolepsy and IH.

Since there is no cure for narcolepsy and long-term disease management is needed, we believe that Xywav represents an important therapeutic option for patients with this sleep disorder. Our commercial efforts are focused on educating patients and physicians about the lifelong impact of high sodium intake, and how the use of Xywav enables them to address what is a modifiable risk factor. We view the adoption of Xywav in narcolepsy as a positive indication that physicians and patients appreciate the benefits of a low-sodium oxybate option.

In June 2021, FDA recognized seven years of Orphan Drug Exclusivity, or ODE, for Xywav in narcolepsy. ODE extends through July 2027. Nevertheless, Lumryz, a fixed-dose, high-sodium oxybate, was approved by FDA on May 1, 2023, for the treatment of cataplexy or EDS in adults with narcolepsy. FDA continues to recognize seven years of ODE for Xywav in narcolepsy. In connection with granting ODE, FDA stated that "Xywav is clinically superior to Xyrem by means of greater safety because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem.” FDA's summary also stated that "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." FDA has also recognized 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. Lumryz has the same sodium content as Xyrem. Xywav is the only approved oxybate therapy that does not carry a warning and precaution related to high sodium intake.

On August 12, 2021, FDA approved Xywav for the treatment of IH in adults. Xywav remains the first and only FDA-approved therapy to treat IH. We initiated the U.S. commercial launch of Xywav for the treatment of IH in adults in November 2021. In January 2022, FDA recognized seven years of ODE for Xywav in IH that extends through August 2028. IH is a debilitating neurologic sleep disorder characterized by chronic EDS (the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness), severe sleep inertia, and prolonged and non-restorative nighttime sleep. An estimated 37,000 people in the U.S. have been diagnosed with IH and are actively seeking healthcare.

We have agreements in place for Xywav with all three major pharmacy benefit managers, or PBMs, in the U.S. To date, we have entered into agreements with various entities and have achieved benefit coverage for Xywav in both narcolepsy and IH indications for approximately 90% of commercial lives.

We have seen strong adoption of Xywav in narcolepsy since its launch in November 2020, and increasing adoption in IH since its launch in November 2021. Exiting the first quarter of 2024, there were approximately 12,950 patients taking Xywav, including approximately 9,900 patients with narcolepsy and approximately 3,050 patients with IH.

We acquired Epidiolex (Epidyolex outside the U.S.) in May 2021 as part of the acquisition of GW Pharmaceuticals plc, or GW, which we refer to as the GW Acquisition, which expanded our growing neuroscience business with a global, high-growth childhood-onset epilepsy franchise. Epidiolex was approved in the U.S. in June 2018 for the treatment of seizures associated with two rare and severe forms of epilepsy, LGS and DS, in patients two years of age and older, and subsequently approved in July 2020 for the treatment of seizures associated with TSC in patients one year of age and older. FDA also approved the expansion of all existing indications, LGS and DS, to patients one year of age and older. The rolling European launch of Epidyolex is also underway following European Commission, or EC, approval in September 2019 for use as adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients two years of age and older. Epidyolex is now launched in all five key European markets: United Kingdom, Germany, Italy, Spain and France. The clobazam restriction is limited to the EU and Great Britain. Epidyolex was also approved for adjunctive therapy of seizures associated with TSC for patients 2 years of age and older in the EU in April 2021 and Great Britain in August 2021, and is approved or under review for this indication in other markets. Outside the U.S. and Europe, Epidiolex/Epidyolex is approved in Israel, Canada, Australia, New Zealand and Taiwan.

Oncology

Rylaze was approved by FDA in June 2021 under the Real-Time Oncology Review program, and was launched in the U.S. in July 2021 for use as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL or LBL in pediatric and adult patients one month and older who have developed hypersensitivity to E. coli-derived asparaginase. Rylaze is the only recombinant erwinia asparaginase manufactured product approved in the U.S. that maintains a clinically meaningful level of asparaginase activity throughout the entire course of treatment. We developed Rylaze to address the needs

of patients and health care providers for an innovative, high-quality erwinia asparaginase with reliable supply. The initial approved recommended dosage of Rylaze was for an intramuscular, or IM, administration of 25 mg/m^2 every 48 hours. In November 2022, FDA approved a supplemental Biologics License Application, or sBLA, for a Monday/Wednesday/Friday 25/25/50 mg/m^2 IM dosing schedule. In April 2022, we submitted a separate sBLA for IV administration. In February 2023, we received a complete response letter from FDA requesting additional clinical data on the IV administration of Rylaze. There is no impact on the approved product labeling for Rylaze IM administration. In September 2023, the EC granted marketing authorization for JZP458 under the trade name Enrylaze and the rolling launch in Europe is ongoing. This product has also been approved in the United Kingdom and Canada.

We acquired U.S. development and commercialization rights to Zepzelca in early 2020, and launched six months thereafter, with an indication for treatment of patients with SCLC with disease progression on or after platinum-based chemotherapy. Our education and promotional efforts are focused on SCLC-treating physicians. We are continuing to raise awareness of Zepzelca across academic and community cancer centers. In collaboration with F. Hoffmann-La Roche Ltd, or Roche, we have an ongoing Phase 3 pivotal clinical trial in first-line extensive stage SCLC of Zepzelca in combination with Tecentriq® (atezolizumab).

Defitelio is the first and only approved treatment for patients with VOD, severe VOD, or sVOD, or VOD with renal or pulmonary dysfunction following HSCT by regulatory authorities in the U.S., Europe, Japan and other markets. There was a significant decline in the number of patients receiving HSCT due to the effects of the COVID-19 pandemic. Moving forward, while HSCT procedures are gradually returning to pre-pandemic numbers, we expect changes in chemotherapy regimens and the increasing use of cell therapies to potentially lower the incidence of sVOD; additionally, there has been a reduction of prophylactic use of Defitelio in Europe.

Vyxeos is a treatment for adults with newly-diagnosed t-AML, or AML-MRC. In March 2021, FDA approved a revised label to include a new indication to treat newly-diagnosed t-AML, or AML-MRC, in pediatric patients aged one year and older. We have a number of ongoing development activities and continue to expand into new markets internationally. With ongoing trends in the U.S. towards lower-intensity treatments and away from intensive chemotherapy regimens for AML, we have seen increasing competition from other therapeutic options.

Research and Development Progress

Our research and development activities encompass all stages of development and currently include clinical testing of new product candidates and activities related to clinical improvements of, or additional indications or new clinical data for, our existing marketed products. We also have active preclinical programs for novel therapies, including neuroscience and precision medicines in oncology. We are increasingly leveraging our growing internal research and development function, and we have also entered into collaborations with third parties for the research and development of innovative early-stage product candidates and have supported additional investigator-sponsored trials that are anticipated to generate additional data related to our products. We also seek out investment opportunities in support of the development of early- and mid-stage technologies in our therapeutic areas and adjacencies. We have a number of licensing and collaboration agreements with third parties, including biotechnology companies, academic institutions and research-based companies and institutions, related to preclinical and clinical research and development activities in hematology and in precision oncology, as well as in neuroscience.

Within our oncology R&D program, in October 2022, we announced an exclusive licensing and collaboration agreement with Zymeworks Inc., or Zymeworks, providing us the right to acquire development and commercialization rights to Zymeworks' zanidatamab across all indications in the United States, Europe, Japan and all other territories except for those Asia/Pacific territories previously licensed by Zymeworks. In December 2022, we exercised the option to continue with the exclusive development and commercialization rights to zanidatamab. Under the terms of the agreement, Zymeworks received an upfront payment of $50.0 million, and following the exercise of our option to continue the collaboration, a second, one-time payment of $325 million. Zymeworks is also eligible to receive regulatory and commercial milestone payments of up to $1.4 billion, for total potential payments of $1.76 billion. Pending approval, Zymeworks is eligible to receive tiered royalties between 10% and 20% on our net sales. Zanidatamab is a bispecific antibody that can simultaneously bind two non-overlapping epitopes of HER2, known as biparatopic binding. Zanidatamab is currently being evaluated in multiple clinical trials as a treatment for patients with HER2-expressing cancers. Following positive data from a pivotal Phase 2 clinical trial evaluating zanidatamab monotherapy in patients with previously treated advanced or metastatic HER2-amplified biliary tract cancer, or BTC, we initiated a rolling BLA submission for accelerated approval in second-line BTC which was completed in March 2024. In addition, we have an ongoing Phase 3 randomized clinical trial evaluating zanidatamab in combination with chemotherapy plus or minus tislelizumab as a first-line treatment for HER2-expressing gastroesophageal adenocarcinoma, or GEA, and an ongoing Phase 2 trial examining zanidatamab in combination with chemotherapy in first-line patients with HER2-expressing metastatic GEA. There are also multiple ongoing clinical trials exploring zanidatamab in breast cancer and other HER2-expressing tumor types.

Our development plan for Zepzelca continues to progress. We are collaborating with Roche on a pivotal Phase 3 clinical trial evaluating Zepzelca in combination with Tecentriq in first-line extensive stage SCLC. In December 2021, our licensor PharmaMar initiated a confirmatory trial in second-line SCLC. This ongoing three-arm trial is comparing Zepzelca as either monotherapy or in combination with irinotecan to investigator's choice of irinotecan or topotecan. Data from either the first-line trial of Zepzelca in combination with Tecentriq or the PharmaMar trial could serve to confirm clinical benefit of Zepzelca and secure full approval in the U.S.

In addition, we have an ongoing Phase 4 observational study to collect real world safety and outcome data in adult Zepzelca monotherapy patients with SCLC who progress on or after prior platinum-containing chemotherapy.

In June 2022, we announced the FDA had cleared our Investigational New Drug application for JZP815 and, in October 2022, we enrolled the first patient in a Phase 1 trial. JZP815 is an investigational stage pan-RAF kinase inhibitor that targets specific components of the mitogen-activated protein kinase pathway that, when activated by oncogenic mutations, can be a frequent driver of human cancer.

In April 2022, we announced that we had entered into a licensing and collaboration agreement with Werewolf Therapeutics, Inc., or Werewolf, to acquire exclusive global development and commercialization rights to Werewolf's investigational WTX-613, now referred to as JZP898. Under the terms of the agreement, we made an upfront payment of $15.0 million to Werewolf, and Werewolf is eligible to receive development, regulatory and commercial milestone payments of up to $1.26 billion. If approved, Werewolf is eligible to receive a tiered, mid-single-digit percentage royalty on net sales of JZP898. This transaction underscores our commitment to enhancing our pipeline to deliver novel oncology therapies to patients, and also provides us with an opportunity to expand into immuno-oncology. JZP898 is a differentiated, conditionally-activated interferon alpha, or IFNα, INDUKINE™ molecule. We initiated a Phase 1 clinical trial of JZP898 in late 2023.

Our neuroscience R&D efforts include an ongoing Phase 3 trial of Epidyolex for LGS, DS and TSC in Japan initiated in October 2022.

In December 2021, we initiated Phase 2 clinical trials for suvecaltamide (JZP385), for essential tremor, or ET. Additionally, in November 2022, we initiated a Phase 2 trial of suvecaltamide in patients with Parkinson's disease tremor. In December 2023, we announced that our Phase 2 clinical trial for JZP150 for treatment of post-traumatic stress disorder, or PTSD, did not meet the primary endpoint. We plan to fully evaluate these data; however, based on top-line results we do not anticipate moving forward with additional JZP150 development in PTSD. We are also pursuing early-stage activities related to the development of JZP324, an extended-release low sodium, oxybate formulation that we believe could provide a clinically meaningful option for narcolepsy patients.

In May 2022, we announced that we had entered into a licensing agreement with Sumitomo Pharma Co., Ltd, or Sumitomo, to acquire exclusive development and commercialization rights in the United States, Europe and other territories for JZP441, also known as DSP-0187, a potent, highly selective oral orexin-2 receptor agonist with potential application for the treatment of narcolepsy, IH and other sleep disorders. Under the terms of the agreement, we made an upfront payment of $50 million to Sumitomo, and Sumitomo is eligible to receive development, regulatory and commercial milestone payments of up to $1.09 billion. If approved, Sumitomo is eligible to receive a tiered, low double-digit royalty on our net sales of JZP441. In November 2023, we announced that we achieved initial proof-of-concept in our Phase 1 clinical trial program in healthy volunteers as demonstrated by the Maintenance of Wakefulness Test (MWT). At that time, we also noted the program was being paused as we analyze safety findings related to visual disturbances and cardiovascular effects; no liver toxicity signals were observed. We are committed to orexin-2 agonist development and have a backup orexin-2 receptor agonist program.

Below is a summary of our key ongoing and planned development projects related to our products and pipeline and their corresponding current stages of development:

Product Candidates	Description
ONCOLOGY	
Regulatory Review	
Zanidatamab	Previously treated, advanced HER2-expressing BTC (ongoing trial) (pivotal trial)
Phase 3	
Zanidatamab	First-line HER2-positive GEA (ongoing trial)
Zanidatamab	First-line HER2-positive BTC (ongoing trial)
Zepzelca	First-line extensive stage SCLC in combination with Tecentriq (collaboration with Roche) (ongoing trial) Confirmatory second-line trial (PharmaMar study) (ongoing trial)
Vyxeos	AML or high-risk Myelodysplastic Syndrome, or MDS (AML18) (cooperative group studies) (ongoing trial) Newly diagnosed adults with standard- and high-risk AML (AML Study Group cooperative group study) (ongoing trial) Newly diagnosed pediatric patients with AML (Children's Oncology Group cooperative group study) (ongoing trial)
Phase 2	
Zanidatamab	HER2-expressing GEA, BTC or colorectal cancer in combination with standard first-line chemotherapy (ongoing trial)
Vyxeos	High-risk MDS (European Myelodysplastic Syndromes) (cooperative group study) (ongoing trial) Newly diagnosed untreated patients with intermediate- and high-risk AML (cooperative group study) (ongoing trial)
Vyxeos + other approved therapies	Relapsed/refractory, or R/R AML or hypomethylating agent failure MDS (MD Anderson collaboration study) (ongoing trial) De novo or R/R AML (MD Anderson collaboration study) (ongoing trial)
Phase 2a	
Zanidatamab	Previously treated HER2+HR+ breast cancer in combination with palbociclib (ongoing trial)
Phase 1b/2	
Zanidatamab	First-line breast cancer and GEA (BeiGene trial) (ongoing trial)
Zanidatamab	HER2-expressing breast cancer in combination with ALX148 (ongoing trial)
Phase 1	
JZP815	Raf and Ras mutant tumors (acquired from Redx Pharma plc, or Redx) (ongoing trial)
Zanidatamab	Previously treated metastatic HER2-expressing cancers in combination with select antineoplastic therapies (ongoing trial)
JZP341 (long-acting *Erwinia* asparaginase)	Solid tumors (licensed from Ligand Pharmaceuticals Incorporated, or Ligand) (ongoing trial)
JZP898	Conditionally-activated IFNα INDUKINE™ molecule in solid tumors (ongoing trial)
Vyxeos	Low intensity dosing for higher risk MDS (MD Anderson collaboration study) (ongoing trial)
Preclinical	
KRAS inhibitor targets	G12D selective and pan-KRAS molecules (acquired from Redx)
Undisclosed target	Ras/Raf/MAP kinase pathway (collaboration with Redx)
Undisclosed targets	Oncology
CombiPlex®	Hematology/oncology exploratory activities
NEUROSCIENCE	
Phase 3	
Epidyolex	LGS, TSC and DS (ongoing trial in Japan)

Phase 2b	
Suvecaltamide (JZP385)	ET (ongoing trial)
Phase 2	
Suvecaltamide (JZP385)	Parkinson's disease tremor (ongoing trial)
Phase 1	
JZP324	Oxybate extended-release formulation (planned trial)
JZP441*	Potent, highly selective oral orexin-2 receptor agonist (paused)
Undisclosed cannabinoids	Other neuroscience (ongoing trials)
Preclinical	
Undisclosed targets	Sleep Epilepsy Other Neuroscience

*Also known as DSP-0187

Operational Excellence

We remain focused on continuing to build excellence in areas that we believe will give us a competitive advantage, including maintaining an increasingly agile and adaptable commercialization engine and strengthening our customer-focused market expertise across patients, providers and payors. We are continuously refining our approach to engage customers by strengthening alignment and integration across functions and across regions. This includes deploying a mix of in-person and digital initiatives at scientific congresses designed to provide promotional and non-promotional interactions as well as supporting our field-based teams with digital customer interaction tools, training and content. These initiatives are representative of our enterprise operating model evolution that is directly linked to our corporate strategy and are designed to better enable our teams to work collaboratively on an aligned and shared agenda through both in-person and digital interactions. In most geographies, medical congresses and healthcare practices have resumed pre-pandemic levels of in-person activities.

Other Challenges, Risks and Trends Related to Our Business

Historically, our business was substantially dependent on Xyrem and our financial results were significantly influenced by sales of Xyrem. Our operating plan assumes that Xywav, with 92% lower sodium compared to high-sodium oxybates, depending on the dose, absence of a sodium warning and dosing titration option, will remain the treatment of choice for patients who can benefit from oxybate treatment. In June 2021, FDA recognized seven years of ODE for Xywav in narcolepsy through July 21, 2027, stating that Xywav is clinically superior to Xyrem by means of greater safety due to reduced chronic sodium burden. While we expect that our business will continue to meaningfully depend on oxybate revenues, there is no guarantee that oxybate revenues will remain at current levels.

Our ability to successfully commercialize Xywav will depend on, among other things, our ability to maintain adequate payor coverage and reimbursement for Xywav and acceptance of Xywav by physicians and patients, including of Xywav for the treatment of IH in adults. In an effort to support strong adoption of Xywav, we are focused on providing robust patient copay and savings programs and facilitating payor coverage for Xywav.

Xywav and Xyrem face competition from a branded product for treatment of cataplexy and/or EDS in narcolepsy. Avadel’s Lumryz was launched in the U.S. market in June 2023. On June 22, 2023, we filed a complaint in the United States District Court for the District of Columbia seeking a declaration that FDA’s approval of the New Drug Application, or NDA, for Avadel's Lumryz was unlawful. In the complaint, we allege that FDA acted outside its authority under the Orphan Drug Act, when, despite ODE protecting Xywav, FDA approved the Lumryz NDA and granted Lumryz ODE based on FDA’s finding that Lumryz makes a major contribution to patient care and is therefore clinically superior to Xywav and Xyrem. We cannot at this time predict the timing or ultimate outcome of this litigation or the impact of this litigation on our business.

In addition, in January 2023, our oxybate products began to face competition from an authorized generic, or AG, version of high-sodium oxybate pursuant to a settlement agreement we entered into with an abbreviated new drug application, or ANDA, filer. In July 2023, a volume-limited ANDA filer launched an AG version of high-sodium oxybate. These AG products have negatively impacted and are expected to continue to negatively impact Xyrem and Xywav sales for patients with narcolepsy. Specifically, a wholly owned subsidiary of Hikma Pharmaceuticals PLC, or Hikma, launched its AG version of sodium oxybate in January 2023 and Amneal Pharmaceuticals LLC, or Amneal, launched its AG version of sodium oxybate in July 2023. Hikma has elected to continue to sell the Hikma AG product, with royalties to be paid to us, for a total of up to four years beginning in January 2024, which election may be terminated by Hikma in accordance with the notice provisions in the agreements between the parties. We have the right to receive a meaningful royalty from Hikma on net sales of the Hikma AG

product; the royalty rate was fixed for the second half of 2023. There was a substantial increase in the royalty rate beginning in January 2024, which will remain fixed for the duration of the agreement's term. We are also paid for supply of the Hikma AG product and reimbursed by Hikma for a portion of the services costs associated with the operation of the Xywav and Xyrem risk evaluation and mitigation strategy, or REMS, and distribution of the Hikma AG product. We also granted Hikma a license to launch its own generic sodium oxybate product but, if it elects to launch its own generic product, Hikma will no longer have the right to sell the Hikma AG product. In addition, Hikma would need to set up its own REMS, which must be open to any other company seeking to commercialize a sodium oxybate product. In our settlements with Amneal, Lupin Inc., or Lupin, and Par Pharmaceutical, Inc., or Par, we granted each party the right to sell a limited volume of an AG product in the U.S. beginning on July 1, 2023 and ending on December 31, 2025, with royalties to be paid to us. Amneal launched its AG version of sodium oxybate in July 2023. At this time, Amneal has rights to sell a low-single-digit percentage of historical Xyrem sales over each 6-month sales period. At this time, Lupin and Par have elected not to launch an AG product. AG products will be distributed through the same REMS as Xywav and Xyrem. We also granted each of Amneal, Lupin and Par a license to launch its own generic sodium oxybate product under its ANDA on or after December 31, 2025, or earlier under certain circumstances, including the circumstance where Hikma elects to launch its own generic product. If Amneal, Lupin or Par elects to launch its own generic product under such circumstance, it will no longer have the right to sell an AG product. In addition, any company commercializing a generic version of high-sodium oxybate would need to establish its own REMS, or join an existing REMS operated by another company.

In the future, we expect our oxybate products to continue to face competition from generic versions of high-sodium oxybate pursuant to settlement agreements we entered into with multiple ANDA filers. In addition, we received notices in June 2021 and February 2023, that Lupin and Teva, respectively, filed ANDAs for generic versions of Xywav. On October 13, 2023, Lupin announced that it has received tentative approval for its application to market a generic version of Xywav. Generic competition can decrease the net prices at which branded products, such as Xywav and Xyrem are sold, as can competition from other branded products. In addition, we have increasingly experienced pressure from third party payors to agree to discounts, rebates or restrictive pricing terms, and we cannot guarantee we will be able to agree to commercially reasonable terms with PBMs, or similar organizations and other third party payors, or that we will be able to ensure patient access and acceptance on formularies. Entering into agreements with PBMs or similar organizations and payors to ensure patient access has and may continue to result in decreased net prices for some of our products. Moreover, generic or AG high-sodium oxybate products or branded high-sodium oxybate entrants in narcolepsy, such as Avadel's Lumryz, have had and may continue to have the effect of changing payor or formulary coverage of Xywav or Xyrem in favor of other products, and indirectly adversely affect sales of Xywav and Xyrem.

Our financial condition, results of operations and growth prospects are also dependent on our ability to maintain or increase sales of Epidiolex/Epidyolex in the U.S. and Europe, which is subject to many risks and there is no guarantee that we will be able to continue to successfully commercialize Epidiolex/Epidyolex for its approved indications. The commercial success of Epidiolex/Epidyolex depends on the extent to which patients and physicians accept and adopt Epidiolex/Epidyolex as a treatment for seizures associated with LGS, DS and TSC, and we do not know whether our or others' estimates in this regard will be accurate. Physicians may not prescribe Epidiolex and patients may be unwilling to use Epidiolex/Epidyolex if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Additionally, any negative development for Epidiolex/Epidyolex in the market, in clinical development for additional indications, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of Epidiolex/Epidyolex. Moreover, we expect that Epidiolex will face competition from generic products in the future. For example, in November and December 2022, we received notices from ten ANDA filers that they have each filed with FDA an ANDA for a generic version of Epidiolex. In addition, there are non-FDA approved cannabidiol preparations being made available from companies through the state-enabled medical marijuana industry, which might attempt to compete with Epidiolex. Thus, significant uncertainty remains regarding the commercial potential of Epidiolex/Epidyolex.

In addition to our neuroscience products and product candidates, we are commercializing a portfolio of oncology products, including Rylaze, Zepzelca, Defitelio and Vyxeos. An inability to effectively commercialize Rylaze, Zepzelca, Defitelio and Vyxeos and to maximize their potential where possible through successful research and development activities could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

A key aspect of our growth strategy is our continued investment in our evolving and expanding R&D activities. If we are not successful in the clinical development of our product candidates, if we are unable to obtain regulatory approval for our product candidates in a timely manner, or at all, or if sales of an approved product do not reach the levels we expect, our anticipated revenue from our product candidates would be negatively affected, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

In addition to continued investment in our R&D pipeline, we intend to continue to grow our business by acquiring or in-licensing, and developing, including with collaboration partners, additional products and product candidates that we believe are highly differentiated and have significant commercial potential. Failure to identify and acquire, in-license or develop additional

products or product candidates, successfully manage the risks associated with integrating any products or product candidates into our portfolio or the risks arising from anticipated and unanticipated problems in connection with an acquisition or in-licensing, such as the GW Acquisition, could have a material adverse effect on our business, results of operations and financial condition.

The success of the GW Acquisition will depend, in part, on our ability to realize the anticipated benefits from the combination of our and GW's historical businesses. Nonetheless, Epidiolex and the other products and technologies acquired may not be successful or continue to grow at the same rate as if our companies operated independently or they may require significantly greater resources and investments than originally anticipated. For example, in the third quarter of 2022, we recorded a $133.6 million asset impairment charge as a result of the decision to discontinue the nabiximols program. As a result, the anticipated benefits of the GW Acquisition may not be realized at the expected level, within the expected timeframe or at all or may take longer to realize or cost more than expected, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

Our industry has been, and is expected to continue to be, subject to healthcare cost containment and drug pricing scrutiny by regulatory agencies in the U.S. and internationally. If new healthcare policies or reforms intended to curb healthcare costs are adopted or if we experience negative publicity with respect to pricing of our products or the pricing of pharmaceutical drugs generally, the prices that we charge for our products may be affected, our commercial opportunity may be limited and/or our revenues from sales of our products may be negatively impacted. For example, the Inflation Reduction Act of 2022 among other things, requires the U.S. Department of Health and Human Services Secretary to negotiate, with respect to Medicare units and subject to a specified cap, the price of a set number of certain high Medicare spend drugs and biologicals per year starting in 2026, penalizes manufacturers of certain Medicare Parts B and D drugs for price increases above inflation, and makes several changes to the Medicare Part D benefit, including a limit on annual out-of-pocket costs, and a change in manufacturer liability under the program, that could negatively affect our business and financial condition. In addition, under the Medicaid Drug Rebate Program, rebates owed by manufacturers are no longer subject to a cap on the rebate amount, which could adversely affect our rebate liability. We are also subject to increasing pricing pressure and restrictions on reimbursement imposed by payors. If we fail to obtain and maintain adequate formulary positions and institutional access for our current products and future approved products, we will not be able to achieve a return on our investment and our business, financial condition, results of operations and growth prospects would be materially adversely affected.

While certain preparations of cannabis remain Schedule I controlled substances, if such products are approved by FDA for medical use in the U.S. they are rescheduled to Schedules II-V, since approval by FDA satisfies the "accepted medical use" requirement; or such products may be removed from control under the Controlled Substances Act entirely. If any of our product candidates receive FDA approval, the Department of Health and Human Services and the U.S. Drug Enforcement Administration will make a scheduling determination. U.S. or foreign regulatory agencies may request additional information regarding the abuse potential of our products which may require us to generate more clinical or other data than we currently anticipate to establish whether or to what extent the substance has an abuse potential, which could increase the cost, delay the approval and/or delay the launch of that product.

Finally, business practices by pharmaceutical companies, including product formulation improvements, patent litigation settlements, and REMS programs, have increasingly drawn public scrutiny from legislators and regulatory agencies, with allegations that such programs are used as a means of improperly blocking or delaying competition. Government investigations with respect to our business practices, including as they relate to the Xywav and Xyrem REMS, the launch of Xywav, our Xyrem patent litigation settlement agreements or otherwise, could cause us to incur significant monetary charges to resolve these matters and could distract us from the operation of our business and execution of our strategy. For example, in July 2022, we received a subpoena from the U.S. Attorney's Office for the District of Massachusetts requesting documents related to Xyrem and U.S. Patent No. 8,772,306 ("Method of Administration of Gamma Hydroxybutyrate with Monocarboxylate Transporters"), product labeling changes for Xyrem, communications with FDA and the U.S. Patent and Trademark Office, pricing of Xyrem, and other related documents. We may also become subject to similar investigations by other state or federal governmental agencies. The investigation by the U.S. Attorney's Office and any additional investigations or litigation related to the subject matter of this investigation may result in damages, fines, penalties, financial charges to resolve the matter or administrative sanctions against us, negative publicity or other negative actions that could harm our reputation, reduce demand for Xyrem and/or reduce coverage of Xyrem, including by federal health care programs and state health care programs. In addition, from June 2020 to May 2022, a number of lawsuits were filed on behalf of purported direct and indirect Xyrem purchasers, alleging that the patent litigation settlement agreements we entered with certain generic companies violate state and federal antitrust and consumer protection laws. For additional information on these lawsuits and other legal matters, see Note 9, Commitments and Contingencies—Legal Proceedings of the Notes to Condensed Consolidated Financial Statements, included in Part I, Item 1 of this Quarterly Report on Form 10-Q. It is possible that additional lawsuits will be filed against us making similar or related allegations. We cannot predict the outcome of these or potential additional lawsuits; however, if the plaintiffs were to be successful in their claims against us, they may be entitled to injunctive relief or we may be required to pay significant monetary damages. Moreover, we are, and expect to continue to be, the subject of various claims, legal proceedings,

and government investigations apart from those set forth above that have arisen in the ordinary course of business that have not yet been fully resolved and that could adversely affect our business and the execution of our strategy. Any of the foregoing risks and uncertainties could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

These risks and uncertainties are discussed in greater detail, along with other risks and uncertainties, in "Risk Factors" in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023, as supplemented by the risks and uncertainties described in "Risk Factors" in Part II, Item 1A of this Quarterly Report on Form 10-Q.

Results of Operations

The following table presents our revenues and expenses (in thousands, except percentages):

	Three Months Ended March 31,		Increase/
	2024	2023	(Decrease)
Product sales, net	$ 842,102	$ 884,219	(5)%
Royalties and contract revenues	59,881	8,593	N/A(1)
Cost of product sales (excluding amortization of acquired developed technologies)	95,487	128,644	(26)%
Selling, general and administrative	351,712	297,917	18 %
Research and development	222,847	189,410	18 %
Intangible asset amortization	155,730	149,786	4 %
Acquired in-process research and development	10,000	1,000	N/A(1)
Interest expense, net	66,116	74,147	(11)%
Foreign exchange (gain) loss	1,693	(3,193)	(153)%
Income tax expense (benefit)	11,669	(15,324)	(176)%
Equity in loss of investees	1,347	1,005	34 %

(1) Comparison to prior period not meaningful.

Revenues

The following table presents our net product sales, royalties and contract revenues, and total revenues (in thousands, except percentages):

	Three Months Ended March 31,		Increase/
	2024	2023	(Decrease)
Xywav	$ 315,300	$ 277,761	14 %
Xyrem	64,232	178,130	(64)%
Epidiolex/Epidyolex	198,716	188,909	5 %
Sativex	2,735	7,098	(61)%
Total Neuroscience	580,983	651,898	(11)%
Rylaze/Enrylaze	102,750	85,927	20 %
Zepzelca	75,100	67,181	12 %
Defitelio/defibrotide	47,676	39,079	22 %
Vyxeos	32,023	36,700	(13)%
Total Oncology	257,549	228,887	13 %
Other	3,570	3,434	4 %
Product sales, net	842,102	884,219	(5)%
High-sodium oxybate AG royalty revenue	49,947	2,096	N/A(1)
Other royalty and contract revenues	9,934	6,497	53 %
Total revenues	$ 901,983	$ 892,812	1 %

(1) Comparison to prior period not meaningful.

Product Sales, Net

Xywav product sales increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to increased sales volumes of 16% and, to a lesser extent, a higher selling price, offset by higher gross to net deductions. We continue to see Xywav adoption in patients with narcolepsy driven by educational initiatives around efficacy and the benefit of lowering sodium intake. In addition, Xywav product sales were positively impacted by adoption in IH; Xywav is the only oxybate therapy approved to treat IH and we see continued growth of new prescribers. Exiting the quarter, there were 9,900 patients taking Xywav for narcolepsy and 3,050 taking Xywav for IH, an increase of approximately 9% and 53%, respectively, compared to the same period in 2023. Xyrem product sales decreased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to decreased sales volumes of 63%, due to the adoption of Xywav by existing Xyrem patients, the availability of high-sodium oxybate competition, changes to formulary coverage impacting narcolepsy patients, and higher gross to net deductions, offset by a higher selling price. Epidiolex/Epidyolex product sales increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to increased sales volumes of 5%, due to increased demand and geographic expansion, and a higher average selling price, partially offset by higher gross to net deductions.

Rylaze/Enrylaze product sales increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to increased sales volumes of 19% and, to a lesser extent, a higher selling price, offset by higher gross to net deductions. The increased volumes reflect the strong demand for Rylaze driven by robust adoption in pediatric asparaginase-based oncology protocols in the U.S, adoption of the Monday/Wednesday/Friday dosing regimen, along with use of Rylaze in the first line setting and in the treatment of adolescents and young adults. Zepzelca product sales increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to increased sales volumes and a higher selling price. Defitelio/defibrotide product sales increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to increased sales volumes and a higher average selling price. Vyxeos product sales decreased in the three months ended March 31, 2024, primarily due to a decrease in sales volumes and higher gross to net deductions, partially offset by a higher average selling price.

We expect total product sales will increase in 2024 over 2023, primarily due to our key growth drivers; Xywav, through continued growth in the IH market, Epidiolex through growth in current markets and expansion into new markets and Rylaze through demand, offset by a decrease in sales of Xyrem due to the impact of high-sodium oxybate competition.

Royalties and Contract Revenues

Royalties and contract revenues increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to royalty revenue received from Hikma Pharmaceuticals plc on net sales of their high sodium
oxybate AG. We expect royalties and contract revenues to increase in 2024 compared to 2023, primarily due to increased royalty revenues arising from net sales of high-sodium oxybate AG, primarily due to higher royalty rates in 2024.

Cost of Product Sales

Cost of product sales decreased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to a reduction in the acquisition accounting inventory fair value step-up expense, or fair value step-up expense. Gross margin as a percentage of net product sales was 88.7% for the three months ended March 31, 2024 compared to 85.5% for the same period in 2023, due to a reduction in fair value step-up expense. We expect our cost of product sales to increase in 2024 compared to 2023, primarily driven by a change in product mix.

Selling, General and Administrative Expenses

Selling, general and administrative expenses increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to an increase in compensation-related expenses of $18.3 million primarily driven by higher headcount in support of our key growth drivers, increased marketing investment in our priority programs of $9.6 million and litigation costs of $8.2 million.

We expect selling, general and administrative expenses in 2024 to increase compared to 2023, primarily due to continued investment in our key growth drivers, such as Xywav in IH, Epidiolex and Rylaze along with increased employee expenses.

Research and Development Expenses

Research and development expenses consist primarily of costs related to clinical studies and outside services, personnel expenses and other research and development costs. Clinical study and outside services costs relate primarily to services performed by clinical research organizations, materials and supplies, and other third party fees. Personnel expenses relate primarily to salaries, benefits and share-based compensation. Other research and development expenses primarily include

overhead allocations consisting of various support and facilities-related costs. We do not track fully-burdened research and development expenses on a project-by-project basis. We manage our research and development expenses by identifying the research and development activities that we anticipate will be performed during a given period and then prioritizing efforts based on our assessment of which development activities are important to our business and have a reasonable probability of success, and by dynamically allocating resources accordingly. We also continually review our development pipeline projects and the status of their development and, as necessary, reallocate resources among our development pipeline projects that we believe will best support the future growth of our business.

The following table provides a breakout of our research and development expenses by major categories of expense (in thousands):

	Three Months Ended March 31,	
	2024	2023
Clinical studies and outside services	$ 131,466	$ 106,345
Personnel expenses	72,996	60,391
Other	18,385	22,674
Total	$ 222,847	$ 189,410

Research and development expenses increased by $33.4 million in the three months ended March 31, 2024, compared to the same period in 2023. Clinical studies and outside services costs increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to higher costs related to zanidatamab programs, and, to a lesser extent, JZP385. Personnel expenses increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily driven by increased compensation costs and higher headcount in support of our development programs.

For 2024, we expect that our research and development expenses will continue to increase compared to 2023 as we prepare for anticipated data read-outs from clinical trials, initiate and undertake additional clinical trials and related development work primarily relating to zanidatamab.

Intangible Asset Amortization

Intangible asset amortization increased in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to the impact of foreign currency translation adjustments. Intangible asset amortization for 2024 is expected to be in line with 2023.

Acquired In-Process Research and Development

Acquired in-process research and development, or IPR&D, expense in the three months ended March 31, 2024, related to the upfront payment of $10.0 million made in connection with our asset purchase and collaboration agreement with Redx to acquire global rights to the Kirsten rat sarcoma virus, or KRAS, Inhibitor Program.

Interest Expense, Net

Interest expense, net decreased by $8.0 million in the three months ended March 31, 2024, compared to the same period in 2023, primarily driven by higher interest income on investments. We expect interest expense, net to decrease in 2024 compared to 2023, primarily due to lower interest expense following the repricing of the seven-year $3.1 billion term loan B facility, or the Dollar Term Loan, for further information on this please refer to Liquidity and Capital Resources.

Foreign Exchange (Gain) Loss

The foreign exchange (gain) loss is primarily related to the translation of sterling and euro-denominated net monetary liabilities, primarily intercompany balances, held by subsidiaries with a U.S. dollar functional currency and related foreign exchange forward contracts not designated as hedging instruments.

Income Tax Expense (Benefit)

Our income tax expense was $11.7 million for the three months ended March 31, 2024, resulting primarily from tax deficiencies from share-based compensation. Our income tax benefit was $15.3 million for the same period in 2023, relating to tax arising on income or losses in Ireland, the U.K., the U.S. and certain other foreign jurisdictions, offset by deductions on subsidiary equity, foreign derived intangible income, or FDII, and patent box benefits.

Liquidity and Capital Resources

As of March 31, 2024, we had cash, cash equivalents and investments of $1.8 billion, borrowing availability under our five-year $500.0 million revolving credit facility, or the Revolving Credit Facility, of $500.0 million and long-term debt principal balance of $5.8 billion. Our long-term debt included $2.7 billion aggregate principal amount of the Dollar Term Loan, $1.5 billion in aggregate principal amount of 4.375% senior secured notes, due 2029, or the Secured Notes, $1.0 billion principal amount on our 2.00% exchangeable senior notes due 2026 and $575.0 million principal amount on our 1.50% exchangeable senior notes due 2024, or 2024 Notes. We generated cash flows from operations of $267.2 million during the three months ended March 31, 2024, and we expect to continue to generate positive cash flows from operations which will enable us to operate our business and de-lever our balance sheet over time.

Since the closing of the acquisition of GW in May 2021, we have fully repaid our Euro Term Loan €625.0 million, or $753.0 million and made voluntary and mandatory repayments of $300.0 million and $85.3 million, respectively, relating to the Dollar Term Loan.

We have a significant amount of debt outstanding on a consolidated basis. For a more detailed description of our debt arrangements, including information relating to our scheduled maturities with respect to our long-term debt, see Note 8, Debt, of the notes to the condensed consolidated financial statements, included in Part I, Item 1 of this Quarterly Report on Form 10-Q. This substantial level of debt could have important consequences to our business, including, but not limited to the factors set forth in “Risk Factors” of our Annual Report on Form 10-K for the year ended December 31, 2023, under the heading “We have incurred substantial debt, which could impair our flexibility and access to capital and adversely affect our financial position, and our business would be adversely affected if we are unable to service our debt obligations.”

We believe that our existing cash, cash equivalents and investments balances, cash we expect to generate from operations and funds available under our Revolving Credit Facility will be sufficient to fund our operations and to meet our existing obligations for the foreseeable future. The adequacy of our cash resources depends on many assumptions, including primarily our assumptions with respect to product sales and expenses, as well as the other factors set forth in "Risk Factors" under the heading "Risks Related to our Lead Products and Product Candidates” in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023, as supplemented by the risks described in “Risk Factors" under the heading “Delays or problems in the supply of our products for sale or for use in clinical trials, loss of our single source suppliers or failure to comply with manufacturing regulations could materially and adversely affect our business, financial condition, results of operations and growth prospects” in Part II, Item 1A of this Quarterly Report on Form 10-Q, as well as those factors set forth in “Risk Factors" under the heading and “To continue to grow our business, we will need to commit substantial resources, which could result in future losses or otherwise limit our opportunities or affect our ability to operate and grow our business”in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023.

Our assumptions may prove to be wrong or other factors may adversely affect our business, and as a result we could exhaust or significantly decrease our available cash resources, and we may not be able to generate sufficient cash to service our debt obligations which could, among other things, force us to raise additional funds and/or force us to reduce our expenses, either of which could have a material adverse effect on our business.

To continue to grow our business over the longer term, we plan to commit substantial resources to product acquisition and in-licensing, product development, clinical trials of product candidates and expansion of our commercial, development, manufacturing and other operations. In this regard, we have evaluated and expect to continue to evaluate a wide array of strategic transactions as part of our strategy to acquire or in-license and develop additional products and product candidates. Acquisition opportunities that we pursue could materially affect our liquidity and capital resources and may require us to incur additional indebtedness, seek equity capital or both. We regularly evaluate the performance of our products and product candidates to ensure fit within our portfolio and support efficient allocation of capital. In addition, we may pursue new operations or continue the expansion of our existing operations. Accordingly, we expect to continue to opportunistically seek access to additional capital to license or acquire additional products, product candidates or companies to expand our operations or for general corporate purposes. Raising additional capital could be accomplished through one or more public or private debt or equity financings, collaborations or partnering arrangements. However, our ability to raise additional capital may be adversely impacted by worsening global economic conditions and the recent disruptions to, and volatility in, the credit and financial markets in the U.S. and worldwide resulting from the effects of inflationary pressures, potential future bank failures, or otherwise. Accordingly, we could experience an inability to access additional capital or our liquidity could otherwise be impacted, which could in the future negatively affect our capacity for certain corporate development transactions or our ability to make other important, opportunistic investments. In addition, under Irish law we must have authority from our shareholders to issue any ordinary shares, including ordinary shares that are part of our authorized but unissued share capital, and we currently have such authorization. Moreover, as a matter of Irish law, when an Irish public limited company issues ordinary shares to new shareholders for cash, the company must first offer those shares on the same or more favorable terms to existing shareholders on a pro rata basis, unless this statutory pre-emption obligation is dis-applied, or opted-out of, by approval of its shareholders. At our annual general meeting of shareholders in August 2023, our shareholders voted to approve our proposal to

dis-apply the statutory pre-emption obligation on terms that are substantially more limited than our general pre-emption opt-out authority that had been in effect prior to August 4, 2021. This current pre-emption opt-out authority is due to expire in February 2025. If we are unable to obtain further pre-emption authorities from our shareholders in the future, or otherwise continue to be limited by the terms of new pre-emption authorities approved by our shareholders in the future, our ability to use our unissued share capital to fund in-licensing, acquisition or other business opportunities, or to otherwise raise capital could be adversely affected. In any event, an inability to borrow or raise additional capital in a timely manner and on attractive terms could prevent us from expanding our business or taking advantage of acquisition opportunities, and could otherwise have a material adverse effect on our business and growth prospects. In addition, if we use a substantial amount of our funds to acquire or in-license products or product candidates, we may not have sufficient additional funds to conduct all of our operations in the manner we would otherwise choose. Furthermore, any equity financing would be dilutive to our shareholders, and could require the consent of the lenders under our credit agreement, or the Credit Agreement, that provides for (i) the Dollar Term Loan, (ii) the Euro Term Loan and, together with the Dollar Term Loan, collectively known as the Term Loan and (iii) the Revolving Credit Facility, and the indenture for the Secured Notes for certain financings.

In November 2016, our board of directors authorized a share repurchase program and as of March 31, 2024 had authorized the repurchase of ordinary shares having an aggregate purchase price of up to $1.5 billion, exclusive of any brokerage commissions. Under this program, which has no expiration date, we may repurchase ordinary shares from time to time on the open market. The timing and amount of repurchases will depend on a variety of factors, including the price of our ordinary shares, alternative investment opportunities, restrictions under the May 2021 credit agreement, corporate and regulatory requirements and market conditions. The share repurchase program may be modified, suspended or discontinued at any time without prior notice. During the three months ended March 31, 2024, no shares were repurchased. As of March 31, 2024, the remaining amount authorized under the share repurchase program was $161.4 million, exclusive of any brokerage commissions.

The following table presents a summary of our cash flows for the periods indicated (in thousands):

	Three Months Ended March 31,	
	2024	2023
Net cash provided by operating activities	$ 267,229	$ 320,708
Net cash used in investing activities	(271,904)	(4,822)
Net cash used in financing activities	(56,552)	(29,788)
Effect of exchange rates on cash and cash equivalents	(1,698)	331
Net increase (decrease) in cash and cash equivalents	$ (62,925)	$ 286,429

Operating activities

Net cash provided by operating activities decreased by $53.5 million in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to the payment of accrued facility expenses of $52.2 million in the three months ended March 31, 2024.

Investing activities

Net cash used in investing activities increased by $267.1 million in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to the following:

- $255.0 million net increase in the acquisition of investments, driven by time deposits; and
- $10.0 million upfront payment to Redx related to our asset purchase and collaboration agreement in the three months ended March 31, 2024.

Financing activities

Net cash used in financing activities increased by $26.8 million in the three months ended March 31, 2024, compared to the same period in 2023, primarily due to:

- A decrease of $20.7 million in proceeds from employee equity incentive and purchase plans; and
- An increase of $6.0 million in payment of employee withholding taxes related to share-based awards.

Debt

The summary of our outstanding indebtedness and scheduled maturities with respect to our long-term debt principal balances is included in Note 8, Debt, of the notes to condensed consolidated financial statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q. In January 2024, we entered into an amendment to the Credit Agreement, as described below. During the three months ended March 31, 2024, there were no other changes to our financing arrangements, as set forth in Note 12, Debt, of the Notes to Consolidated Financial Statements included in our Annual Report on Form 10-K for the year ended December 31, 2023.

Credit Agreement

On May 5, 2021, the Company, Jazz Financing Lux S.à.r.l., or Jazz Lux, and certain of our other subsidiaries, as borrowers, or, collectively with the Company and Jazz Lux, the "Borrowers", entered into the Credit Agreement by and among the Borrowers, the lenders and issuing banks from time to time party thereto, Bank of America, N.A., as administrative agent and U.S. Bank Trust Company, National Association, as collateral trustee, or the Credit Agreement, that provided for (i) the Dollar Term Loan which was drawn by Jazz Lux on the Closing Date in U.S. dollars (ii) the Euro Term Loan which was drawn by Jazz Lux on the Closing Date in Euros and (iii) the Revolving Credit Facility.

In January 2024, Jazz Lux entered into an amendment, or Repricing Amendment, to the Credit Agreement. Upon entry into the Repricing Amendment, certain existing lenders converted outstanding Dollar Term Loans into a new tranche of U.S. dollar term loans, or the Tranche B-1 Dollar Term Loans, and Jazz Lux borrowed $201.9 million aggregate principal amount of additional Tranche B-1 Dollar Term Loans, the proceeds of which were used to repay the outstanding Dollar Term Loans that were not converted. The Tranche B-1 Dollar Term Loans are a separate class of term loans under the Credit Agreement with the same material terms (including with respect to maturity, prepayment, security, covenants and events of default) as the previously outstanding Dollar Term Loans, with the interest rate amended as described below. The principal amount of Dollar Term Loans outstanding immediately prior to the Repricing Amendment and the outstanding principal amount of Tranche B-1 Dollar Term Loans immediately following the Repricing Amendment, each totaled $2.723 billion. The Tranche B-1 Dollar Term Loans bear interest at a rate equal to either (a) U.S dollar Secured Overnight Financing Rate, or Term SOFR, or (b) the prime lending rate, in each case, plus an applicable margin. The applicable margin for the Tranche B-1 Dollar Term Loans is 3.00% (in the case of Term SOFR borrowings) and 2.00% (in the case of borrowings at the prime lending rate), a decrease of 50 basis points from the applicable margin on the Initial Dollar Term Loans. The Tranche B-1 Dollar Term Loans are subject to a Term SOFR floor of 0.50%. The applicable margin for the Revolving Credit Facility ranges from 3.25% to 2.75% (in the case of Term SOFR borrowings) and 2.25% to 1.75% (in the case of borrowings at the prime lending rate), depending on our first lien secured net leverage ratio level. The Tranche B-1 Dollar Term Loan is subject to a Term SOFR floor of 0.50% and loans under the Revolving Credit Facility are not subject to a floor. The Revolving Credit Facility has a commitment fee payable on the undrawn amount ranging from 0.50% to 0.40% per annum based upon our first lien secured net leverage ratio. As of March 31, 2024, the interest rate and effective interest rate on the Tranche B-1 Dollar Term Loans were 8.44% and 9.04%, respectively. As of March 31, 2024, we had an undrawn Revolving Credit Facility totaling $500.0 million.

Contractual Obligations

During the three months ended March 31, 2024, there were no material changes to our contractual obligations as set forth in Part II, Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the year ended December 31, 2023.

Critical Accounting Estimates

To understand our financial statements, it is important to understand our critical accounting estimates. The preparation of our financial statements in conformity with U.S. generally accepted accounting principles requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Significant estimates and assumptions are required in determining the amounts to be deducted from gross revenues and also with respect to the acquisition and valuation of intangibles and income taxes. Some of these judgments can be subjective and complex, and, consequently, actual results may differ from these estimates. For any given individual estimate or assumption we make, there may also be other estimates or assumptions that are reasonable. Although we believe our estimates and assumptions are reasonable, they are based upon information available at the time the estimates and assumptions were made.

Our critical accounting policies and significant estimates are detailed in our Annual Report on Form 10-K for the year ended December 31, 2023. Our critical accounting policies and significant estimates have not changed substantially from those previously disclosed in our Annual Report on Form 10-K for the year ended December 31, 2023.

Cautionary Note Regarding Forward-Looking Statements

This Quarterly Report on Form 10-Q contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, which are subject to the "safe harbor" created by those sections. Forward-looking statements are based on our management's current plans, objectives, estimates, expectations and intentions and on information currently available to our management. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expect," "plan," "anticipate," "believe," "estimate," "project," "predict," "propose," "intend," "continue," "potential," "possible," "foreseeable," "likely," "unforeseen" and similar expressions intended to identify forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance, time frames or achievements to be materially different from any future results, performance, time frames or achievements expressed or implied by the forward-looking statements. These known and unknown risks, uncertainties and other factors include, without limitation:

- Our inability to maintain or increase sales from our oxybate franchise would have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- The introduction of new products in the U.S. market that compete with, or otherwise disrupt the market for, our oxybate products and product candidates has adversely affected and may continue to adversely affect sales of our oxybate products and product candidates.
- The distribution and sale of our oxybate products are subject to significant regulatory restrictions, including the requirements of a risk evaluation and mitigation strategy and safety reporting requirements, and these regulatory and safety requirements subject us to risks and uncertainties, any of which could negatively impact sales of Xywav and Xyrem.
- While we expect our oxybate products and Epidiolex/Epidyolex to remain our largest products, our success also depends on our ability to effectively commercialize our other existing products and potential future products.
- We face substantial competition from other companies, including companies with larger sales organizations and more experience working with large and diverse product portfolios, and competition from generic drugs.
- Adequate coverage and reimbursement from third party payors may not be available for our products and we may be unable to successfully contract for coverage from pharmacy benefit managers and other organizations; conversely, to secure coverage from these organizations, we may be required to pay rebates or other discounts or other restrictions to reimbursement, either of which could diminish our sales or adversely affect our ability to sell our products profitably.
- The pricing of pharmaceutical products has come under increasing scrutiny as part of a global trend toward healthcare cost containment and resulting changes in healthcare law and policy, including changes to Medicare, may impact our business in ways that we cannot currently predict, which could have a material adverse effect on our business and financial condition.
- In addition to access, coverage and reimbursement, the commercial success of our products depends upon their market acceptance by physicians, patients, third party payors and the medical community.
- Delays or problems in the supply of our products for sale or for use in clinical trials, loss of our single source suppliers or failure to comply with manufacturing regulations could materially and adversely affect our business, financial condition, results of operations and growth prospects.
- Our future success depends on our ability to successfully develop and obtain and maintain regulatory approvals for our late-stage product candidates and, if approved, to successfully launch and commercialize those product candidates.
- We may not be able to successfully identify and acquire or in-license additional products or product candidates to grow our business, and, even if we are able to do so, we may otherwise fail to realize the anticipated benefits of these transactions.
- Conducting clinical trials is costly and time-consuming, and the outcomes are uncertain. A failure to prove that our product candidates are safe and effective in clinical trials, or to generate data in clinical trials to support expansion of the therapeutic uses for our existing products, could materially and adversely affect our business, financial condition, results of operations and growth prospects.
- It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection.

- We have incurred and may in the future incur substantial costs as a result of litigation or other proceedings relating to patents, other intellectual property rights and related matters, and we may be unable to protect our rights to, or commercialize, our products.
- Significant disruptions of information technology systems or data security breaches could adversely affect our business.
- We are subject to significant ongoing regulatory obligations and oversight, which may subject us to civil or criminal proceedings, investigations, or penalties and may result in significant additional expense and limit our ability to commercialize our products.
- If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- We have incurred substantial debt, which could impair our flexibility and access to capital and adversely affect our financial position, and our business would be adversely affected if we are unable to service our debt obligations.
- To continue to grow our business, we will need to commit substantial resources, which could result in future losses or otherwise limit our opportunities or affect our ability to operate and grow our business.

Additional discussion of the risks, uncertainties and other factors described above, as well as other risks material to our business, can be found under “Risk Factors” in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023, as supplemented by the risks and uncertainties described in "Risk Factors" Part II, Item 1A.in this Quarterly Report on Form 10-Q.

Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements. Also, these forward-looking statements represent our plans, objectives, estimates, expectations and intentions only as of the date of this filing. You should read this Quarterly Report on Form 10-Q completely and with the understanding that our actual future results and the timing of events may be materially different from what we expect. We hereby qualify our forward-looking statements by our cautionary statements. Except as required by law, we undertake no obligation to update or supplement any forward-looking statements publicly, or to update or supplement the reasons that actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

Item 3. Quantitative and Qualitative Disclosures About Market Risk

During the three months ended March 31, 2024, there were no material changes to our market risk disclosures as set forth in Part II, Item 7A“Quantitative and Qualitative Disclosures About Market Risk” in our Annual Report on Form 10-K for the year ended December 31, 2023.

Item 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures. We have carried out an evaluation under the supervision and with the participation of management, including our principal executive officer and principal financial officer, of our disclosure controls and procedures (as defined in Rule 13a-15(e) and 15d-15(e) of the Exchange Act) as of the end of the period covered by this Quarterly Report on Form 10-Q. Based on their evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures were effective as of March 31, 2024.

Limitations on the Effectiveness of Controls. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues, if any, within an organization have been detected. Accordingly, our disclosure controls and procedures are designed to provide reasonable, not absolute, assurance that the objectives of our disclosure control system are met and, as set forth above, our principal executive officer and principal financial officer have concluded, based on their evaluation as of the end of the period covered by this report, that our disclosure controls and procedures were effective to provide reasonable assurance that the objectives of our disclosure control system were met.

Changes in Internal Control over Financial Reporting. During the quarter ended March 31, 2024, there were no changes to our internal control over financial reporting that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II – OTHER INFORMATION

Item 1. Legal Proceedings

The information required to be set forth under this Item 1 is incorporated by reference to Note 9, Commitments and Contingencies—Legal Proceedings of the notes to condensed consolidated financial statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q.

Item 1A. Risk Factors

Below we are providing, in supplemental form, changes to our risk factors from those previously disclosed in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023. Our risk factors disclosed in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023 provide additional discussion regarding these supplemental risks and we encourage you to read and carefully consider all of the risk factors disclosed in Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2023, together with the below, for a more complete understanding of the risks and uncertainties material to our business.

Delays or problems in the supply of our products for sale or for use in clinical trials, loss of our single source suppliers or failure to comply with manufacturing regulations could materially and adversely affect our business, financial condition, results of operations and growth prospects.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of process controls required to consistently produce the API and the finished product in sufficient quantities while meeting detailed product specifications on a repeated basis. We and our suppliers may encounter difficulties in production, including difficulties with the supply of manufacturing materials, production costs and yields, process controls, quality control and quality assurance, including testing of stability, impurities and impurity levels and other product specifications by validated test methods, and compliance with strictly enforced U.S., state and non-U.S. regulations. In addition, we and our suppliers are subject to FDA's current Good Manufacturing Practices, or cGMP, requirements, federal and state controlled substances obligations and equivalent rules and regulations prescribed by non-U.S. regulatory authorities. If we or any of our suppliers encounter manufacturing, quality or compliance difficulties with respect to any of our products, whether due to the ongoing military conflict in Ukraine and related sanctions imposed against Russia (including as a result of disruptions of global shipping, the transport of products, energy supply, cybersecurity incidents and banking systems as well as of our ability to control input costs) or otherwise, we may be unable to obtain or maintain regulatory approval or meet commercial demand for such products, which could adversely affect our business, financial condition, results of operations and growth prospects. In addition, we could be subject to enforcement action by regulatory authorities for our failure to comply with cGMP with respect to the products we manufacture in our facilities as well as for our failure to adequately oversee compliance with cGMP by any of our third party suppliers operating under contract. Moreover, failure to comply with applicable legal and regulatory requirements subjects us and our suppliers to possible regulatory action, including restrictions on supply or shutdown, which may adversely affect our or a supplier's ability to supply the ingredients or finished products we need.

We have a manufacturing and development facility in Athlone, Ireland where we manufacture Xywav and Xyrem, a manufacturing plant in Villa Guardia, Italy where we produce the defibrotide drug substance and a manufacturing and development facility in the U.K. at Kent Science Park, where we produce Epidiolex/Epidyolex and have capability to develop product candidates. We currently do not have our own commercial manufacturing or packaging capability for our other products, their APIs or product candidates outside of those developed at Kent Science Park. As a result, our ability to develop and supply products in a timely and competitive manner depends primarily on third party suppliers being able to meet our ongoing commercial and clinical trial needs for API, other raw materials, packaging materials and finished products.

In part due to the limited market size for our products and product candidates, we have a single source of supply for most of our marketed products, product candidates and their APIs. Single sourcing puts us at risk of interruption in supply in the event of manufacturing, quality or compliance difficulties. If one of our suppliers fails or refuses to supply us for any reason, it would take a significant amount of time and expense to implement and execute the necessary technology transfer to, and to qualify, a new supplier. FDA and similar international or national regulatory bodies must approve manufacturers of the active and inactive pharmaceutical ingredients and certain packaging materials used in our products. If there are delays in qualifying new suppliers or facilities or a new supplier is unable to meet FDA's or similar international regulatory body's requirements for approval, there could be a shortage of the affected products for the marketplace or for use in clinical studies, or both, which could negatively impact our anticipated revenues and could potentially cause us to breach contractual obligations with customers or to violate local laws requiring us to deliver the product to those in need.

We are responsible for the manufacture and supply of Epidiolex/Epidyolex and other cannabinoid product candidates for commercial use and for use in clinical trials. The manufacturing of Epidiolex/Epidyolex and our product candidates

necessitates compliance with Good Manufacturing Practice, or GMP, and other regulatory requirements in jurisdictions internationally. Our ability to successfully manufacture Epidiolex/Epidyolex and other cannabinoid product candidates involves cultivation of botanical raw material from specific cannabinoid plants, extraction and purification processes, manufacture of finished products and labeling and packaging, which includes product information, tamper evidence and anti-counterfeit features, under tightly controlled processes and procedures. In addition, we must ensure chemical consistency among our batches, including clinical batches and, if approved, marketing batches. Demonstrating such consistency may require typical manufacturing controls as well as clinical data. We must also ensure that our batches conform to complex release specifications. We have a second site at which we can grow the specific cannabinoid plants that produce the CBD used in Epidiolex/Epidyolex and a second site at which we can crystallize the purified CBD from the liquid plant extract. A number of our product candidates (excluding Epidiolex/Epidyolex) consist of a complex mixture manufactured from plant materials, and because the release specifications may not be identical in all countries, certain batches may fail release testing and not be able to be commercialized. If we are unable to manufacture Epidiolex/Epidyolex or other product candidates in accordance with regulatory specifications, including GMP or if there are disruptions in our manufacturing process due to damage, loss or otherwise, or failure to pass regulatory inspections of our manufacturing facilities, we may not be able to meet current demand or supply sufficient product for use in clinical trials, and this may also harm our ability to commercialize Epidiolex/Epidyolex and our product candidates on a timely or cost-competitive basis, if at all. Our manufacturing program requires significant time and resources and may not be successful, may lead to delays, interruptions to supply or may prove to be more costly than anticipated.

Vyxeos is manufactured by Simtra Biopharma Solutions, which is a sole source supplier from a single site location. Moreover, the proprietary technology that supports the manufacture of Vyxeos is not easily transferable. Consequently, engaging an alternate manufacturer may be difficult, costly and time-consuming. If we fail to obtain a sufficient supply of Vyxeos in accordance with applicable specifications on a timely basis, our sales of Vyxeos, our future maintenance and potential growth of the market for this product, our ability to conduct ongoing and future clinical trials of Vyxeos, and our business, financial condition, results of operations and growth prospects could be materially adversely affected.

Rylaze drug substance is manufactured by AGC Biologics A/S at its facility in Copenhagen, Denmark and the drug product is manufactured and packaged by Patheon at its facility in Greenville, North Carolina. Both sites have ample capacity to support forecast demand and we have secured supply for more than one year's forecast demand. To successfully manufacture Rylaze, the manufacturer must have an adequate master and working cell bank. If we fail to obtain a sufficient supply of Rylaze in accordance with applicable specifications on a timely basis, our sales of Rylaze, our future maintenance and potential growth of the market for this product, our competitive advantage over competing products that have supply constraints, and our business, financial condition, results of operations and growth prospects could be materially adversely affected.

In addition, in order to conduct our ongoing and any future clinical trials of, complete marketing authorization submissions for, and potentially launch our other product candidates, we also need to have sufficient quantities of product manufactured. We currently rely on WuXi Biologics Co., Ltd., or WuXi, a company based in the People's Republic of China, or PRC, as the sole supplier of our product candidate, zanidatamab. Accordingly, there is a risk that supplies of our product candidate may be significantly delayed by, or may become unavailable as a result of, manufacturing, equipment, process, regulatory or business-related issues affecting that company. We may also face additional manufacturing and supply-chain risks due to the regulatory and political structure of the PRC, or as a result of the international relationship between the PRC and the U.S., including but not limited to potential sanctions imposed by the U.S. government on WuXi. Although to date there has been no impact on our ability to obtain supply of zanidatamab, there can be no assurance that operations would not be impacted in the future with a negative impact on supply of our product candidate.

Moreover, to obtain approval from FDA or a similar international or national regulatory body of any product candidate, including zanidatamab, we or our suppliers for that product must obtain approval by the applicable regulatory body to manufacture and supply product, in some cases based on qualification data provided to the applicable body as part of our regulatory submission. Any delay in generating, or failure to generate, data required in connection with submission of the chemistry, manufacturing and controls portions of any regulatory submission could negatively impact our ability to meet our anticipated submission dates, and therefore our anticipated timing for obtaining FDA or similar international or national regulatory body approval, or our ability to obtain regulatory approval at all. In addition, any failure of us or a supplier to obtain approval by the applicable regulatory body to manufacture and supply product or any delay in receiving, or failure to receive, adequate supplies of a product on a timely basis or in accordance with applicable specifications could negatively impact our ability to successfully launch and commercialize products and generate sales of products at the levels we expect.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds

None

Item 5. Other Information

Insider Trading Arrangements

The following is a summary of the material terms of the contracts, instructions or written plans for the purchase or sale of the Company's securities adopted or terminated by our officers (as defined in Rule 16a-1(f) under the Securities Exchange Act of 1934, as amended) and directors during the quarter ended March 31, 2024:

Type of Trading Arrangement

Name and Position	Date	Action	Rule 10b5-1*	Expiration Date	Total Ordinary Shares to be Sold
Robert Iannone Executive Vice President, Global Head of Research and Development	March 7, 2024	Modification	X	March 7, 2025	10,681

* Contract, instruction or written plan intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) under the Securities Exchange Act of 1934, as amended.

Item 6. Exhibits

Exhibit Number	Description of Document
2.1‡	Transaction Agreement, dated as of February 3, 2021, by and among Jazz Pharmaceuticals UK Holdings Limited, Jazz Pharmaceuticals Public Limited Company and GW Pharmaceuticals PLC (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on February 4, 2021).
3.1	Amended and Restated Memorandum and Articles of Association of Jazz Pharmaceuticals plc, as amended on August 4, 2016 (incorporated herein by reference to Exhibit 3.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2016, as filed with the SEC on August 9, 2016).
4.1	Reference is made to Exhibit 3.1.
4.2	Indenture, dated as of April 29, 2021, among Jazz Securities Designated Activity Company, the guarantors party thereto, U.S. Bank National Association, as trustee and acknowledged by U.S. Bank National Association, as collateral trustee. (incorporated herein by reference to Exhibit 4.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-033500), as filed with the SEC on April 29, 2021).
10.1+	Offer Letter from Jazz Pharmaceuticals, Inc. to Philip Johnson dated as of January 30, 2024.
10.2+	Amended and Restated Non-Employee Director Compensation Policy (approved April 25, 2024).
31.1	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as amended.
31.2	Certification of Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as amended.
32.1*	Certifications of Chief Executive Officer and Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document - The instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

‡ Certain portions of this exhibit have been omitted pursuant to Item 601(b)(2) of Regulation S-K.

* The certification attached as Exhibit 32.1 accompanies this Quarterly Report on Form 10-Q pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, and shall not be deemed "filed" by the Registrant for purposes of Section 18 of the Securities Exchange Act of 1934, as amended.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Date: May 2, 2024

JAZZ PHARMACEUTICALS PUBLIC LIMITED COMPANY
(Registrant)

/s/ Bruce C. Cozadd
Bruce C. Cozadd
Chairman and Chief Executive Officer and Director
(Principal Executive Officer)

/s/ Philip L. Johnson
Philip L. Johnson
Executive Vice President and Chief Financial Officer
(Principal Financial Officer)

/s/ Patricia Carr
Patricia Carr
Senior Vice President, Chief Accounting Officer
(Principal Accounting Officer)

[Jazz Pharmaceuticals Letterhead]

January 30, 2024

Philip Johnson
[address on file]

Re: Offer of employment with Jazz Pharmaceuticals

Dear Philip,

As discussed, I am very pleased to invite you to join the Jazz Pharmaceuticals group. This letter sets out the terms of your employment with Jazz Pharmaceuticals, Inc. ("**Jazz Pharmaceuticals**" or the "**Company**").

1. Position, Location and Responsibilities. Your initial assignment will be as Executive Vice President and Chief Financial Officer, reporting to me. This offer is for a full time position, and is a home-based role located in the United States. In this position, you will perform all duties and responsibilities of your position, and you will be a member of the Executive Committee. This position will require periodic domestic and international business travel as necessary to fulfill your responsibilities. As part of your employment relationship, you agree to comply with Jazz Pharmaceuticals' policies and procedures in effect during your employment.

2. Base Salary, Sign-On Bonus and Annual Bonus. Your initial annual base salary rate will be $700,000.00, less all applicable deductions and withholdings and payable in accordance with Jazz Pharmaceuticals' customary payroll practices. As an exempt employee, you will be paid on a salaried basis and you will be expected to work the number of hours required to do your job well and you are not eligible for overtime compensation. Salary is subject to periodic review and adjustment by Jazz Pharmaceuticals, in accordance with its normal practices; we have a Company-wide performance review process that takes place early in each calendar year.

You will be eligible to receive a cash sign-on bonus in the amount of USD $150,000.00 subject to applicable tax withholdings and paid within 30 days of your date of hire. Receipt of your sign-on bonus will be contingent upon you signing a Sign-On Bonus Repayment Agreement under which you will be required to repay the full sign-on bonus if your employment terminates prior to your 24-month anniversary of your start date under the terms and conditions set forth in the Sign-On Bonus Repayment Agreement. The Sign-On Bonus Repayment Agreement will be reviewed and signed in the Onboarding Portal.

You will be eligible for consideration of an annual bonus, and in this position, your annual target bonus will be sixty percent (60%) of your annual base salary rate, pursuant to the Jazz Pharmaceuticals Global Cash Bonus Plan. The amount of your bonus will be based on the Company's level of achievement of its annual objectives, and on your level of achievement of your objectives. Bonuses are not guaranteed, and whether there will be a bonus in any year, and the amount of any bonus, is within the discretion of the Board of Directors of Jazz Pharmaceuticals plc. The Global Cash Bonus Plan year runs January through December, and annual bonus awards are typically paid in the first quarter of the following year. Your bonus for 2024 will be prorated due to your partial year of employment and in accordance with your start date.

3. Employee Benefits. You generally will be eligible to participate in all employee benefits which are extended to other similarly-situated employees at Jazz Pharmaceuticals, including medical and dental benefits, life insurance and other benefits offered to regular employees, subject to the terms and conditions of the benefit plans. You will be eligible for paid time off and holidays in accordance with Jazz Pharmaceuticals' policies, and you will be deemed a participant in the Jazz Pharmaceuticals Amended and Restated Executive Change in Control and Severance Benefit Plan.

4. New Hire Equity Awards. Your offer includes eligibility to receive a new hire equity award with a grant date value of $4,000,000.00, of which $2,000,000.00 will be in the form of Restricted Stock Units ("**RSUs"**) and $2,000,000.00 will be in the form of Performance Stock Units ("**PSUs**"), giving you a right to receive Jazz Pharmaceuticals plc ordinary shares at a future date, subject to approval by the Compensation and Management Development Committee ("**CMDC**"), the terms and conditions of the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan, and the terms and conditions of the applicable award agreements. Your new hire RSUs will vest in four equal annual installments, subject to your continued employment through each vesting date. Your new hire PSUs will vest based on the achievement of certain pre-established financial and/or strategic performance goals as determined at the end of the applicable performance period (typically, three years) by the Jazz Board of Directors.

The RSUs and PSUs will be granted on the second trading day following the filing date of the Company's next quarterly or annual report filed with the U.S. Securities and Exchange Commission following your start date in accordance with the Company's Equity Incentive Grant Policy. Each of your new hire RSUs and PSUs will be converted from the dollar value shown above to a number of units based on the average closing price of Jazz plc common shares for the 30-day period ending the day prior to the grant date.

In addition, as part of the annual compensation review, you may receive annual equity awards subject to approval by the CMDC.

5. Confidential Information and Inventions Agreement, Outside Employment. To enable Jazz Pharmaceuticals to safeguard its proprietary and confidential information, it is a condition of employment that you sign and comply with Jazz Pharmaceuticals' standard form of "Employee Confidential Information and Inventions Agreement." We understand that you are likely to have signed similar agreements with prior employers, and wish to impress upon you that Jazz Pharmaceuticals does not want to receive the confidential or proprietary information of others, and does not want you to use such information in the course of your employment with us, and Jazz Pharmaceuticals will support you in respecting your lawful obligations to prior employers. By accepting this offer, you are representing to Jazz Pharmaceuticals that your employment with Jazz Pharmaceuticals and the performance of your duties will not violate any agreements you may have with, or trade secrets of, any third parties. You agree that, during your employment with Jazz Pharmaceuticals and in accordance with our Outside Employment policy, you will not engage in any business activity that competes with Jazz Pharmaceuticals, and you will notify me (for review and approval) if you are considering accepting or continuing outside work, including self-employment, consulting arrangements, or any roles on any Boards of Directors.

6. Code of Conduct. Jazz Pharmaceuticals is committed to integrity and the pursuit of excellence in all we do. We fulfill these commitments while upholding a high level of ethical conduct. The Code of Conduct is one element of Jazz Pharmaceuticals' efforts to ensure lawful and ethical conduct by the Company and its subsidiaries and their employees, officers and directors. It is a condition of employment that you read, agree to and sign Jazz Pharmaceuticals' Code of Conduct in the first week of employment. If you have questions about the Code of Conduct, please let Human Resources know and we will ensure that you receive answers to your inquiries as quickly as possible.

7. At-Will Employment Status. Should you decide to accept our offer, you will be an "at-will" employee of Jazz Pharmaceuticals. This means that either you or Jazz Pharmaceuticals may terminate the employment relationship at any time, with or without cause, and with or without advance notice. Due to your at-will employment status, Jazz Pharmaceuticals also retains the discretion to modify the terms and conditions of your employment (with exception of your at-will status), including but not limited to your salary, incentive compensation and benefits, as well as your job title, location, duties, responsibilities, assignments and reporting relationships. Participation in any benefit, compensation or bonus program does not change the nature of the employment relationship, which remains "at-will".

8. Authorization To Work. Federal government regulations require that all employees present documentation verifying their identity and demonstrating that they are authorized to work in the United States. Your employment is contingent on your ability to prove your identity and authorization to work in the United States, and your compliance with the government's employment verification requirements.

9. Offer Contingencies. This offer is contingent upon satisfactory completion (as determined by the Company) of your background and reference checks, including but not limited to verification of previous employment record, academic achievement and criminal background.

10. Complete Offer and Agreement. This letter, including the Employee Confidential Information and Inventions Agreement referenced herein, contains our complete understanding and agreement regarding the terms of your employment with Jazz Pharmaceuticals, and it is entered into without reliance on any promise or representation, written or oral, other than those expressly contained herein, and it supersedes any other such promises, warranties or representations. There are no other, different or prior agreements or understandings on this or related subjects.

11. Start Date, Acceptance of Offer. Let's continue to discuss your start date with the aim to finalize your start date by end of this week. To accept our offer of employment, please sign the enclosed copy of this letter in the space provided below by the close of business on Friday February 2, 2024.

Philip, we are impressed by your accomplishments and potential, and we are enthusiastic at the prospect of you joining us. I look forward to your early acceptance of this offer, and to your contributions to the growth and success of Jazz Pharmaceuticals.

If you have any questions about this letter, please let me know or feel free to contact Heidi Manna, our Chief People Officer.

Sincerely,

/s/ Bruce C. Cozadd
Bruce Cozadd
Chairman & CEO

ACCEPTANCE OF EMPLOYMENT OFFER:

I hereby accept the offer of employment by Jazz Pharmaceuticals on the terms set forth in this letter.

Signature: /s/ Philip L. Johnson

Date: 06 February 2024

JAZZ PHARMACEUTICALS PLC

NON-EMPLOYEE DIRECTOR COMPENSATION POLICY

Non-employee members of the board of directors (the "***Board***") of Jazz Pharmaceuticals plc (the "***Company***") shall be eligible to receive cash and equity compensation as set forth in this Non-Employee Director Compensation Policy (this "***Policy***"). The cash compensation and equity grants described in this Policy shall be paid or be made, as applicable, automatically and without further action of the Board, to each member of the Board who is not an employee of the Company or any parent or subsidiary of the Company (each, a "***Non-Employee Director***") who may be eligible to receive such cash compensation or equity grants, unless such Non-Employee Director declines the receipt of such cash compensation or equity grants by written notice to the Company. This Policy shall remain in effect until it is revised or rescinded by further action of the Board.

1. Cash Compensation.

(a) Subject to Section 1(b) and Section 3 below, each Non-Employee Director shall be eligible to receive cash compensation of $75,000 for service on the Board. In addition, a Non-Employee Director serving as:

(i) lead independent director of the Board shall be eligible to receive additional cash compensation of $50,000 per year for such service;

(ii) chairperson of the Audit Committee shall be eligible to receive additional cash compensation of $25,000 per year for such service;

(iii) members (other than the chairperson) of the Audit Committee shall be eligible to receive additional cash compensation of $15,000 per year for such service;

(iv) chairperson of the Compensation & Management Development Committee (the "***Compensation Committee***") shall be eligible to receive additional cash compensation of $25,000 per year for such service;

(v) members (other than the chairperson) of the Compensation Committee shall be eligible to receive additional cash compensation of $12,500 per year for such service;

(vi) chairperson of the Nominating and Corporate Governance Committee shall be eligible to receive additional cash compensation of $20,000 per year for such service;

(vii) members (other than the chairperson) of the Nominating and Corporate Governance Committee shall be eligible to receive additional cash compensation of $10,000 per year for such service;

(viii) chairperson of the Science & Medicine Committee shall be eligible to receive additional cash compensation of $25,000 per year for such service;

(ix) members (other than the chairperson of the Science & Medicine Committee) shall be eligible to receive additional cash compensation of $12,500 per year for such service;

(x) chairperson of the Transaction Committee shall be eligible to receive additional cash compensation of $5,000 per meeting up to $20,000 per year for such service; and

(xi) members (other than the chairperson) of the Transaction Committee shall be eligible to receive additional cash compensation of $2,500 per meeting up to $10,000 per year for such service.

The additional cash compensation for the Non-Employee Director's service on the Committees other than the Transaction Committee shall be paid in four equal quarterly installments, earned upon the completion of service in each calendar quarter. The additional cash compensation for the Non-Employee Director's service on the Transaction Committee shall be paid in four quarterly installments, earned upon the completion of services in each calendar quarter.

(b) Each person who is elected or appointed to be a Non-Employee Director or who is appointed to serve as lead independent director or a member or chairperson of one of the Committees described above, in each case other than on the first calendar day of a calendar quarter, shall be eligible to receive a pro rata amount of the annual retainers described above with respect to the calendar quarter in which such person becomes a Non-Employee Director, lead independent director or a member or chairperson of one of the Committees, as applicable, which pro rata amount reflects a reduction for each calendar day during the calendar quarter prior to the date of such election or appointment.

(c) Each Non-Employee Director will be entitled to reimbursement from the Company for his or her reasonable travel (including airfare and ground transportation), lodging and meal expenses incidental to meetings of the Board or committees thereof. If any reimbursement payment is subject to tax imposed by the Irish Revenue Commissioners ("***Revenue***"), each Non-Employee Director will be entitled to a payment, up to an amount ("***Tax Reimbursement Payment***") such that after the deduction of all taxes (including, without limitation, any income taxes calculated at the rate applicable to each Non-Employee Director for the year in which the expenses were incurred) on the Tax Reimbursement Payment, the Non-Employee Director will retain an amount equal to the full reimbursement payment. All taxes due will be paid by the Company to Revenue.

2. Equity Compensation. The restricted stock unit ("***RSU***") awards described below shall be granted under and shall be subject to the terms and provisions of the Company's Amended and Restated 2007 Non-Employee Directors Stock Award Plan (the "***NEDSAP***").

(a) Eligibility. Subject to Section 3 below, beginning with the annual general meeting of the Company's shareholders (an "***AGM***") held in 2021, each person who is a Non-Employee Director at an AGM and who continues as a Non-Employee Director following such meeting automatically shall be granted an RSU award (an "***Annual Grant***") on the grant date set forth in Section 2(b) below. In addition, subject to Section 3 below, each person who is elected or appointed to be a Non-Employee Director for the first time other than at an AGM and after the AGM held in 2021, automatically shall be granted a prorated RSU award (a "***Prorated Annual Grant***") on the grant date set forth in Section 2(b) below, provided that such person is a Non-Employee Director on such grant date.

(b) Grant Date. The grant date of each Annual Grant shall be the day of the applicable AGM, and the grant date of each Prorated Annual Grant shall be the second trading day following the filing date of the Company's next quarterly or annual report filed under the Securities Exchange Act of 1934, as amended, that occurs after the date of the Non-Employee Director's initial election or appointment.

(c) Grant Date Value. The grant date value of each Annual Grant shall be equal to approximately $400,000. The grant date value of each Prorated Annual Grant shall be prorated to reflect the shortened

period of service (by multiplying $400,000 by the quotient (rounded to the nearest hundredth) obtained by dividing the number of calendar days from and including the date of the Non-Employee Director's initial election or appointment to and including the date that is the first anniversary of the prior AGM by 365).

(d) Number of Ordinary Shares. The number of ordinary shares of the Company ("***Ordinary Shares***") subject to each Annual Grant and Prorated Annual Grant shall be determined by dividing the grant date value, in each case as set forth in Section 2(c) above, by the average of the daily closing prices per share of the Ordinary Shares during the 30 calendar day period ending on and including the grant date, rounded to the nearest share by application of regular rounding.

(e) Vesting. Each Annual Grant granted to a Non-Employee Director shall vest in full on the first anniversary of the AGM in the year of grant and each Prorated Annual Grant granted to a Non-Employee Director shall vest in full on the first anniversary of the AGM held prior to the Non-Employee Director's initial election or appointment, in each case subject to the Non-Employee Director's Continuous Service (as defined in the NEDSAP) through such vesting date. Notwithstanding the foregoing, if a Non-Employee Director does not stand for reelection at an AGM in the year in which his or her term expires or otherwise resigns effective at an AGM and, in either case, the Non-Employee Director's Continuous Service terminates at such AGM, then effective as of the date of such AGM, the unvested portion, if any, of such Non-Employee Director's Annual Grant or Prorated Annual Grant shall become vested in full.

(f) Terms and Conditions. The terms and conditions applicable to each Annual Grant and Prorated Annual Grant granted to Non-Employee Directors pursuant to this Policy shall be subject to the terms and conditions in the forms of RSU notice of grant and RSU award agreement previously approved by the Board or the Compensation Committee, as applicable, and the NEDSAP.

3. Non-Employee Director Compensation Limit. The aggregate value of all compensation granted or paid, as applicable, by the Company to any individual for service as a Non-Employee Director with respect to any period commencing on the date of the AGM for a particular year and ending on the calendar day immediately prior to the date of the AGM for the subsequent year (the "***Annual Period***"), including equity awards granted and cash fees paid by the Company to such Non-Employee Director, will not exceed (i) $750,000 in total value or (ii) in the event such Non-Employee Director is first appointed or elected to the Board during such Annual Period, $1,350,000 in total value, in each case calculating the value of any equity awards based on the grant date fair value of such equity awards for financial reporting purposes.

*****

Adopted by the Board of Directors of Jazz Pharmaceuticals plc on 2 May 2013.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 1 August 2013.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 1 May 2014.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 30 October 2014.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 30 April 2015.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 4 May 2016.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 3 May 2018.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 21 July 2020.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 28 April 2021.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 29 July 2021.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 28 April 2022.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 4 May 2023.

Amended and restated by the Board of Directors of Jazz Pharmaceuticals plc on 25 April 2024.

Exhibit 31.1

CERTIFICATION

I, Bruce C. Cozadd, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Jazz Pharmaceuticals public limited company;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 2, 2024

By: /s/ Bruce C. Cozadd

Bruce C. Cozadd
Chairman and Chief Executive Officer and Director

Exhibit 31.2

CERTIFICATION

I, Philip L. Johnson, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Jazz Pharmaceuticals public limited company;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 2, 2024

By: /s/ Philip L. Johnson

Philip L. Johnson
Executive Vice President and Chief Financial Officer

Exhibit 32.1

CERTIFICATION[1]

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. Section 1350), Bruce C. Cozadd, Chief Executive Officer of Jazz Pharmaceuticals public limited company (the "Company"), and Philip L. Johnson, Executive Vice President and Chief Financial Officer of the Company, each hereby certifies that, to the best of his knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2024, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: May 2, 2024

/s/ Bruce C. Cozadd

Bruce C. Cozadd

Chairman and Chief Executive Officer and Director (Principal Executive Officer)

/s/ Philip L. Johnson

Philip L. Johnson

Executive Vice President and Chief Financial Officer (Principal Accounting Officer)

(1) This certification accompanies the Quarterly Report on Form 10-Q to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Jazz Pharmaceuticals public limited company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-Q), irrespective of any general incorporation language contained in such filing. A signed original of this written statement required by Section 906 of the Sarbanes-Oxley Act of 2002 has been provided to Jazz Pharmaceuticals public limited company and will be retained by Jazz Pharmaceuticals public limited company and furnished to the Securities and Exchange Commission or its staff upon request.

EXHIBIT 7

Q1 2024 Earnings Call *(Corrected version)*

Event Details

Date: 2024-05-01
Company: Jazz Pharmaceuticals Plc
Ticker: JAZZ-US

Company Participants

Andrea N. Flynn - Jazz Pharmaceuticals Plc, Vice President & Head-Investor Relations
Bruce C. Cozadd - Jazz Pharmaceuticals Plc, Chairperson & Chief Executive Officer
Renée D. Galá - Jazz Pharmaceuticals Plc, President & Chief Operating Officer
Robert Iannone - Jazz Pharmaceuticals Plc, Executive Vice President & Global Head-Research and Development
Philip L. Johnson - Jazz Pharmaceuticals Plc, Chief Financial Officer & Executive Vice President

Other Participants

Jessica Fye - Analyst
Jason Gerberry - Analyst
Marc Goodman - Analyst
Annabel Samimy - Analyst
Akash Tewari - Analyst
Ami Fadia - Analyst
Joseph Thome - Analyst
Ashwani Verma - Analyst
Joon Lee - Analyst
Gregory Renza - Analyst
David Amsellem - Analyst
Gary Nachman - Analyst
Charles C. Duncan - Analyst
Balaji Prasad - Analyst

MANAGEMENT DISCUSSION SECTION

Operator

00:00:05 Thank you for standing-by. My name is Christa, and I will be your conference operator today. At this time, I would like to welcome everyone to the Jazz Pharmaceuticals First Quarter 2024 Earnings Conference Call. All lines have been placed on mute to prevent any background noise. After the speakers' remarks, there will be a question-and-answer session. Thank you.

00:00:35 I would now like to turn the conference over to Andrea Flynn, Vice President, Head of Investor Relations. Andrea, you may begin your conference.

Andrea N. Flynn

00:00:46 Thank you, operator, and good afternoon, everyone. Today, Jazz Pharmaceuticals reported its first quarter 2024 financial result. The slide presentation accompanying this webcast is available on the Investors section of our website. Investors may also refer to the press release we issued earlier today, which is also posted to our website.

00:01:04 On the call today are Bruce Cozadd, Chairman and Chief Executive Officer; Renée Galá, President and Chief Operating Officer; Rob Iannone, Executive Vice President and Global Head of R&D; and Phil Johnson, Executive Vice President and Chief Financial Officer.

00:01:19 On slide 2, I'd like to remind you that today's webcast includes forward-looking statement such as those related to our future financial and operating results, growth potential and anticipated development and commercialization milestones and goals, which involve risks and uncertainties that could cause actual events, performance and results to differ materially from those contained in these forward-looking statement.

00:01:40 We encourage you to review the statements contained in today's press release, in our slide deck, and the risks and uncertainties described in our SEC filings, which identify certain factors that may cause the company's actual events, performance and results to differ materially from those contained in the forward-looking statements made on today's webcast. We undertake no duty or obligation to update our forward-looking statement.

00:02:03 As noted on slide 3, we will discuss non-GAAP financial measures on this webcast. Descriptions of these non-GAAP financial measures and reconciliations of GAAP to non-GAAP financial measures are included in today's press release and the slide presentation available on the Investors section of our website.

00:02:20 I'll now turn the call over to Bruce.

Bruce C. Cozadd

00:02:23 Thanks, Andrea. Good afternoon, everyone, and thank you for joining us today to review our first quarter results.

00:02:29 I want to begin by welcoming Phil Johnson, who joined Jazz in March as our Chief Financial Officer. We're very excited to have Phil on our executive team, and look forward to his contributions to delivering value for patients and shareholders.

00:02:44 Beginning on slide 5, we made important progress during the first quarter, including year-over-year combined double-digit revenue growth from our key growth drivers; Xywav, Epidiolex and Rylaze, along with meaningful advances in our pipeline. I'm also pleased to report that we are affirming our 2024 financial guidance.

00:03:06 On the commercial front, we generated more than $900 million in total revenues across our growing and diversified portfolio of medicines. Xywav revenues increased 14% year-over-year, reinforcing our confidence in its trajectory and durability. Epidiolex demand remained strong, and we continue to be confident in its blockbuster potential. Our oncology therapeutic area delivered another strong quarter with 13% year-over-year revenue growth. This continues the momentum we established last year when we surpassed $1 billion in annual oncology revenue for the first time.

00:03:45 Moving to our R&D and pipeline efforts. 2024 is an important year for Jazz with multiple late-stage catalysts for therapies targeting substantial market opportunities. We achieved a significant milestone for zanidatamab in March, with the completion of our rolling BLA submission for the treatment of HER2-positive biliary tract cancer or BTC, and we expect commercial launch in 2025 or earlier.

00:04:13 If approved, zanidatamab would be the first HER2-targeted treatment specifically for BTC in the US. We also expect important clinical data readouts in the near future for suvecaltamide in essential tremor, zanidatamab in gastroesophageal cancer, Epidiolex in Japan, and Zepzelca in first line small cell lung cancer.

00:04:36 On the operational front, we are maintaining our focus on disciplined capital allocation. Our financial strength, including healthy operating cash flow, enables us to invest in the continued growth of our commercial portfolio and pipeline, while also positioning us to execute on corporate development opportunities.

00:04:55 Turning to slide 6. We remain focused on advancing the three core tenets of Vision 2025. This includes advancing leading therapies in sleep disorders and epilepsy, along with a growing oncology portfolio, investing in R&D to expand our capabilities and pipeline, and making disciplined capital allocation decisions to enhance value to shareholders as we realize our ambition to be a high-growth global biopharma leader.

00:05:23 I'll now turn the call over to Renée to review our commercial performance, after which Rob will share an update on our R&D progress. Phil will provide a financial overview, and then we'll open the call to Q&A.

00:05:36 Renée?

Renée D. Galá

00:05:37 Thanks, Bruce. I'm excited to report on the continued progress across our commercial portfolio. We delivered strong first quarter revenue, growing combined revenue from our key growth drivers, Xywav, Epidiolex and Rylaze, by 12% compared to the same period in 2023. As is typical of the first quarter of the year, revenue was impacted by seasonal headwinds from payer reauthorizations and inventory drawdown.

00:06:06 Let's get into the details starting on slide 8 with our sleep franchise. Total revenue from sleep, which includes Xywav and Xyrem net sales plus royalties from high-sodium oxybate Authorized Generics or AGs, was $430 million in the first quarter of 2024, and we remain confident in the growth and durability of Xywav. In the first quarter of 2024, Xywav revenue grew 14% year-over-year to $315 million. I'll take a few minutes to discuss our view of the overall oxybate market, as well as several items of note from the quarter.

00:06:47 In 2023, we saw the first competitive entrant to the oxybate market with the commercial availability of both high-sodium AG and branded fixed dose high-sodium oxybate. We were pleased to deliver Xywav revenue growth through this period, and continue to expect Xywav to remain the oxybate of choice, including the number one treatment for narcolepsy.

00:07:12 As expected, at the start of 2024, Xyrem was excluded from certain commercial formularies, based on the availability of multiple newer oxybate products, including Xywav. Many of these patients

and their physicians recognize the benefits of low sodium, and chose to initiate treatment with Xywav. I want to call out several downstream dynamics of this transition.

00:07:39 First, we saw a significant increase in the number of active narcolepsy patients benefiting from Xywav at the end of the first quarter of 2024 compared to the fourth quarter of 2023.

00:07:52 Second, we saw an increase in utilization of our patient support programs in the first quarter, as patients navigated the transition from Xyrem to Xywav with their insurance providers. These programs provide free product for a limited duration, helping to ensure patients have uninterrupted access to therapy as they obtain Xywav coverage.

00:08:16 As a reminder, we have achieved benefit coverage in both narcolepsy and IH indications for approximately 90% of commercial lives. While we anticipate that other plans may exclude Xyrem from formulary going forward, we expect these changes will be less concentrated and spread out over time. We view the large number of patient transitions that occurred from the fourth quarter of 2023 to the first quarter of 2024 as a one-time event.

00:08:49 Finally, this transition resulted in a significant decrease in Xyrem branded revenues. I'll note that all of these dynamics were accounted for in our 2024 neuroscience revenue guidance.

00:09:03 Looking at our quarterly patient metrics, there were approximately 9,900 narcolepsy patients taking Xywav exiting the first quarter, an increase of 375 patients from the prior quarter. Given the increased use of patient support programs, revenues for the quarter do not fully reflect these patient additions. We believe patient numbers are the best indicator of the long-term value and durability of this product, and expect that revenues will be more aligned with patient numbers going forward as newly transitioned patients revert to being fully covered by their insurance providers.

00:09:43 Turning to IH. The transition dynamics associated with coverage for narcolepsy patients did not impact the IH market. We continue to view IH as the strongest growth opportunity for Xywav; and exiting the quarter, there were approximately 3,050 active IH patients on Xywav, an increase of 275 from the prior quarter. We are prioritizing investments to further build the market, and our expanded field force is now fully deployed. These additional field personnel are focused on increasing the depth and breadth of IH prescribers.

00:10:23 Outside of the branded oxybate business, we recognized approximately $50 million in AG royalty revenue, which was driven by both patient transition and our increased royalty rate. Given our results for the quarter and increased visibility into oxybate market dynamics since the entry of high-sodium oxybates, we remain confident in the durability of Xywav and believe that we are well-positioned to achieve our Vision 2025 goal of $2 billion in sleep revenue.

00:10:57 Moving to slide 9. We are pleased with the continued growth of Epidiolex with net product sales of approximately $200 million in the first quarter, representing a 5% increase compared to the same quarter in 2023. As a reminder, with Epidiolex, we typically see a build in inventory throughout the second half of the year, which then burns off in the first half of the following year, primarily in the first quarter. We expect future growth to be driven by underlying demand and geographic expansion, and remain confident in the blockbuster potential of Epidiolex.

00:11:37 Key drivers of increased demand in the US included the positive response to data on the benefits of Epidiolex beyond seizure control, such as language and communication, cognition, executive function, and emotional and social function, as well as synergies from treatment with Epidiolex plus clobazam. We're also continuing to see increased penetration in the adult patient setting,

which is supported in part by data showing that many patients may reach adulthood without a specific LGS diagnosis and by providing HCPs with clear diagnostic tools for adult patients.

00:12:19 Further opportunities for growth include continued education to support optimal dosing, focused data generation and geographic expansion beyond the more than 35 countries where Epidiolex is currently approved, with additional launches and market reimbursement expected in 2024.

00:12:39 Shifting to our oncology business on slide 10. Total oncology revenue for the quarter was approximately $258 million, led by Rylaze and Zepzelca. Rylaze delivered another strong quarter with net product sales of $103 million, representing a 20% increase from the first quarter of 2023.

00:13:03 Strong demand for Rylaze continues to be driven by several factors, including its near universal adoption and pediatric asparaginase-based oncology protocols in the US, and adoption of the Monday, Wednesday, Friday dosing regimen. We are also seeing usage of Rylaze in the first line setting based on the benefits of its short-acting profile relative to current first line asparaginase therapies. In addition, we remain focused on continued growth of Rylaze in the treatment of adolescents and young adults, or the AYA market.

00:13:42 Turning to slide 11 and Zepzelca. Net product sales for the first quarter increased 12% year-over-year to $75 million. We have established Zepzelca as the number one treatment for second line small cell lung cancer patients, and we continue to hear positive feedback from healthcare providers on its clinical benefit as well as the ease of use and administration for patients and their healthcare practices.

00:14:10 In addition to the second line setting, there remains an unmet need for small cell lung cancer patients in earlier lines of therapy. We believe positive data from the ongoing Phase 3 trial in first line small cell lung cancer is the biggest opportunity to drive significant growth and, most importantly, would provide a further opportunity to improve patient lives and outcomes. We expect data from that trial in late 2024 or early 2025.

00:14:42 With that, I'll turn it over to Rob for an update on our pipeline and upcoming milestones. Rob?

Robert Iannone

00:14:49 Thank you, Renée. 2024 represents an exciting time for our pipeline. And we anticipate multiple meaningful catalysts across oncology and neuroscience.

00:15:00 On slide 13, we provided an overview of the key clinical programs in our diversified pipeline. And I'll highlight several milestones we expect to reach in the near term.

00:15:13 Starting with oncology and zanidatamab, we have completed our BLA submission for second-line biliary tract cancer or BTC, in the US with potential for accelerated approval. Additionally, we are targeting late this year to report topline data from the ongoing Phase 3 first-line gastroesophageal adenocarcinoma, or GEA trial. If positive, we expect this trial would support registration. I'll speak more to our zanidatamab development plan in just a moment.

00:15:49 We're also pleased with the progress of the Zepzelca first-line trial, which completed enrollment in January. Topline progression-free survival data for Zepzelca in combination with Tecentriq in first-line extensive-stage small cell lung cancer is expected at the end of 2024 or early 2025. If approved, this new indication would enable more patients with small cell lung cancer to potentially benefit from longer duration of therapy with Zepzelca.

00:16:22 Turning to neuroscience. We expect topline data from our Phase 3 trial of Epidiolex in Japan in the second half of 2024. We also have ongoing trials for suvecaltamide, or JZP385 in both essential tremor or ET, and Parkinson's disease tremor, with topline data from the ET trial expected late in the first half of 2024. If trial findings are positive, we believe this trial could serve as part of the pivotal regulatory package.

00:16:57 I'd also like to provide an update on JZP441, our clinical stage orexin-2 receptor agonist. We paused the JZP441 Phase 1 trial last November, after observing a signal for QTc interval prolongation on automated ECG recordings. Since that time, we engaged external experts to perform manual reads of ECGs.

00:17:24 That work was recently completed with the initial report indicating there may be a therapeutic index to exposures predicted to be efficacious in narcolepsy Type 1 patients. We are reviewing this information with our alliance partner, Sumitomo Pharma, and Jazz will then make a decision on next steps, if any. I expect to be in a position to provide an update on our 2Q earnings call.

00:17:51 Returning to zanidatamab, slide 14 provides more detail on our development plan. We have meaningfully progressed zanidatamab development across multiple indications since bringing it to Jazz. And based on emerging strong data across indications, we remain excited about the potential of zanidatamab to transform the current standard of care in multiple HER2-expressing cancers.

00:18:18 As was noted earlier, we completed our BLA submission for second-line BTC at the end of March and anticipate a response from FDA within the usual 60-day window. Upon acceptance, FDA would also establish the priority of review and PDUFA timeline. I'll also note we are planning to present more mature data from the ongoing BTC trial at ASCO this year, including overall survival.

00:18:49 Our development plan represents a robust investigation of this molecule in multiple tumor types, including an ongoing trial in GEA that we believe would support registration in that indication in several trials in breast cancer. We've recently announced plans to initiate the Phase 3 EMPOWHER trial in the second half of this year, which will evaluate zanidatamab in combination with chemotherapy after progression on Enhertu, where we have the opportunity to be the first HER2-targeted therapy to demonstrate efficacy and safety in breast cancer patients post Enhertu.

00:19:31 In summary, we're executing a regulatory strategy that we believe will enable us to bring zanidatamab to the market in the near term with an initial indication in second-line BTC and the opportunity to rapidly advance other indications.

00:19:48 In total, we believe our development program can deliver for patients in need and generate a significant commercial opportunity of more than $2 billion. I would encourage listeners to go to our IR website and access the R&D Day webcast we hosted on zanidatamab in March, which included a detailed overview of data demonstrating zanidatamab's differentiation from other HER2-targeted agents, how it would fit in the HER2 treatment landscape and perspectives from external thought leaders on the potential of zanidatamab to improve the quality of care for patients with HER2-expressing tumors.

00:20:29 Turning to slide 15. With the topline data readout from the essential tremor trial anticipated in the second quarter of this year, I'd like to highlight suvecaltamide, which is a highly selective and state-dependent modulator of T-type calcium channels in clinical development for the treatment of ET and Parkinson's disease tremor.

00:20:52 There is a high unmet need for ET treatment with no new medicines approved in more than 50 years. ET can be highly debilitating with significant negative effects on a patient's quality of life and activities of daily living, such as eating, drinking, dressing, shaving, and writing and can lead to substantial impairment in physical functioning. Some patients also experience cognitive deficits, anxiety, social phobia, depression, and sleep disturbance. In the US and key European markets, there are approximately 2 million diagnosed patients with the prevalence estimated at approximately 11 million patients.

00:21:37 Moving to slide 16. I want to touch on suvecaltamide's differentiated mechanism of action. While the exact underlying pathophysiology of ET is not clear, there is strong evidence to support the role of T-type calcium channels. T-type calcium channels regulate the balance of calcium ions acting as a gatekeeper to help ions both enter and leave the cell membrane. In some pathological states such as ET, increased activation of these channels leads to excessive rhythmic signals that prompt tremor.

00:22:20 The high selectivity of suvecaltamide for T-type calcium channels makes it a promising candidate for the treatment of ET, which was demonstrated in the Phase 2 T-CALM trial. Importantly, suvecaltamide is differentiated from other T-type calcium channel blockers in development as it is state-dependent, meaning that it targets channels under conditions of hyperexcitability, while sparing the form of the channel, important for normal neuronal signaling

00:22:51 Now I will turn the call over to Phil for financial update. Phil?

Philip L. Johnson

00:22:55 Thanks, Rob. First, I'd like to express how excited I am to join Jazz. I came to the company because of its history of success innovating to transform the lives of patients and their families. And because of the quality, integrity and enthusiasm of its people, which Jazz has accomplished since its founding, is impressive, and we have great opportunities ahead of us to enhance our impact on the lives of the patients we serve and to create significant shareholder value.

00:23:18 Turning now to our first quarter 2024 financial performance. Slide 18 summarizes the highlights. As a reminder, more information on our financial results is available in our press release and 10-Q. We saw continued topline growth in the first quarter of 2024 with $902 million in total revenues, representing a 1% increase over the same period in 2023. As Renée noted, our first quarter revenues have historically been affected by several factors, including reauthorizations, which drive the use of patient support programs and inventory build in the latter part of the prior year, which leads to inventory burn in Q1.

00:24:02 Our Q1 results are in line with our expectations and we are affirming our full year revenue guidance of $4.0 billion to $4.2 billion, including our expectation for combined double-digit growth from our key growth drivers, Xywav, Epidiolex and Rylaze, and double-digit growth in our oncology therapeutic area.

00:24:23 Moving to slide 19. Non-GAAP adjusted SG&A reflect the investments dedicated to our key growth drivers, including the Xywav IH commercial initiatives, commercial support for Epidiolex in the US

where the market is promotionally sensitive, geographic expansion of Epidiolex outside the US and educational efforts for Rylaze and AYA.

00:24:47 Non-GAAP adjusted R&D expense for the quarter was driven by investment in multiple late-stage programs, which we view as critical to enhancing the future value of our pipeline. We are executing on a robust development plan for zanidatamab with trials across multiple tumor types, as well as Phase 2 trials for suvecaltamide in two different disease areas and programs for Epidiolex and Zepzelca that have the potential to expand those products into new geographies and patient populations, respectively.

00:25:18 I'll note that our operating margin and expenses are not linear and we incur spend at the time to best support strategic initiatives for our commercial business and pipeline. Investments in our commercial business to support our key growth drivers ramped up in the fourth quarter of 2023 and extended into the first quarter of 2024. We expect these investments to positively impact revenue as the year progresses.

00:25:44 SG&A expenses in 1Q 2024 also included a bad debt expense and higher litigation costs, primarily related to the Avadel patent infringement trial. Our R&D expenses, along with clinical trial activity ramped up in 2023, and we expect these expenses to remain at relatively consistent levels throughout 2024. Therefore, we are affirming our full year 2024 SG&A and R&D guidance.

00:26:13 I'd also point out that we recorded a discrete tax expense related to expired stock options. While this significantly increased our non-GAAP effective tax rate for the quarter, we expect our full year 2024 non-GAAP effective tax rate to remain in the range of 10% to 13%. We continue to generate significant cash from our business, driven by the strength and diversity of our portfolio. We recorded approximately $267.2 million of cash from operations in the first quarter and ended the quarter with $1.8 billion in cash on hand. Our strong financial position and operating cash flow provide flexibility to invest in priority commercial and R&D programs, as well as corporate development opportunities.

00:27:00 Non-GAAP adjusted net income of $182 million and non-GAAP adjusted EPS of $2.68 were driven by our topline growth, along with significant investment in our key growth drivers and pipeline, including multiple late-stage clinical programs for zanidatamab, Epidiolex, suvecaltamide and Zepzelca, all of which have the potential to generate significant long-term value. Based on our results from the quarter and continued focus on disciplined and strategic capital allocation, we are affirming our non-GAAP adjusted net income guidance of $1.275 billion to $1.35 billion.

00:27:39 Since joining Jazz, I've spent considerable time speaking with investors and analysts and greatly appreciate the perspective and input they shared. In these conversations, I heard a concern that Jazz will overpay for an acquisition to meet our goal of corporate development, contributing $500 million to 2025 revenue.

00:27:57 Here's how we're thinking about this. First, acquiring or licensing innovation from outside our walls is central to how we'll achieve our purpose of transforming the lives of patients and their families.

00:28:09 Second, as we allocate capital to internal projects and to corporate development, we are focused on making investments that can deliver sustainable revenues and create value for shareholders. We will remain disciplined on price and will not make an acquisition just to meet our Vision 2025 goal.

00:28:26 I'll close by noting that while I'm still getting up to speed, I'm incredibly excited about the future of this company and the opportunities we have to deliver value to both patients and investors.

00:28:36 With that, I'll turn the call back to Bruce for closing remarks.

Bruce C. Cozadd

00:28:40 I'll conclude our prepared remarks on slide 21. We've made important progress towards delivering on our 2024 guidance and objectives and are pleased to be affirming our guidance today. On the commercial side, we expect continued growth of our key products in 2024.

00:28:57 And on the R&D front, we continue to advance our pipeline and to invest in long-term growth. We see multiple catalysts in the near term, including data readouts for suvecaltamide, zanidatamab, Epidiolex, and Zepzelca.

00:29:34 That concludes our prepared remarks. I would now like to turn the call over to the operator to open the line for Q&A.

QUESTION AND ANSWER SECTION

Operator

00:29:46 Thank you. We will now begin the question-and-answer session. Your first question comes from the line of Jessica Fye with JPMorgan. Please go ahead.

Analyst: Jessica Fye

00:29:53 **Question – Jessica Fye:** Hey guys. Good afternoon. Thanks for taking my two-part question on the oxybate-narcolepsy dynamics in the quarter. First can you quantify the headwinds to 1Q from the increase in user patients per programs, as those Xyrem patients transition to Xywav? And second, do you have an understanding of how many Xyrem patients losing coverage transition to generic Xyrem or once-nightly and not to Xywav? Thank you.

00:30:23 **Answer – Bruce C. Cozadd:** Thanks Jess for the question and Renée, maybe I'll let you take both parts of that.

00:30:28 **Answer – Renée D. Galá:** Sure. So Jess, in terms of the – I'll take the second question first. We're not disclosing a breakdown of those patients in part because that AG data is not our data to share. But with respect to being able to quantify how many patients came over, I would say there was a good portion of patients that made the decision along with their HCPs to adopt low sodiums Xywav. And we did see and establish those patient support programs to ensure that we have uninterrupted access for those patients to be able to go from Xyrem directly to Xywav. So what we'll see in future quarters is you should see a better representation of those patients in the revenue and the net sales that come from Xywav.

Operator

00:31:37 Your next question comes from Jason Gerberry with Bank of America. Please go ahead.

Analyst: Jason Gerberry

00:31:43 **Question – Jason Gerberry:** Hi, guys. Thanks for taking my question. My question is about your Phase 2b essential tremor study. So if this trial is successful, I'm wondering how you're thinking about the subsequent second confirmatory trial. Would it look something like this trial, which took roughly two-and-a-half years from start to data? Or could there be some sort of more abbreviated randomized withdrawal study that you could run to get yourself to goal line in a more expeditious manner? Thanks.

00:32:22 **Answer – Bruce C. Cozadd:** Rob, you want to jump in on that?

00:32:24 **Answer – Robert Iannone:** Yeah, happy to. So first of all, Jason, remember, this is a Phase 2b trial. It would count, we believe, or contribute to the pivotal regulatory package. But we call it the Phase 2b because we included three dose levels of suvecaltamide. And when we would move to, let's call it the confirmatory Phase 3 trial, we wouldn't necessarily have to bring all those dose levels forward and ideally, we expect we would choose one dose level. So that creates a more streamlined design. And to your point, when we have data in hand and we engage regulatory authorities, we certainly, with compelling data, would be looking for the fastest path to approval and look at all possible trial designs to support that.

Operator

00:33:16 Your next question comes from the line of Marc Goodman with Leerink. Please go ahead.

Analyst: Marc Goodman

00:33:23 **Question – Marc Goodman:** Bruce had a lot of discussions with investors over the past six months about what Jazz wants to be and what it's transitioning from and to and just the whole big picture discussion and a lot of investors believe you want to become an oncology company, at least that's the perception out there. Just curious, can you talk about just what is it that you expect Jazz to become, what you're looking for Jazz to be in five years, six years, seven years, just because all the investments you're making today are obviously going to be reflected in five or six years and just talk about that and how maybe it's evolved since what Jazz was 5, 10 years ago? Thanks.

00:34:05 **Answer – Bruce C. Cozadd:** Yeah. Thanks, Marc. So we're in a nice position of having growing assets on the neuroscience side of our business in Xywav and Epidiolex with, we believe, promise in front of us, including pipeline programs like the JZP385 program, we were just talking about. We're also excited about what's going on, on the oncology side of the business with double-digit growth coming from our current portfolio, led by Rylaze but also opportunities in front of us with zanidatamab, where we've already got the submission complete and looking forward to a launch in 2025 or earlier, Zepzelca data upcoming, but also an earlier stage pipeline, including particular expansion opportunities with zanidatamab and beyond. So we're excited about both those franchises. While there has been a lot of focus on oncology and certainly the single largest program in our R&D pipeline right now is zanidatamab, I would not say we're trying to turn the company into an oncology company. We'd like to have strength in both of our franchises.

00:35:14 The investments we're making, and I think Phil described it nicely in his comments are designed to both help the short term, particularly some of our commercial investments that we think can continue to generate great growth from our commercial portfolio. And R&D investments that will continue to broaden that pipeline and provide growth over both the near term and the medium and long term, but then also those corporate development opportunities, fueled by our strong

cash flow, balance sheet, and a history of doing transactions that continue to add to our portfolio allow us to impact more patients in more diseases, in more territories around the world. So I think about it as having to make smart investment decisions, which we're in a position to do given the financial strength of the company to fuel both the short and the long term to create value for our shareholders. So execution in the short term important, investment decisions are always important, but I think that should give you a better sense for where we're headed.

Operator

00:36:22 Your next question comes from the line of Annabel Samimy with Stifel. Please go ahead.

Analyst: Annabel Samimy

00:36:29 **Question – Annabel Samimy:** Hi. Thanks for taking my question. I had a two-part in on zani. I guess the first is, how should we think about the opportunity for zani in GEA in light of the better KEYNOTE data, OS that they announced today on KEYTRUDA? And I guess, secondly, where would zani sit into this paradigm. Separately, for launch of zani and as we think about all these indications, how should we think about how rapidly new cancer drugs with superior efficacy profiles can disrupt mainstay standard of care? I guess, in other words, are these ramps going to be more rapid or just as challenging as, say, in other nonfatal conditions. So I just wanted to get some characterization there. Thanks.

00:37:22 **Answer – Bruce C. Cozadd:** Yes, Annabel, thanks for the question. And on the zanidatamab, first question, GEA, we had been expecting positive OS results at some point out of that trial, I think most people had. So I don't think that changes the landscape, but I'll let Rob comment on where zani could fit into the GEA landscape. And then on your second question, it's all about results and uniqueness of mechanism of action and benefit relative to other therapies that determine how fast you can make progress from launch. And when we have the opportunity to bring something really new to patients in terms of benefit, particularly in the oncology space, where I think things can move sometimes even ahead of a regulatory approval, if there's strong data that's been presented that's picked up in the NCCN guidelines and allows for reimbursement, you can get fairly rapid traction with a better option. Rob, you want to talk about the landscape in GEA?

00:38:28 **Answer – Robert Iannone:** Yes. So in the context of HER2 positive over expressed gastroesophageal adenocarcinoma, we think zanidatamab has the potential to be the HER2 antagonist of choice because of its differentiated mechanism of action and because of the differentiated efficacy and safety profile. Certainly in the PD-L1 negative population, which we think is sizable, there is no approved PD-1 agents. And so the comparator there is Herceptin chemotherapy. But even in the PD-L1 positive population, where we think PD-1 agents are essentially interchangeable, we have the opportunity in combination with tislelizumab to show the benefit of zanidatamab, again, has a differentiated HER2 antagonist in combination with backbone chemotherapy and a PD-1 antagonist.

Operator

00:39:26 Your next question comes from the line of Akash Tewari with Jefferies. Please go ahead.

Analyst: Akash Tewari

00:39:33 **Question – Akash Tewari:** Hey, thanks so much. Just going on the HERIZON-GEA study, how should we really interpret the JACOB trial? Here, we saw the addition of PERJETA didn't provide any

OS benefit in GEA on top of tras chemo, and this is a large scale Phase 3. What gives your team confidence that ZW25's early data will hold up in this setting?

00:39:53 And then maybe just on essential tremor, JZP358 (sic) [JZP385] effectively showed no benefit on an accelerometer measurement in its Phase 2 trial. Do you feel like there was something about how the kits were administered in that study that may have skewed those results and how confident do you feel in your ability to show a signal on the accelerometer endpoint with your upcoming data? Thank you.

00:40:21 **Answer – Bruce C. Cozadd:** Yes, Akash, thanks for the two questions. Maybe I'll start on the essential tremor and then let Rob add anything he'd like on the ongoing trial and then comment on your zani question. Just to remember that the prior T-CALM study for essential tremor did demonstrate a nice benefit on TETRAS activities of daily living, which we believe is a measure that's actually more important to patients than the measurement of the quantity of tremor. What patients want is to be able to live their life to do the things they need to do to be able to drink out of a cup, to be able to button and unbutton clothes, to be able to apply makeup, to do the things they care about.

00:41:13 And we were very pleased that that became more of a focus for the pivotal endpoints in later-stage trials. I think FDA too understands you want to do what's really going to provide a benefit to patients. Rob, you want to talk a little bit about our ongoing trial and then pivot to zani.

00:41:33 **Answer – Robert Iannone:** Yes, happy to. And so I would agree, Bruce, that the endpoints that we prioritize as primary are not only the most meaningful to patients, but endorsed by FDA. And on those endpoints, we have confidence from the T-CALM trial. And I would just add to that, in the current Phase 2b trial with a new once-daily formulation, we've been able to push that dose to exposures that would be higher than in the T-CALM trial itself because we have 10, 20 and 30 milligram doses in that trial. So we think based on that, we're positioned for success.

00:42:13 And then coming back to the question on JACOB and GEA, the key point I'd like to make is we really believe that zanidatamab is differentiated from even the combination of Herceptin and PERJETA. As we presented at our R&D Day, we stepped through some important data that were published in Nature Communications, showing how zanidatamab is differentiated.

00:42:35 With two epitopes necessarily binding two distinct receptors, causing more effective receptor clustering and internalization and have demonstrated better immune function, for example, complement fixation. And so in that paper head-to-head and preclinical experiments better than Herceptin and PERJETA and the clinical data bear that out without going into great detail, if you look at the BTC data, where the response rates are over 40% and duration of response greater than 12 months. That compares very favorably to prior data with the combination of Herceptin and PERJETA. And, of course, we have data in breast cancer showing activity of zanidatamab even after patients have failed frontline therapy with Herceptin and PERJETA as part of a CLEOPATRA regimen.

00:43:28 So that in combination with the data that you referred to, zani and chemo and then separately a cohort of zani, chemo, tislelizumab showing very promising not only response rates, but very, very durable responses. That's what gives us confidence that our Phase 3 trial will be successful.

Operator

00:43:49 Your next question comes from the line of Ami Fadia with Needham & Company. Please go ahead.

Analyst: Ami Fadia

00:43:56 **Question – Ami Fadia:** Hi, good evening. Thanks for taking my question. Perhaps I had a question for Phil, just with regards to his comments around business development. And that's a question that we get often from investors as well. Can you talk about some of the metrics that you would use to really evaluate potential deals in terms of kind of what really would meet the bar in terms of what Jazz would be interested in executing on? And also, can you talk about use of capital across R&D, business development, but also perhaps buyback of shares? Thank you.

00:44:42 **Answer – Bruce C. Cozadd:** Thanks, Ami. Phil, go ahead and jump right in.

00:44:45 **Answer – Philip L. Johnson:** Great, Ami. Thank you for the question. My first one on a Jazz earnings call and even I've been around for a while my mom still listen to these. So thanks for giving her early Mother's Day present.

00:44:54 In terms of our corporate development evaluation, first and foremost, there are a number of non-financial criteria that we would look at. Primarily, the things like is there an area with significant unmet need with the medicine that we're looking at acquiring are medicines really meaningfully impact patients, is there an efficient commercial call point. We do have a relatively focused business and want to make sure that we're set up for success to commercialize the assets that we're bringing in, will allow us to leverage the expertise we've got in-house, the commercial footprint we've built out and continue to build out, for example, with Japan coming soon.

00:45:34 And we'll stay largely focused, as we talked in the past, in neuroscience as well as oncology. But we have looked at things in the rare orphan space as well given the kinds of capabilities that we built up selling products with these types of limited patient populations.

00:45:52 From a financial perspective, it really, is I think, some of the traditional things that you would expect. We do want to have line of sight to getting a good return on the investment. We'll look at things that would vary some of the key assumptions, not only draft launch label and competitive landscape, but also timeline to continue to make a return on investment in the marketplace, different options for exclusivity, be that through orphan drug exclusivity, through patent life or other extensions.

00:46:26 So we find nothing unusual in terms of the financial evaluation that we'd have there. But first and foremost, we need to figure out is this a Jazz asset and one where there can be a significant value proposition for patients.

00:46:39 In terms of capital priorities, I'd say, first and foremost, very consistent what you've heard in the past from Bruce, Renée and the team, we're focused on driving the commercial opportunities for the in-market products that we have are dedicating significant monies to get those to as many patients as possible that can benefit from those medicines.

00:47:00 We then are looking to rapidly progress the existing pipeline that we have. Obviously, we're making significant investments behind zanidatamab, given the data that we generated post the licensing deal and then looking at business development to further augment our growth prospects for the future. Once we've exhausted those possibilities, then we look to return excess cash to shareholders. So I hope that gives you a sense for how we're looking at prioritizing capital going forward.

Operator

00:47:31 Your next question comes from the line of Joseph Thome with TD Cowen. Please go ahead.

Analyst: Joseph Thome

00:47:38 **Question – Joseph Thome:** Hi, there. Good afternoon and thank you for taking my question. Maybe one on the upcoming essential tremor readout. What is sort of the bar for clinical meaningfulness on the TETRAS endpoint? Or I guess what is your internal bar, you think, for kind of taking the program forward?

00:47:52 And then one just point of clarification because I think in response to one of the earlier questions, the Phase 3 for essential tremor was referred to as a confirmatory trial. So I just want to make sure that was actually confirming the dose and not that, that Phase 2b could potentially be used for approval and then you would do a Phase 3 confirmatory study? Thanks.

00:48:12 **Answer – Robert Iannone:** Yes. Thanks for giving me the opportunity to clarify. I didn't mean to imply that we would get approval based on the Phase 2b just that it will be part of a package and typically in the space, FDA will be looking for independent studies to confirm efficacy. I did want to point out that when we go to that second efficacy study we're likely to only use one dose, which would be a streamlined design because I think the earlier question had to do with, could you move more quickly than you did with the Phase 2b study.

00:48:45 We haven't said, in particular or specifically, what level of difference on the ADS or the performance scale that would be meaningful enough for approval or for patients. But I would just highlight that there really hasn't been any therapies for this disease almost ever, even though things like propranolol and primidone are used. They really have minimal efficacy.

00:49:12 So there's a substantial unmet need. And I would just say, based on what we saw from the T-CALM study, we think that suvecaltamide really has an opportunity to make a meaningful difference on the endpoints that matter to patients. And overall, in terms of its provability, it will be based on that, the effect size of those primary and secondary endpoints as well as the overall tolerability, which we think will be good given the once-daily extended release and the titration that we did in the trial.

Operator

00:49:47 Your next question comes from the line of Ash Verma with UBS. Please go ahead.

Analyst: Ashwani Verma

00:49:53 **Question – Ashwani Verma:** Hi, there. Yes. Thanks for taking my question. I just wanted to get a sense like in the long term for narcolepsy. I understand from your perspective that you believe that Xywav will remain an oxybate of choice. But in your view, like what percentage of patients do you think may ultimately switch to a once-nightly or generic Xyrem? And then as you're trying to extend your leadership in the sleep arena, are you committed to potentially pursuing another orexin or try to internally develop a once-nightly candidate? Thanks.

00:50:28 **Answer – Bruce C. Cozadd:** Yes. Ash, maybe I'll take the second part of your question first. And then, Renée, maybe you can hop in on the narcolepsy side. Rob gave you a little bit of an update

on the 441 program. We're doing a little more work there and conferring with our partner before we announce next steps. We have previously said we have other backup programs behind that as well. We find this an interesting area, certainly with a lot of promise, though development remains early in the orexin space. But in terms of a new mechanism of action, it already has proof of concept, and we're definitely interested in the benefit that can bring to patients. Renée?

00:51:16 **Answer – Renée D. Galá:** Yeah. Thanks, Bruce. So I would say with respect to Xywav, clearly we saw both strong patient growth and net sales growth year-over-year, that was 14% in terms of net sales growth. And we believe that reflects Xywav as being a differentiated therapy, the only low-sodium oxybate on the market and the number one treatment for narcolepsy.

00:51:42 I would say, with respect to people trying a fixed dose high-sodium oxybate, we said we do expect some patients to try that branded therapy. We do expect that certain patients and HCPs will want to get experience with a fixed dose regimen. What we are hearing anecdotically and also seeing with respect to patients is that we are seeing some patients not get a full night's coverage. We believe that there is benefit to being able to have a full night's coverage in terms of sleep and the flexibility that comes with the twice-nightly dosing.

00:52:31 But more importantly, as the only low-sodium oxybate on the market, we are seeing that educating on the benefits of low sodium, publishing and investing in evidence generation on this front, that message is resonating with HCPs, we have seen data showing the faster-than-expected negative impact from a cardiovascular perspective that patients have when they start a high-sodium oxybate therapy, and we believe that patients and HCPs will ultimately continue to prioritize long-term health when it comes to their oxybate therapy with respect to narcolepsy (00:53:23). These are both chronic conditions, and that gives us continued confidence in the long-term growth and durability of Xywav.

Operator

00:53:37 Your Next question comes from Joon Lee with Truist Securities. Please go ahead.

Analyst: Joon Lee

00:53:44 **Question – Joon Lee:** Hey. Thanks for the updates and for taking our questions. You had a lot of presentations at AAN, and one in particular was on the efficacy of Epidiolex in focal-onset seizures in the context of an Expanded Access Program. And the study showed immediate (00:53:57) seizure reduction in the mid-7% range. How prevalent is the off-label use of Epidiolex and what sort of growth opportunities do you think you have there? There's a lot of investor interest in focal-onset seizures these days. Thank you.

00:54:15 **Answer – Bruce C. Cozadd:** Renée, you want to take that?

00:54:19 **Answer – Renée D. Galá:** Sure. Well, clearly with respect to our promotional activities, we focus our promotional activities on those indications where we are approved, that being LGS, Dravet and TSC. However, we do see continued use based on seizure type. And we do see continued use in other refractory epilepsies, and that is an area that we assume will continue to provide growth for Epidiolex. The reality, when you think about the overall benefits of Epidiolex in terms of being a highly-differentiated treatment, it has broad spectrum efficacy, working through a novel MLA (00:55:09).

00:55:11

And in an area which is characterized by polypharmacy, having a favorable and well-characterized safety profile means that the product lends itself well to being combined with multiple other therapies, in particular, for physicians that see patients that are refractory with respect to seizures. And on top of that, they're really starting to appreciate even more based on the data that we continue to generate and present around the benefits beyond seizures, and also underpins our further investment in generating additional data such as the EpiCom study that we're getting underway.

00:55:58 So we do believe we'll continue to see growth with Epidiolex, both in our approved indications and also in other refractory epilepsy, which, again, we do not promote for. This is a long-lived durable asset for us that we will continue to look at as a global growth product with additional growth opportunities outside the US.

Operator

00:56:26 Your next question comes from the line of Gregory Renza with RBC Capital Markets. Please go ahead.

Analyst: Gregory Renza

00:56:33 **Question – Gregory Renza:** Hey, good afternoon, Bruce and team. Thanks for taking my question. Bruce, we certainly appreciate all the color you and Philip provided on the strategic thinking, as well as capital allocation, especially when it comes to internal investments. And just aside from the diversification of top line when it comes to neuroscience and sleep, as well as the oncology portfolios, can you just speak to the synergies, the benefits and even the cross-talk that you think is important for us to know when it comes to keeping both portfolios under the Jazz umbrella? Thanks so much.

00:57:08 **Answer – Bruce C. Cozadd:** Yeah. Well, Greg, we're fortunate to have growth opportunities on both sides, places that are worth investing, whether that's commercial or R&D. And I also believe there is benefit in being able to look across these two therapeutic areas on the corporate development side. As we've all seen over the past few decades, there are times when an area heats up and valuations get high. And if you can look more broadly across therapeutic categories and across stages of development, I think you're often more likely to find an opportunity that's both a strategic fit, but also offers a nice return profile.

00:57:50 There are a number of services we provide across the company that are centralized and may provide some marginal benefit by not having to reproduce things across multiple therapeutic areas. I would say that's the strategic driver. But again, we're in a position where we've got nice opportunities in front of us, short and long term, on both sides of the business.

Operator

00:58:18 Your next question comes from the line of David Amsellem with Piper Sandler. Please go ahead.

Analyst: David Amsellem

00:58:26 **Question – David Amsellem:** Hey. Just have a quick question on the balance sheet and the cap structure. Can you talk to any potential long-term leverage targets that you have? You've done a lot of deleveraging in the year since the GW transaction. Obviously, you're active on Biz Dev. But

are you thinking about perhaps accelerating debt paydown as a means of potentially supporting the equity? Is that something you're contemplating? And just help us better understand how you're thinking about leverage ratios over time. Thank you.

00:59:11 **Answer – Bruce C. Cozadd:** Phil, you want to jump in on that?

00:59:13 **Answer – Philip L. Johnson:** Yeah, happy to. So, David, as you mentioned, when we had the GW acquisition, there was a really strong interest in communication that we would rapidly delever down to about 3.5 turns by the end 2022. You saw us actually beat that by about six months. We currently sit with about 2.5 times net leverage. I think still a very strong position at this point in time. We feel very good about the overall debt complex that we've got with about 60% of that being fixed and about 40% of that being variable, exposed to interest rate movements, and with a weighted average cost of debt of south of 5.5% at this point in time.

00:59:57 As you're probably aware, we do have an upcoming maturity of our 2024 convert. We're in active planning as you'd expect, looking at some alternatives for how we might approach that particular financing opportunity or repayment opportunity.

01:00:12 I would say, if we were to engage in additional business development, we have the debt increase in the near term, I think, like we did with GW. We have a strong plan to reduce that quickly to get back into the kind of levels that we currently got or below where we've got significant flexibility to continue to look at ways to build the business through business development or corp dev opportunities.

01:00:37 To date, we have not specified any kind of a specific target below where we're currently sitting and where we'd like to get to, but this will be actively discussed and work through as we move forward, looking at the investment opportunities in front of us, both internal as well as external.

01:00:54 So, Bruce, do you want to comment additionally? No?

01:00:58 **Answer – Bruce C. Cozadd:** No, Phil. I think you covered it well. I think we've seen some recent positive commentary from the rating agencies in general about the financial profile of the company. We've used leverage to do transactions when we thought that was the best thing for shareholders. But as Phil said, we've always tried to delever rapidly after that.

Operator

01:01:21 Your next question comes from the line of Gary Nachman with Raymond James. Please go ahead.

Analyst: Gary Nachman

01:01:29 **Question – Gary Nachman:** Thanks. Good afternoon. So, on Xywav, understanding that the patient support program was the key factor for the lower revenue in 1Q. Is Xywav also still getting a lot of the oxybate-naive patients in narcolepsy? And is that a factor that can impact revenue in coming quarters to consider?

01:01:52 And then in IH. Are physicians staying strictly on label? Or are you hearing there could be some off-label use with LUMRYZ if it's with younger patients, I guess, in particular? And maybe talk about the competitive dynamics in IH going forward since that space is going to get a lot more crowded, I guess, in the coming years. Thank you.

01:02:16 **Answer – Renée D. Galá:** Yeah. Thanks for the question. I'll hop right in there. So, with respect to oxybate-naive patients starting on Xywav for narcolepsy, while we don't have full visibility into the new-to-oxybate patient numbers, based on our estimates we do believe we continue to capture more of those new-to-oxybate narcolepsy patients (01:02:40) any other available therapy. And I would say that speaks to the differentiation of the product. It speaks to our host of patient support services more broadly, and being a (01:02:57) leader in sleep, the high overlap when we're looking at narcolepsy and IH of being in front of physicians and continuing to be able to educate them on the benefits of low sodium.

01:03:17 With respect to IH, we don't – we're not really seeing much, if any, off-label use with LUMRYZ, given the payer restrictions on these products and the need for a validated week test for either narcolepsy or for IH. We tend to see that being required in order to receive a prescription. And so it would be pretty unusual to be able to see a prescription for the AG or for LUMRYZ for idiopathic hypersomnia.

01:04:02 And then with respect to competitive dynamics, I think we'll continue to probably see wake-promoting agents studied for idiopathic hypersomnia. Keep in mind, we had a rather large percentage of patients that came into our idiopathic hypersomnia study on wake-promoting agents and continue to see meaningful benefit while on therapy with Xywav, in addition to being on that wake-promoting agent as part of their baseline. Very much like we've seen the wake-promoting agents end up being complementary to Xywav in narcolepsy, we would expect a very similar dynamic in idiopathic hypersomnia, for example, with WAKIX coming on to the market for narcolepsy. We saw little to no impact to our oxybate franchise, and would expect the largely the same dynamic with respect to IH.

Operator

01:05:14 Your next question comes from the line of Charles Duncan with Cantor Fitzgerald. Please go ahead.

Analyst: Charles C. Duncan

01:05:21 **Question – Charles C. Duncan:** Thank you. Good afternoon, Bruce and team. Thanks for taking our question, and congrats on the BLA submission being completed with zani. That said, the next data read is actually neuro with suvecaltamide in essential tremor. And so I'm going to ask for a little bit more granularity. I know others have tried, but I'm really wondering what would you like to see out of the Phase 2b to move forward? If it's supportive of a registrational strategy, definitely seems like (01:05:52) is important, but will you be looking at certain effect sizes and responder analysis? And of the two composites, which of the two are important to you? Thanks.

01:06:08 **Answer – Bruce C. Cozadd:** Yeah. Charles, I'll start with the dangerously general comments, and then let Rob jump in if he wants to provide more specifics.

01:06:17 What we want aside from a package that would generate a regulatory approval is something that really adds value, something that is of value to patients, that patients and prescribers and payers will all see as providing a really meaningful benefit. And certainly, our trials are designed with

prospective key endpoints that we need to hit. But we measure lots of things in these trials that really go to establishing that benefit profile for patients against the backdrop, as Rob said, of really nothing that's currently available that's providing that kind of benefit.

01:07:03 Rob, do you want to talk about anything specific?

01:07:07 **Answer – Robert Iannone:** Again, I don't want to necessarily specify an effect size that we think is meaningful because it really is the holistic picture that matters. But what I would say is when you look at the TCOM (01:07:17) data, we thought there was an important effect there. We've optimized our trial in many respects, honing the primary endpoint in agreement with FDA, optimized the dose, made some changes to how we measure to be sure we get more accurate measurements. And I think all of that would bode well for the trial.

01:07:42 I think the other reference point you have is other T-type calcium channel inhibitors in development. We certainly think suvecaltamide is differentiated in a couple of respects. It's a state-dependent inhibitor, which means it really targets the hyperactive iron channels that are pathologic in the essential tremor condition. And with that, we think it potentially gives us a better therapeutic index, which is why we've been able to push the dose even to doses and exposures that are higher than we would have achieved in TCOM (01:08:14). So, again, it's the totality of the data around the primary and secondary endpoints that we've included that will be meaningful to patients and we know are acceptable to FDA.

Operator

01:08:27 Your next question comes from Balaji Prasad with Barclays. Please go ahead.

Analyst: Balaji Prasad

01:08:35 **Question – Balaji Prasad:** Hi, good evening, everyone. Just a couple for me. On Epidiolex, can you comment on the adult opportunity, either quantify it or qualify it, primarily asking because I'm curious at most, I thought the primary indications approved were childhood diseases that patients tend to outgrow? And also, when do you expect to see this additional data and what is the data that you're expecting?

01:08:58 Secondly, on the 2024 guide, can you help us understand the double-digit per stage growth that you provided for Xywav, Epidiolex and Rylaze combined? Since all three are in different categories, it would be helpful if you could dissect this further. Thanks.

01:09:15 **Answer – Bruce C. Cozadd:** Yeah. Balaji, on the first part of your question, we often refer to these childhood-onset seizure disorders to point out they're not only childhood disorders. They do persist into adulthood, and we think there's substantial opportunity there that I'm going to let Renée jump in on if she wants to.

01:09:35 But let me also hit the second part of your question and say, we were emphasizing the double-digit combined growth of our key growth drivers, Xywav, Epidiolex and Rylaze just because we don't provide single product guidance for the year, as you know, and that's not different this year from any other year. That's why we do it on that basis. Obviously, each quarter we're reporting actual results for each of those products.

01:10:03 Renée, anything you want to add on adult opportunity for Epidiolex?

01:10:10 **Answer – Renée D. Galá:** Yeah. I'm not sure if we'll quantify it here, Balaji, but I would just say that as we look at the broader growth drivers, we do see the adult population, the long-term care environment, one that is currently underserved. With respect to Epidiolex. Epidiolex is weight-based dosing, so you do end up with higher dosing when it comes to that population. But at times, when you move from an environment of pediatric care into long-term care, there is, I would say, perhaps less attention placed on the actual indication of what the adult has.

01:10:57 You would have heard in my prepared remarks, a focus on ensuring that we have the right diagnostic tools with respect to long-term care centers and continuing to ensure whether it's getting the right diagnosis or getting to the right level of dosing where you can optimize results or better educating on the combined impact of clobazam and Epidiolex, those are all opportunities that we see going forward.

Operator

01:11:34 Ladies and gentlemen, that concludes our question-and-answer session. And I will now turn the call over to Bruce Cozadd for closing remarks.

01:11:43 Thanks, operator. As always, I'd like to close today's call by recognizing our Jazz colleagues for their efforts on behalf of patients and their families. And thank our partners and shareholders for their continued confidence and support. Thank you all for joining us today.

Operator

01:11:59 This concludes today's conference call. Thank you for your participation. And you may now disconnect.

EXHIBIT 8

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES L.P.
and TCD ROYALTY SUB LP,

Plaintiffs,

v. No. 21-cv-1710

LUPIN INC. and LUPIN LTD.,

Defendants.

Jack B. Blumenfeld, Jeremy A. Tigan, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, Delaware; Andrew J. Cochran, Gerald J. Flattman, Jr., CAHILL GORDON & REINDEL LLP, New York, New York.

Counsel for Plaintiffs

Megan C. Haney, John C. Phillips, Jr., PHILLIPS, MCLAUGHLIN & HALL, P.A., Wilmington, Delaware; Adrianne C. Rose, Joseph T. Jaros, Katie A. Boda, Natasha L. White, William A. Rakoczy, RAKOCZY MOLINO MAZZOCHI SIWIK LLP, Chicago, Illinois.

Counsel for Defendants

MEMORANDUM OPINION

April 11, 2024

BIBAS, *Circuit Judge*, sitting by designation.

In its emergency-injunction motion, Galderma rehashes many of the same arguments that I rejected at trial. Unsurprisingly, that leads to the same result. I deny its motion for injunctive relief.

I. BACKGROUND

Galderma sells Oracea, a once-daily treatment for rosacea. D.I. 197, at 2. Oracea works by releasing doxycycline in two portions: a 30-mg immediate-release portion and a 10-mg delayed-release portion. *Id.* That maintains consistent steady-state blood levels of doxycycline, staving off rosacea. *Id.*

Hoping to make a generic version of Oracea, Lupin submitted an Abbreviated New Drug Application to the FDA. *Id.* at 3. The application described a drug with a 22-mg immediate-release portion and an 18-mg delayed-release portion. *Id.* at 3. But after the FDA tentatively approved it, Galderma sued Lupin for patent infringement. *Id.* at 4.

After a bench trial, I rejected Galderma's patent-infringement claim. *Id.* at 2, 19. I found that Galderma's sole witness, Dr. Edward Rudnic, was not credible. *Id.* at 11–12. And I concluded that no version of its ever-shifting theory of infringement satisfied its burden by a preponderance of evidence on the main contested issue: whether Lupin's drug contained a 30-mg immediate-release portion and a 10-mg delayed-release portion. *Id.* at 12–17. Rather, I ruled that the trial evidence confirmed that Lupin's drug contains a 22-mg immediate-release portion and an 18-mg delayed-release portion. *Id.* at 17.

Undeterred, Galderma now wants injunctive relief. It asks for an injunction to stop Lupin from manufacturing, marketing, selling, or using its generic drug during Galderma's appeal. Pls.' Emergency Mot. 1 (relying on 35 U.S.C. § 283 and Fed. R. Civ. P. 62(d)). It also asks for a temporary restraining order. *Id.* (relying on Fed. R. Civ. P. 65(b) and Fed. R. App. P. 8(a)).

II. INJUNCTIVE RELIEF IS NOT WARRANTED

"An injunction pending appeal is extraordinary relief … [that is] within the discretion of the district court." *Cipla Ltd. v. Amgen Inc.*, 2019 WL 2053055, at *1 (D. Del. May 9, 2019) (internal quotation marks omitted). To decide whether to grant injunctive relief here, I consider the usual four factors:

(1) Has Galderma made a strong showing that it is likely to succeed on the merits?

(2) Will it be irreparably injured without an injunction?

(3) Will the injunction substantially injure other interested parties?

(4) Does the public interest favor an injunction?

Hilton v. Braunskill, 481 U.S. 770, 776 (1987). To get an injunction, the moving party must show "*both* of the first two factors." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001). But because Galderma has shown neither, I deny its requested relief.

A. Galderma cannot show a likelihood of success on the merits

A likelihood of success cannot be "shown if an alleged infringer raises a substantial question regarding … infringement." *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015). Lupin has raised more than a substantial question about an essential element of infringement—the amount of its immediate- and delayed-release portions. So Galderma cannot show a likelihood of success on the merits.

To resist this conclusion, Galderma makes five arguments. All fail.

First, it argues that the Opinion incorrectly found that pH 4.5 is not biorelevant for a fasted stomach. Opening Br. 4. But its own evidence undermines its position:

The Kalantzi article, relied on by Dr. Rudnic at trial and Galderma in this motion, says that "the generally accepted value for fasting gastric pH … is usually measured to be about 2 or slightly lower." PTX-149, at 5–6. It also notes that when it did find higher stomach-pH values, "in most cases they probably reflect the dilution of gastric contents with saliva and/or nasal secretions." *Id.* at 5. And Galderma's entire theory of patent infringement relies on the behavior of Lupin's capsules at pH 4.5 (plus bioequivalence data). Thus, to win on appeal, it must prove that my factual finding on that point was clearly erroneous—a tall task.

Galderma also asserts that the Opinion improperly placed a thirty-minute cut-off between immediate and delayed release. Opening Br. 5. But even if that were true, it was harmless because I evaluated Galderma's theory at every time in the two-stage test that it suggested. *See* D.I. 197, at 16 (discussing doxycycline release at 30 minutes, 1 hour, and 2 hours after exposure to pH 4.5).

Second, Galderma argues that the Opinion misapplies Hatch-Waxman case law and "errs as a matter of law by dismissing the controlling data submitted in Lupin's [application]." Opening Br. 6. But I already considered and rejected those legal arguments in the Opinion. D.I. 197, at 15–17. And I explained in detail why a person of ordinary skill in the art would not have relied on the second stage of one test in Lupin's application to prove patent infringement, especially when Oracea's data displayed errors. *Id.* at 12–15.

Third, Galderma contends that I improperly considered results from Lupin's small batch manufactured during this litigation. But I have repeatedly addressed

and rejected this argument. *See* D.I. 152; D.I. 197, at 15–16. And even if it were error for me to consider the small batch, the testing on that batch merely reinforced the lack of patent infringement. *See* D.I. 197, at 15 ("Lupin gave yet another *clue* by doing more testing." (emphasis added)). So Galderma finds no succor in this argument either.

Fourth, Galderma claims that the Opinion "disregards … that even one instance of infringement is sufficient." Opening Br. 10. On its face, this claim is incredible: the Opinion stated that "if I credited that Capsule 1's behavior at 30 minutes into the second stage reflects *in vivo* behavior at that time in the stomach, Galderma would have shown infringement." D.I. 197, at 17. Galderma then plays a shell game, arguing that Judge Stark found "*in vitro* testing at the 30-minute time point is factually relevant." Opening Br. 10. I agree. But the testing Galderma relies on was 30 minutes *into the second stage*—in other words, at 150 minutes. *See* D.I. 197, at 7. And Galderma did not show that the *in vitro* test results in that second stage reliably correlate to results in the body.

Fifth, Galderma says that the Opinion disregards evidence of infringement based on mean release at later time points. Opening Br. 12. Not so. Rather, I simply did not find that its evidence supported infringement under the doctrine of equivalents. *See* D.I. 197, at 17–18. And Galderma cites no law to support this argument.

In sum, Galderma repeats many of the same arguments that I found thoroughly unconvincing at trial. Most of these arguments rely heavily on factual findings,

meaning they would need to overcome clear-error review. So Galderma has not made a "strong showing" that it is likely to succeed on the merits. *Hilton*, 481 U.S. at 776.

B. Galderma has not shown irreparable harm

The irreparable-harm inquiry looks for "harms that no damages payment, however great, could address." *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012). For a harm to be irreparable, "[m]ere injuries, … in terms of money, time[,] and energy necessarily expended in the absence of a stay, are not enough." *Sampson v. Murray*, 415 U.S. 61, 90 (1974).

Lupin argues that things have changed because it launched its drug. Updated Resp. Br. 14. Though it was within its rights to do so, it launched its drug while this emergency motion was pending and in an apparent attempt to change the status quo. I will not reward such gamesmanship by considering Lupin's argument on that point.

For its part, Galderma makes various arguments for irreparable injury, including: (1) losses in sales and market shares; (2) net price erosion from Lupin's entry; (3) loss of preferred status with Pharmacy Benefit Managers; (4) disruption to their workforce; (5) loss of research and development efforts; and (6) harm to reputation and loss of goodwill. Opening Br. 12–13.

Even accepting that Lupin's drug will cause the first three injuries, Galderma cannot show that they are irreparable. True, an independent generic entering the market will likely cause a decline in price and sales for Oracea. D.I. 204-1, at ¶ 38. But "branded drugs have been able to return to their long-term sales and prescriptions trends once exclusivity has been restored." D.I. 216-25, at 3. Plus, "courts have routinely decided that market share and price erosion do not amount to irreparable

harm." *King Pharms., Inc. v. Sandoz, Inc.*, 2010 WL 1957640, at *5 (D.N.J. May 17, 2010). And Galderma has already authorized a generic of Oracea. D.I. 204-1, at ¶ 15. So I credit the declaration of Lupin's expert that the losses suffered by Galderma would be quantifiable. D.I. 214, at ¶¶ 27, 58–61.

Nor does Galderma show that disruption to its workforce or loss of research and development will cause irreparable injury. True, a "potential reduction in work force" can be an irreparable injury. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006). As can loss of business opportunities, such as decreased research and development. *Celsis*, 664 F.3d at 930. But neither *always* amounts to irreparable injury. *See, e.g.*, *Eli Lilly & Co. v. Am. Cyanamid Co.*, 82 F.3d 1568, 1578 (Fed. Cir. 1996); *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 532 F. Supp. 2d 666, 682 (D.N.J. 2007) (rejecting irreparable harm based on "loss of research opportunities [and] reduction in workforce"). Plus, in 2023, Galderma had over $4 billion in sales, of which Oracea is less than fifty million. D.I. 214, at ¶ 52; D.I. 204-1, at ¶ 36. And Galderma does not show how many employees work solely on Oracea or what research and development opportunities it might lose due to Lupin's drug. D.I. 214, at ¶¶ 51, 53. These losses are thus speculative at best.

Finally, Galderma argues that it might suffer reputational damage because of quality issues with Lupin's product. Opening Br. 16. It gives the example of a generic rosacea cream that caused adverse events incorrectly attributed to the patented cream. *Id.* But that is a different drug. And Galderma points to nothing showing that

Lupin's drug would cause such adverse events. So I find that alleged injury speculative too.

"[D]elay [also]… militates against the issuance of an … injunction by demonstrating that there is no apparent urgency." *High Tech Med. Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1557 (Fed. Cir. 1995). And Galderma delayed: After closing arguments on February 22, 2024, I told the parties the outcome of the case. D.I. 193, at 49–55. Then, on March 22, 2024, I issued the Opinion to the parties under seal. D.I. 197. Still, Galderma waited until April 4, 2024, to file this emergency motion—three days before Lupin could get final approval from the FDA. Opening Br. 2. Though Galderma argues that the final judgment was not entered until April 1, that judgment contains what it already knew a month and a half earlier.

In sum, Galderma's "irreparable" injuries are either quantifiable or speculative. And its delay weighs against irreparable injury. So I find no irreparable injury.

* * * * *

Galderma shows neither a likelihood of success on the merits nor irreparable injury. But it needed to show both. Thus, I reject its request for the potent relief of an injunction or temporary restraining order.

EXHIBIT 9

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-691-GBW

JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-1138-GBW

JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-1594-GBW

HIGHLY CONFIDENTIAL

Videotaped Deposition of MARK RAINEY, Ph.D.

Boston, Massachusetts

Friday, November 17, 2023

9:03 a.m.

Job No.: 515237

Pages: 1 - 248

Reported By: Michelle Keegan, RMR, CRR, CSR

paragraph is a sustained-release oxybate formulation. Do you see that? 09:21:30 09:21:33

A. Yes. 09:21:35

Q. You do not have an opinion yourself about whether or not LUMRYZ is a sustained-release oxybate formulation. Correct? 09:21:41 09:21:43 09:21:47

A. No. I'm relying on -- make an assumption in my report that LUMRYZ infringes. 09:21:49 09:21:55

Q. So no, you don't have an opinion on that? Is that correct? Just to fix the double negative. 09:21:57 09:22:00

MS. RYCROFT: Objection, asked and answered. 09:22:03 09:22:04

A. Yes. I don't have an opinion. 09:22:05

Q. And the same is true with respect to the controlled release and modified release? You don't have an opinion as to whether or not LUMRYZ is or is not in fact one of those types of formulations? 09:22:09 09:22:11 09:22:13 09:22:15 09:22:18

A. Yes. 09:22:19

Q. It's correct you don't have an opinion? 09:22:22

A. It is. 09:22:24

Q. And you say in here you understand that other Jazz experts have opined on the technical scope of the asserted claims. Correct? 09:22:25 09:22:28 09:22:31

A. Yes. 09:22:33

Q. You, yourself, did not speak to Jazz's technical experts. Correct? 09:22:33 09:22:37

A. No. I reviewed their reports. 09:22:39

Q. And you didn't have any conversations? 09:22:41

A. I did not. 09:22:44

Q. Okay. I want to look at page 6, Section 4. It starts at Paragraph 25. 09:22:51 09:22:54

And this section you've labeled "Approach to Damages." Do you see that? 09:22:56 09:22:59

A. Yes. 09:23:00

Q. And you state in Paragraph 26 that two categories of damages available to compensate for patent infringement are, one, lost profits; and, two, a reasonable royalty. Do you see that? 09:23:00 09:23:07 09:23:10 09:23:13

A. Yes. 09:23:15

Q. You are offering in this case an opinion about a reasonable royalty. Correct? 09:23:16 09:23:22

A. Yes, that's right. 09:23:24

Q. You are not offering an opinion about lost profits damages. Correct? 09:23:26 09:23:32

A. That's correct. 09:23:33

Q. On page 7 there is a Footnote 20 in which you state that you are reserving the right to conduct a lost profits analysis if consolidation between this case and another case is granted. Do 09:23:33 09:23:41 09:23:45 09:23:50

you see that? 09:23:52
A. Yes. 09:23:52
Q. You are aware that consolidation was not granted? 09:23:53 09:23:59
A. I am aware there was a ruling on that. I don't know whether it's final or anything, but I'm aware there is a ruling on that. 09:24:04 09:24:06 09:24:10
Q. If consolidation is not granted, you will not be offering a lost profits opinion. Correct? 09:24:12 09:24:19
A. Yes. That's what I say in Footnote 20. 09:24:22
Q. You're not reserving the right to offer a lost profits opinion in any other circumstance other than consolidation. Correct? 09:24:24 09:24:31 09:24:34
A. That's what I say in Footnote 20. Correct. 09:24:38 09:24:41
Q. So -- 09:24:41
A. Although, to be clear, I should also say, elsewhere in my report I say that I reserve the right to respond to opinions of other experts. So if, for example, Dr. Meyer were to offer a lost profits opinion, I would reserve the right to respond to that. 09:24:50 09:24:53 09:24:56 09:25:00 09:25:04 09:25:06
Q. And that has not happened to date. Correct? 09:25:07 09:25:09
A. That has not happened to date, but I 09:25:09

understand that she will be testifying next week. 09:25:12
Q. Now, you have served as an expert before. 09:25:15
You're familiar with -- an expert previously. 09:25:20
You're familiar with the process of exchanging 09:25:23
reports? 09:25:24
A. Yes. 09:25:25
Q. And you, in fact, reviewed a report from 09:25:28
Dr. Meyer? 09:25:31
A. Yes, I did. 09:25:31
Q. You responded to that report? 09:25:32
A. Yes. 09:25:38
Q. In neither your opening report nor your 09:25:38
reply report did you offer a lost profits 09:25:40
analysis. Correct? 09:25:43
A. That's correct. It's a reasonable royalty 09:25:43
analysis. 09:25:46
Q. And you're aware that, as a general 09:25:46
matter, that's the end of the reports, opening 09:25:50
report, answering report, reply report? 09:25:54
MS. RYCROFT: Objection, asking for a 09:25:57
legal conclusion. 09:25:59
A. I've been involved in lots of cases over 09:26:00
the years. Sometimes -- I mean, things happen. 09:26:03
So I can't say that categorically that that's 09:26:06
always the case. 09:26:11

Q. Okay. Can you look in Paragraph 27 of your report, your opening report. And this is a paragraph talking about lost profits. Do you see that? 09:26:11 09:26:27 09:26:31 09:26:36

A. Yes. 09:26:36

Q. You state, "The lost profits calculation assesses the actual damages to a patentee whose sales are affected by the infringement." Do you see that? 09:26:36 09:26:38 09:26:42 09:26:44

A. Yes. 09:26:44

Q. Now, you in the past, not in this case but elsewhere, have done a lost profits analysis. Correct? 09:26:45 09:26:51 09:26:54

A. Yes, that's correct. 09:26:54

Q. You have in the past offered a lost profits opinion as an alternative to a reasonable royalty. Is that right? 09:26:55 09:26:59 09:27:03

A. Yes. I mean, it's both as a testifying expert and as a consulting expert, I've worked on cases where there have been both a lost profits analysis and a reasonable royalty analysis. And the reasonable royalty applies to that portion of sales to which the lost profits does not apply. 09:27:04 09:27:15 09:27:18 09:27:21 09:27:26 09:27:31

Q. You can't have both lost profits and reasonable royalty on the same set of sales? 09:27:34 09:27:37

A. That's correct. 09:27:39
Q. When you conducted lost profits analysis 09:27:43
in the past, did you apply a test known as the 09:27:46
Panduit factors? 09:27:54
A. Yes. 09:27:56
Q. You're familiar with the test that can be 09:27:56
used to analyze lost profits? 09:27:59
A. Yes. 09:28:01
Q. There are four Panduit factors. Is that 09:28:02
right? 09:28:08
A. Yes, that's correct. 09:28:08
Q. And so in the past when you provided a 09:28:09
lost profits opinion, you analyzed those four 09:28:11
factors? 09:28:14
A. Yes. 09:28:15
Q. Panduit factors require the patent owner 09:28:15
to prove, one, demand for the patented product; 09:28:19
two, absence of acceptable noninfringing 09:28:24
substitutes; three, manufacturing and marketing 09:28:28
capability to exploit demand; and four, the amount 09:28:31
of the profit the patentee would have made. 09:28:34
Is that your understanding of the test? 09:28:36
A. That sounds correct. 09:28:38
Q. You did not apply that test here. 09:28:39
Correct? 09:28:41

A. Correct. Because I was doing a reasonable royalty analysis, not a lost profits analysis. 09:28:41 09:28:46

Q. You are qualified to do a lost profits analysis, in your opinion? 09:28:48 09:28:51

A. Yes. 09:28:52

Q. Did you have available to you information from which you believe you could have done a lost profits analysis in this case? 09:28:52 09:28:59 09:29:01

A. I didn't attempt to perform a lost profits analysis. So I don't know that I -- I believe that would be the case. But since I didn't perform that analysis, I can't say that with 100 percent certainty. 09:29:03 09:29:20 09:29:32 09:29:35 09:29:39

Q. There might be information missing that you would need to do a lost profits analysis? 09:29:40 09:29:41

MS. RYCROFT: Objection, calls for speculation, assumes facts not in evidence. 09:29:44 09:29:45

A. Yeah. I just don't know whether that would be the case or not. 09:29:48 09:29:57

Q. You were aware that there have been sales of LUMRYZ. Correct? 09:29:57 09:30:00

A. Yes. 09:30:01

Q. You have evidence of the sales of LUMRYZ? 09:30:03

A. Yes, I do. 09:30:05

Q. You could have done a lost profits 09:30:06

analysis for the few months of sales of LUMRYZ that exist? You're qualified to do that? 09:30:14 09:30:17

A. Yes. 09:30:19

Q. There's no rule you're aware of that prevents a lost profits analysis from being done when it's only a few months of sales. Correct? 09:30:20 09:30:24 09:30:27

A. Not that I'm aware of. No. 09:30:30

Q. So it is theoretically possible that you could have done a lost profits analysis with the few months of LUMRYZ sales to date? 09:30:34 09:30:38 09:30:42

MS. RYCROFT: Objection to the extent it calls for a legal conclusion. 09:30:44 09:30:45

A. I guess in theory that's the case. Yes. 09:30:47

Q. But you didn't do it? 09:30:50

A. I did a reasonable royalty analysis. 09:30:52

Q. You do not know whether or not Jazz has lost any profits as a result of the sales of LUMRYZ to date? 09:30:56 09:31:03 09:31:06

A. I didn't -- I have not performed a calculation relating to that, since I did a reasonable royalty instead of a lost profits analysis. So I didn't do that calculation. 09:31:12 09:31:15 09:31:20 09:31:22

Q. And so it's correct that you do not know whether or not Jazz has, in fact, lost any profits up through the set of sales that you had available 09:31:24 09:31:28 09:31:34

to you? 09:31:36

A. Yes. I didn't perform a calculation of 09:31:36

that. 09:31:43

Q. When you did lost profits in the past, the 09:31:43

set of sales that you looked at was past sales. 09:31:50

Correct? 09:31:54

MS. RYCROFT: Objection, ambiguous. 09:32:01

A. I believe that's the case. I don't recall 09:32:08

100 percent, but I think that's probably correct. 09:32:14

Q. The lost profits analysis looks at past 09:32:16

sales and attempts to determine with respect to 09:32:22

past sales what profits have been lost. Correct? 09:32:27

MS. RYCROFT: Objection to the extent it 09:32:31

calls for a legal conclusion. 09:32:33

A. That's generally the way a lost profits 09:32:34

calculation is performed. 09:32:40

Q. Lost profits calculations, in your 09:32:41

experience, are not performed on a forward-looking 09:32:44

basis for sales that have not happened? 09:32:50

MS. RYCROFT: Objection to the extent that 09:32:52

it calls for a legal conclusion, assumes facts not 09:32:54

in evidence. 09:32:57

A. Yeah. I don't know whether that's -- I 09:32:58

just don't recall whether that's something I've 09:33:09

looked at before in regards to lost profits or 09:33:11

not. 09:33:15

Q. Sitting here today, have you, yourself, 09:33:15

ever done a lost profits analysis that attempted 09:33:17

to calculate future lost profits that have not -- 09:33:20

for sales that have not happened? 09:33:24

A. Not that I recall. But again, I can't 09:33:26

rule it out. I can't -- I don't recall anything 09:33:33

specifically like that. 09:33:38

Q. You've only done a lost profits analysis 09:33:38

with respect to historical sales? 09:33:41

A. To the -- to the best of my recollection, 09:33:42

that's correct. 09:33:50

Q. Looking at your opening report, 09:33:54

Paragraph 28, you talk about a reasonable royalty. 09:34:01

Are you there? 09:34:04

A. Yes. 09:34:05

Q. You offer the opinion that a reasonable 09:34:06

royalty is the amount that the patentee as a 09:34:10

willing licensor would have agreed to accept and 09:34:14

that the accused infringer as a willing licensee 09:34:17

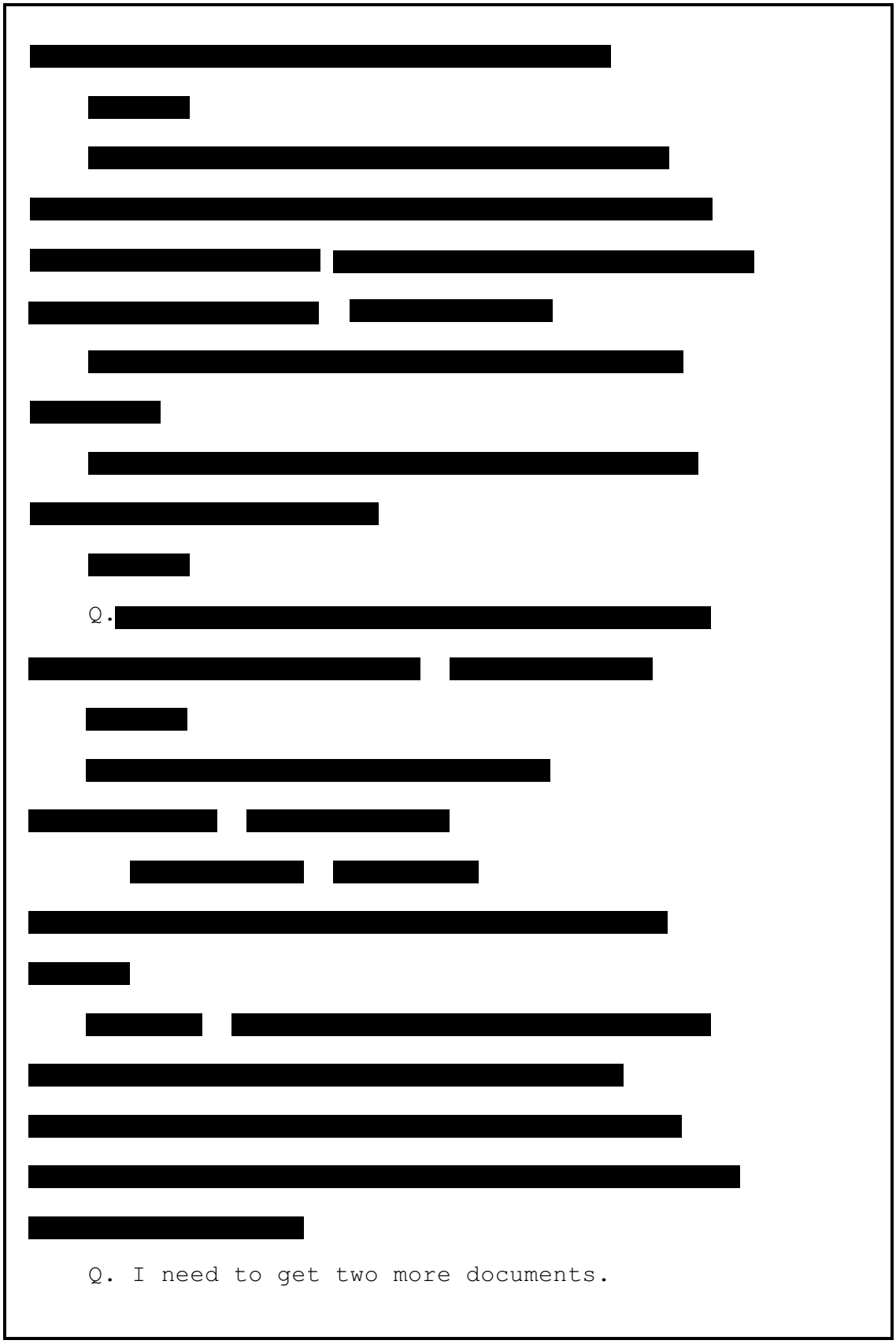
would have agreed to pay, had they both 09:34:20

voluntarily and reasonably tried to reach an 09:34:22

agreement for a license to the asserted patent. 09:34:25

Do you see that? 09:34:29

A. Yes. 09:34:30



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12	Q. [redacted]	10:35:43
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24	[redacted]	10:36:23
25	Q. I need to get two more documents.	10:36:24

(Rainey Exhibits 9 and 10 were marked for identification and are attached to the transcript.) 10:37:14

Q. [redacted] 10:37:14

[redacted] 10:37:21

[redacted] 10:37:25

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[redacted] 10:37:33

Q. You considered these two agreements in connection with preparing your opinions in this case. Correct? 10:37:34 10:37:41 10:37:44

A. Yes. I reviewed them. 10:37:44

Q. And you considered Jazz's agreements with generic manufacturers of XYREM, including these two, to be relevant to illustrate general economic principles. Correct? 10:37:47 10:37:53 10:37:56 10:38:01

A. In certain respects, yes. 10:38:02

Q. [redacted] 10:38:05

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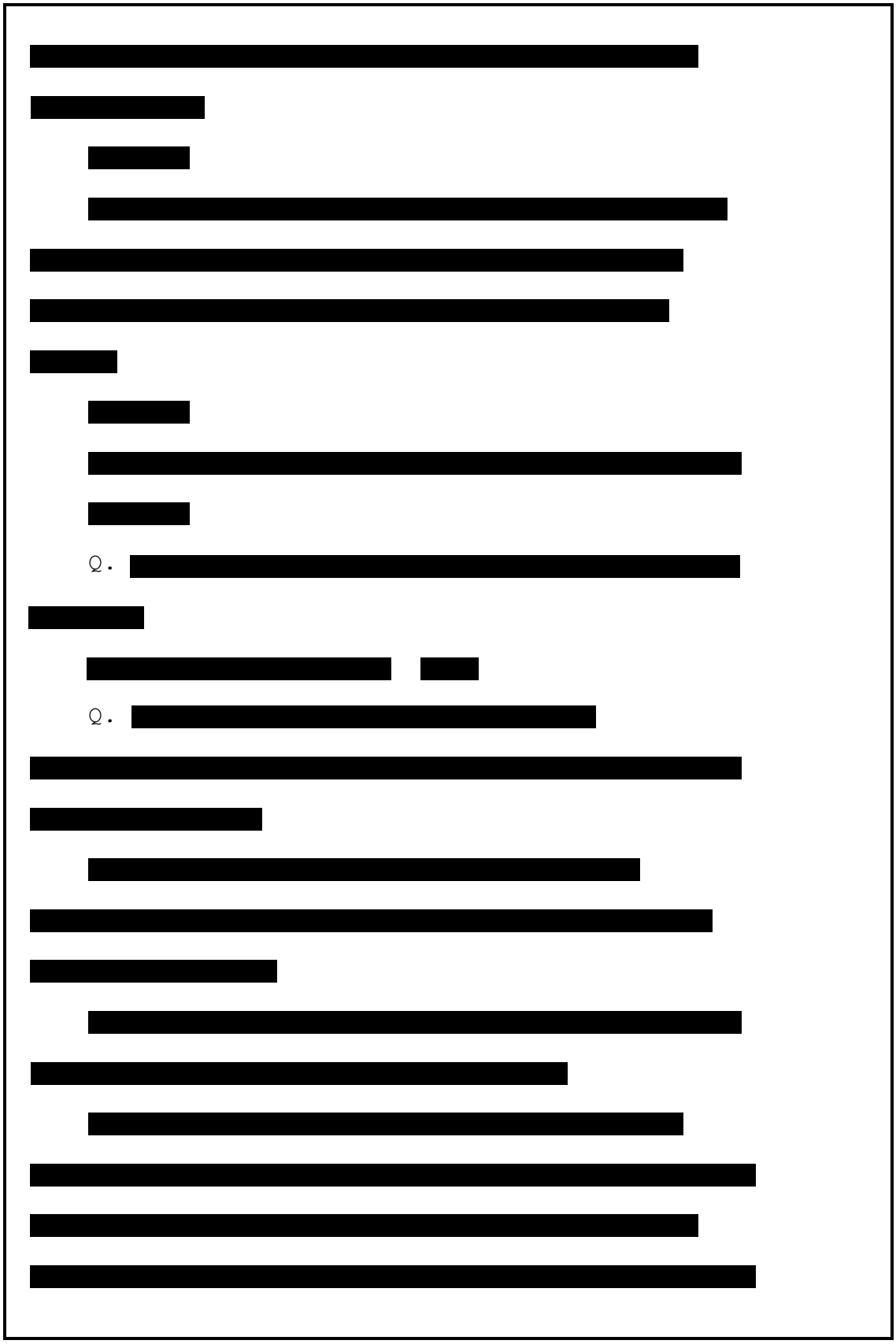

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11	Q. [redacted]	10:38:50
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13	[redacted]	10:38:55
14	Q. [redacted]	10:38:58
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22	[redacted]	10:39:35
23	[redacted]	10:39:42
24	[redacted]	10:39:47
25	[redacted]	10:39:49

Q. [redacted] 10:39:53

[redacted] 10:39:56

[redacted] 10:39:58

[redacted] 10:40:01

[redacted] 10:40:02

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MS. RYCROFT: Objection, calls for speculation. 10:40:19 10:40:21

A. [redacted] 10:40:21

[redacted] 10:40:24

[redacted] 10:40:27

[redacted] 10:40:35

[redacted] 10:40:38

[redacted] 10:40:40

[redacted] 10:40:42

MS. RYCROFT: Objection, calls for speculation. 10:40:43 10:40:46

Q. Do you have an understanding of what the relevant circumstances will be in the market as of December 31st, 2025, with respect to XYREM sales? 10:40:46 10:40:49 10:40:53

MS. RYCROFT: Objection, incomplete hypothetical, speculation. 10:41:02 10:41:04

A. Can you repeat the question? 10:41:05

Q. Do you have an understanding of what the relevant circumstances will be in the market as of December 31st, 2025, with respect to XYREM sales? 10:41:15 10:41:16 10:41:20

MS. RYCROFT: Objection, incomplete hypothetical, calls for speculation, also to the extent it calls for a legal conclusion. 10:41:25 10:41:28 10:41:30

A. That's something that's going to be occurring over two years in the future, so I don't know precisely what the market will look like at that point. 10:41:32 10:41:39 10:41:42 10:41:44

Q. Patients can't take at the same time a generic version of XYREM and XYREM itself. Correct? 10:41:44 10:41:49 10:41:52

A. I think that sounds highly unlikely. 10:41:52

Q. Sodium oxybate is a drug with -- that is -- the distribution of which is carefully controlled. Is that right? 10:42:00 10:42:11 10:42:14

A. Yes, that's correct. 10:42:15

Q. You would not expect there to be any patients who are simultaneously taking generic XYREM and XYREM. Correct? 10:42:15 10:42:18 10:42:23

A. It seems unlikely. 10:42:25

Q. [redacted] 10:42:26 10:42:34 10:42:40

A. [redacted] 10:42:44

[redacted] 10:42:59

[redacted] 10:43:07

[redacted] 10:43:10

[redacted] 10:43:10

[redacted] 10:43:16

[redacted] 10:43:20

MS. RYCROFT: Objection, incomplete hypothetical, calls for speculation. 10:43:23 10:43:25

A. [redacted] 10:43:27

Q. Did you do anything to look into whether or not Jazz considers future sales of generic XYREM to result in harm to Jazz? 10:43:31 10:43:33 10:43:39

A. In thinking about the XYREM settlement agreements, as I explained in my report, I took into account the fact that they were settlement agreements and hence that there was uncertainty about invalidity and infringement of the patents. 10:43:44 10:44:01 10:44:07 10:44:09 10:44:11

I also took into account the fact that there were multiple generic manufacturers that made the settlements. I think we're up to ten at this point. 10:44:17 10:44:19 10:44:31 10:44:34

So I think in those circumstances the -- I think those circumstances I think help explain economically the royalty rates that you see in 10:44:36 10:44:51 10:44:56

these agreements. 10:44:59

Q. When multisource generics start being 10:45:01

sold, do you agree that Jazz will make fewer sales 10:45:08

of XYREM because of the multisource generics being 10:45:11

available? 10:45:16

A. It's possible. Yes. 10:45:16

Q. Is it possible or is it in fact certain 10:45:22

that Jazz will make fewer sales at that point in 10:45:24

time? 10:45:26

A. I don't think it's 100 percent certain 10:45:27

just because the timing is unknown and Jazz is in 10:45:33

the process of transitioning patients from XYREM 10:45:41

to XYWAV. I don't think it's 100 percent certain. 10:45:46

Q. When you mentioned timing, is the timing 10:45:52

that is unknown the entry date for multisource 10:45:54

generics? 10:45:58

A. Yes. That's primarily what I was thinking 10:45:58

of. 10:46:05

Q. [redacted] 10:46:05

[redacted] 10:46:11

[redacted] 10:46:15

Q. And the fact that that timing is uncertain 10:46:15

causes you to be uncertain as of the date that 10:46:23

Jazz will lose sales to the multisource generics? 10:46:27

MS. RYCROFT: Objection, 10:46:31

mischaracterization.

A. It causes uncertainty about whether -- for the reasons I explained in my previous answer, what the status of Jazz's portfolio looks like at the time of launch.

Q. At the time of launch of multisource generics?

A. Yes.

Q. So there is uncertainty as to the status of Jazz's portfolio, what it will look like as of the time of launch of multisource generics?

A. Yes. I mean, it's not known with certainty.

Q. When the multisource generics do start being sold, do you agree that Jazz will lose sales to them to at least some degree?

A. Like I said before, not with 100 percent certainty. There's certainly a possibility that they will lose sales to at least some degree.

[redacted]

[redacted]. 10:48:02

10:48:04

Q. And the circumstances in which these agreements were reached that you just mentioned, you referenced -- you meant what about that? 10:48:06 10:48:10 10:48:13

A. I mentioned that these were license agreements that were entered into as part of the settlement of litigation about the XYREM patents. So there was uncertainty about, say, the validity of the XYREM patents at the time these were entered into. 10:48:20 10:48:23 10:48:25 10:48:28 10:48:33 10:48:35

Q. And the second item you mentioned was the competitive situation with the number of generic manufacturers. Is that right? 10:48:35 10:48:38 10:48:41

A. Yes. 10:48:41

Q. And what did you mean by that? 10:48:42

A. So there are -- I think we're up to ten generic manufacturers with this that have this license agreement to sell generic XYREM. 10:48:44 10:48:50 10:48:55

And so in that competitive situation, there are ten manufacturers selling a nondifferentiated product. So it's going to be a highly competitive market. 10:49:01 10:49:04 10:49:06 10:49:08

Q. [redacted] 10:49:09

[redacted] 10:49:15

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[redacted]. 10:50:55

Q. Have you ever considered settlement agreements in the past when -- specifically for purposes of using their royalty rates when conducting a damages analysis? 10:50:57 10:51:00 10:51:06 10:51:09

A. I don't recall specifically. 10:51:11

Q. Is it possible that you considered a settlement agreement royalty rate when conducting a reasonable royalty damages analysis? 10:51:22 10:51:24 10:51:27

A. It's possible I would have considered it and analyzed the circumstances of the settlement. Whether I would have relied on it, it would have depended on whether I thought the circumstances were comparable enough to make it reliable. 10:51:29 10:51:36 10:51:44 10:51:46 10:51:49

Q. Can you turn in your opening report to page 12. You have a heading that refers to Jazz intercompany licenses. Are you there? 10:51:54 10:51:59 10:52:16

A. Yes. 10:52:17

Q. Your conclusion was that the Jazz intercompany licenses did not provide a royalty rate for purposes of the reasonable royalty calculation here. Is that right? 10:52:18 10:52:24 10:52:29 10:52:33

A. Yeah. What I said in my report, Paragraph 55, was that it does not prove and establish a royalty for the patents in suit. 10:52:34 10:52:37 10:52:42

Q. And the same is also true of Avadel intercompany licenses. Correct? 10:52:44 10:52:49

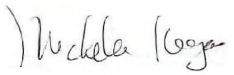
A. Yes. I concluded in Paragraph 68 of my opening report that the agreements between Avadel, CNS, and Flamel are not relevant to the hypothetical negotiation between Jazz and Avadel. 10:52:51 10:53:08 10:53:12 10:53:17

CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

I, MICHELLE KEEGAN, Registered Merit Reporter and Notary Public in and for the Commonwealth of Massachusetts, the officer before whom the foregoing deposition was taken, do hereby certify that the foregoing transcript is a true and correct record of the testimony given; that said testimony was taken by me stenographically and thereafter reduced to typewriting under my direction; that reading and signing was requested; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 20th day of November, 2023.

My commission expires May 15, 2026.



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The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on May 13, 2024 on the following counsel in the manner indicated below.

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