CNS Drugs (2023) 37:323–335
https://doi.org/10.1007/s40263-023-00992-y

ORIGINAL RESEARCH ARTICLE

Long-Term Safety and Tolerability During a Clinical Trial and Open-Label Extension of Low-Sodium Oxybate in Participants with Narcolepsy with Cataplexy

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Accepted: 13 February 2023 / Published online: 22 March 2023

Abstract

Background The safety and efficacy of low-sodium oxybate (LXB; Xywav®) were established in a randomized, double-blind, placebo-controlled, phase 3 withdrawal study in adults with narcolepsy with cataplexy; however, the longer-term safety profile has not yet been examined. The aim of the current analysis was to assess the time of onset and duration of common treatment-emergent adverse events (TEAEs) for LXB throughout the open-label optimized treatment and titration period (OLOTTP) and the stable dose period (SDP) portions of the main study, and the subsequent 24-week open-label extension (OLE).

Methods In a double-blind, placebo-controlled, randomized withdrawal trial of LXB, TEAEs were evaluated during the 12-week OLOTTP, the 2-week SDP, and the subsequent 24-week OLE. Eligible participants were aged 18–70 years with a diagnosis of narcolepsy with cataplexy. At study entry, participants were taking sodium oxybate (SXB) alone, SXB with other anticataplectics, other anticataplectics alone, or were anticataplectic-treatment naive; other anticataplectics were tapered and discontinued during the OLOTTP. All participants initiated LXB during week 1 of the OLOTTP, and their dose was individually titrated based on safety and efficacy. Following the main study period, participants entered the OLE after rescreening (re-entry) after discontinuing LXB treatment or directly after completing the main study (rollover). TEAEs were assessed in the safety population as of database lock. TEAE duration was defined as time from TEAE start date to end date (or end of SDP or OLE, if end date was unrecorded).

Results The safety population included 201 participants (SXB alone, $n = 52$; SXB with other anticataplectics, $n = 23$; other anticataplectics alone, $n = 36$; anticataplectic-treatment naive, $n = 90$). During the OLOTTP/SDP, headache was the most common LXB-emergent TEAE overall (71 events; $n = 42$ (21%); median (range) duration = 1 (1–147) day), followed by nausea (31 events; $n = 26$ (13%); median (range) duration = 9 (1–54) days) and dizziness (26 events; $n = 21$ (10%); median (range) duration = 7 (1–117) days). Among the 74 participants in the OLE, the most commonly reported TEAEs were headache (14 events; $n = 7$, 9%; peak incidence month 3 ($n = 5/72$); median (range) duration = 1 (1−25) day), dizziness (8 events; $n = 5$, 7%; peak incidence month 1 ($n = 3/74$); median (range) duration = 26 (1−181) days), and nasopharyngitis (6 events; $n = 6$, 8%; peak incidence month 6 ($n = 2/69$); median (range) duration = 9 (1−24) days). Overall, study discontinuations attributed to TEAEs were 21/65 (32%) during the OLOTTP and SDP and 3/7 (43%) during the OLE.

Conclusions In this long-term analysis, the safety and tolerability profile of LXB was generally consistent with the known safety profile of SXB. During the OLOTTP and SDP, most TEAEs occurred early and were generally of short duration. TEAE prevalence decreased throughout the duration of the OLE; the most common TEAEs reported during the OLE were headache, dizziness, and nasopharyngitis.

Trial registration ClinicalTrials.gov identifier NCT03030599 (25 January 2017).

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Graphical abstract

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PEER-REVIEWED FEATURE

Long-term Safety During a Clinical Trial and Open-Label Extension of Low-Sodium Oxybate in Participants With Narcolepsy With Cataplexy

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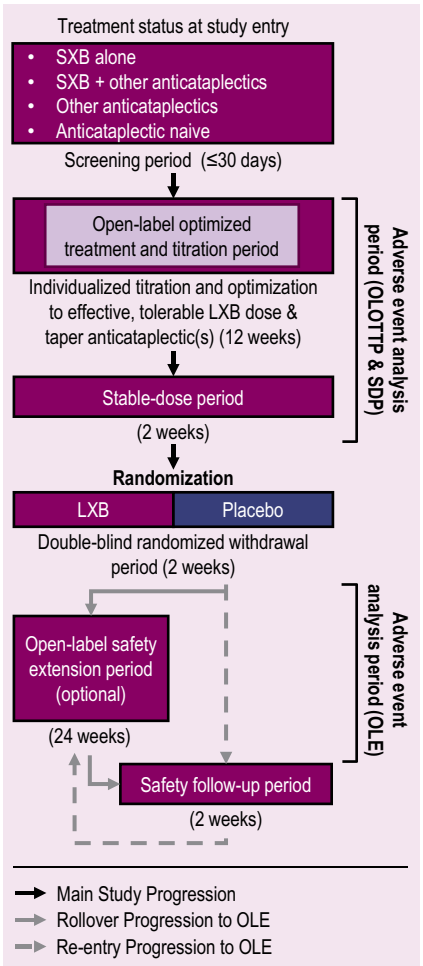
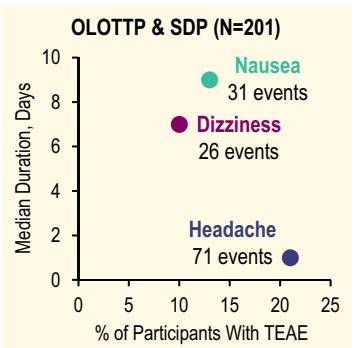
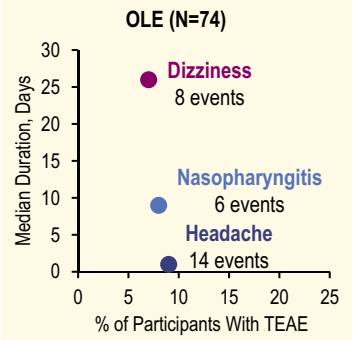
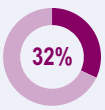
Background

The long-term safety of low-sodium oxybate (LXB; Xywav®) was evaluated during the open-label periods (12-week OLOTTP & 2-week SDP; 24-week OLE) of a double-blind, placebo-controlled, randomized withdrawal trial.









OLOTTP & SDP: 21/65 discontinuations were attributed to TEAEs.

OLE: 3/7 discontinuations were attributed to TEAEs.

Conclusions

- The safety and tolerability profile of LXB was consistent with that of SXB.
- During the OLOTTP and SDP, most TEAEs occurred early and were of short duration; prevalence decreased throughout the OLE.
- The most common TEAEs reported during the OLE were headache, dizziness, and nasopharyngitis.

LXB, low-sodium oxybate; OLE, open-label extension; OLOTTP, open-label optimized treatment and titration period; SDP, stable-dose period; SXB, sodium oxybate; TEAE, treatment-emergent adverse event.

Plain Language Summary

Low-sodium oxybate (LXB) is a medicine for narcolepsy. LXB treats daytime sleepiness and cataplexy (sudden muscle weakness). LXB is like sodium oxybate (SXB) but has 92% less sodium. This study looked at side effects in people taking LXB for many months. Three study periods were looked at in this report. In period 1, people could change their LXB dose for 12 weeks. This was to find their best dose. In period 2, people took that same best dose for 2 weeks. In period 3, some people kept taking LXB for 24 weeks. This was to study the longer-term effects. Everyone knew that they were taking LXB. During periods 1 and 2, the most common side effect was headache. Nausea and dizziness were also common. During period 3, headache was also the most common side effect. Dizziness and nasopharyngitis were also common. Nasopharyngitis is a cold in the nose and throat. In periods 1 and 2, most side effects happened early on. They also ended quickly. Fewer side effects happened in period 3. Among people leaving the study early, 32% left because of side effects during periods 1 and 2. During period 3, 43% left because of side effects. Overall, long-term side effects in people taking LXB were similar to those seen with SXB.

Key Points

This analysis of treatment-emergent adverse events during the open-label treatment titration and optimization, stable dose, and extension periods of a phase 3 study in participants with narcolepsy found that the safety and tolerability profile of low-sodium oxybate was generally consistent with the known safety profile of sodium oxybate.

The incidence of treatment-emergent adverse events declined over time across the duration of the study, and most events were of short duration.

The most common treatment-emergent adverse events reported with longer-term low-sodium oxybate use were headache, dizziness, and nasopharyngitis.

The most common treatment-emergent adverse events leading to discontinuation during the main study period were cataplexy, headache, nausea, and psychiatric disorders; of these, only headache was common during the open-label extension.

1 Introduction

Narcolepsy is a central disorder of hypersomnolence with two subtypes (type 1 (NT1) and type 2 (NT2)); the estimated overall prevalence is 30.6–56.3 per 100,000 persons in the USA [1–4]. The primary symptom of narcolepsy is excessive daytime sleepiness, which is experienced by all patients. Cataplexy, the sudden loss of muscle tone, is present only in NT1; patients of both subtypes also often experience hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted night-time sleep [3, 5, 6]. Sodium oxybate (SXB; Xyrem®) is a central nervous system depressant recommended by the American Academy of Sleep Medicine and in European guidelines for the treatment of cataplexy or excessive daytime sleepiness in patients with narcolepsy [7–9]. Low-sodium oxybate (LXB; Xywav®) is an oxybate medication with the same active moiety at the same concentration as SXB and a unique composition of cations resulting in 92% less sodium [10–13]. The US Food and Drug Administration (FDA) approved LXB in July 2020 for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy [14, 15]. In June 2021, the FDA's Office of Orphan Products Development granted Orphan Drug Exclusivity to LXB, indicating in their summary that LXB is clinically superior to SXB by means of greater safety because LXB provides a greatly reduced sodium burden and the differences in sodium content would be clinically meaningful in a substantial portion of patients for whom the drug is indicated [16].

The safety profile of SXB in participants with narcolepsy has been characterized over multiple clinical trials. Across these studies, the most frequently reported adverse events have included headache, nausea, dizziness, vomiting, somnolence, enuresis, and tremor [9, 17–20]. In terms of their timing, adverse events associated with SXB have been reported to occur primarily early on in the treatment course with diminishing frequency over time [17]. Adverse events associated with open-label SXB treatment were also reported over a 12-month period in a long-term analysis [21]. Similar to shorter-term studies, the most commonly reported adverse events were headache, nausea, viral infection, dizziness, pain, enuresis, and somnolence. One case study reported on four instances of psychosis after the introduction of SXB, which occurred in patients with no family history of psychiatric disease. However, symptoms

in this small group seemed to resolve with the tapering of SXB [22].

While SXB was approved in 2002, it has become increasingly established in clinical practice for a number of years in the treatment of narcolepsy compared to other medications, some of which have been in use longer [9]. According to one study published in 2022 in Sweden, the most utilized treatments for narcolepsy between 2005 and 2017 were modafinil, antidepressants, and amphetamines, which were found to have been mostly initiated prior to 2005 [23]. SXB, along with dexamphetamine and lisdexamphetamine, were prescribed mainly after 2014. Therefore, long-term data are desirable to evaluate the effects of SXB and other oxybate formulations in patients with narcolepsy. Additionally, patients with narcolepsy treated with SXB had more outpatient narcolepsy-related visits than those treated with other medications, indicating that SXB was used to treat patients with more severe symptomology compared to other medications, and demonstrating its utility in this disease space [23]. SXB is also an economical option for management of narcolepsy. In one Scandinavian study, SXB was found to be cost effective and efficient, and to involve lower healthcare utilization than other medications in the treatment of narcolepsy [24].

The safety and efficacy of LXB were established in a phase 3, placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy (NCT03030599); however, the longer-term safety profile of LXB has not been examined. In the main study period of the phase 3 randomized withdrawal study, treatment-emergent adverse events (TEAEs) were reported by 76.1% of participants overall and were less frequent in participants who were taking SXB alone at study entry, prior to transitioning to LXB. The most common TEAEs associated with LXB were headache (20%), nausea (13%), and dizziness (10%). The aim of the current analysis was to assess the time of onset and duration of common TEAEs throughout the open-label optimized treatment and titration period (OLOTTP) and stable-dose period (SDP) portions of the main study, and the subsequent 24-week open-label extension (OLE).

2 Methods

2.1 Study Design

The study design and outcomes relating to the primary and key secondary endpoints have been reported previously [10] and are summarized here. The main study comprised a screening period, a 12-week OLOTTP, a 2-week SDP, and a 2-week double-blind randomized withdrawal period (DBRWP). Following these study periods, participants who had completed the DBRWP could enroll in an optional 24-week OLE (Fig. 1). Participants entering the OLE could do so either directly after completing the main study (i.e., with no gap in enrollment—termed "rollover"), or they could re-enter at a later date after completing the main study (i.e., with a gap—termed "re-entry"). There was a safety follow-up visit either 2 weeks after DBRWP or 2 weeks after the OLE, depending on participants' enrollment in the optional OLE.

The study was approved by institutional review boards or ethics committees at all sites and was performed in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent. ClinicalTrials.gov identifier, NCT03030599 (25 January 2017).

2.2 Participants

Eligible participants were adults (18–70 years of age) who had been diagnosed with narcolepsy with cataplexy

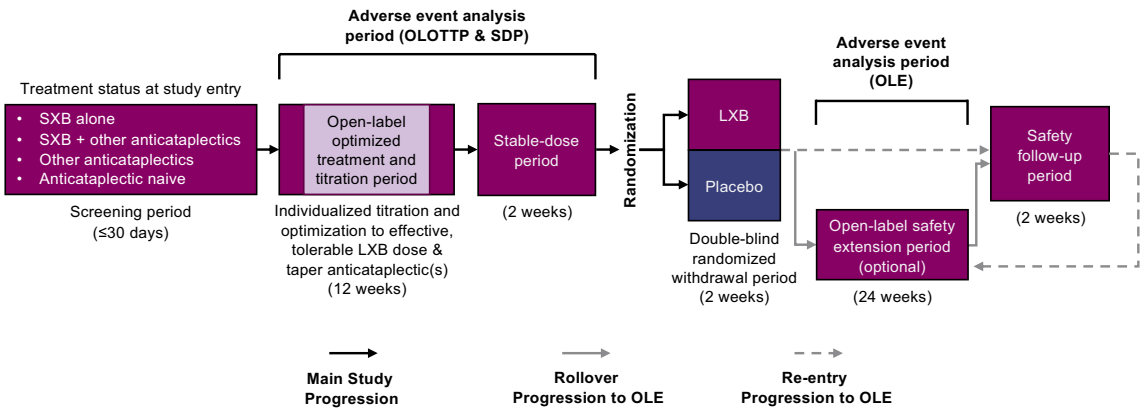


Fig. 1 Study design. *LXB* low-sodium oxybate, *OLE* open-label extension, *OLOTTP* open-label optimized treatment and titration period, *SDP* stable-dose period, *SXB* sodium oxybate

based on criteria from the International Classification of Sleep Disorders, 3rd Edition (NT1) [6, 25] or Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [26]. Participants currently taking medication(s) for narcolepsy were eligible only if they had been taking a stable regimen of that medication for at least 2 months prior to study entry. Participants who were taking SXB at study entry were required to have prior documented improvement in cataplexy and excessive daytime sleepiness with SXB treatment. Participants who were taking wake-promoting agents (such as modafinil, armodafinil, and pitolisant) or stimulants at study entry were required to remain on the same dose and regimen throughout the duration of the study. Participants were categorized as taking SXB but not other anticataplectics (SXB alone), SXB with other anticataplectics, anticataplectics other than SXB (other anticataplectics alone), or as anticataplectic-treatment naive. Anticataplectics other than SXB included antidepressants and pitolisant.

2.3 Treatments

Across all groups, participants initiated LXB treatment during week 1 of the OLOTTP and underwent individualized optimization of dosing based on efficacy and tolerability.

Participants taking SXB alone at study entry initiated LXB at a dose equivalent to their nightly SXB dose (gram-for-gram) and remained on that dose of LXB during the first 2 weeks of OLOTTP. Titration of LXB occurred, if needed, during the following 8 weeks at a rate of up to 1.5 g/night per week, with a maximum dose of 9 g/night split across two doses (except for two participants who entered taking SXB thrice nightly) [14].

Participants taking SXB and other anticataplectics at baseline were switched to LXB gram-for-gram. They continued taking this dose of LXB and a stable dose of anticataplectics for the first 2 weeks of the OLOTTP. From week 3 onwards, these prior anticataplectic medications were tapered (the rate of which was determined by investigator discretion) and discontinued, with discontinuation by week 10 or earlier. During this time, the dose of LXB could also have been further titrated if necessary, as already described. If needed, additional time for tapering and withdrawal of prior anticataplectic medications was permitted through week 12.

Participants taking other anticataplectics without SXB at study entry had their dose of LXB titrated to a tolerable level over the first 2 weeks of the OLOTTP and remained on a stable dose of their prior anticataplectics during this time. After this initial titration of LXB, prior anticataplectic medications were tapered (the rate of which was determined by investigator discretion) and discontinued from week 3 to week 10, with discontinuation by week 10 or earlier. During this 8-week period, the dose of LXB could also have been further titrated if necessary.

Treatment-naive participants initiated LXB at a dose of 4.5 g/night (split across two doses), after which dosing optimization occurred over a minimum of 2 weeks. Dose adjustments proceeded at the same rate as for those previously taking SXB: up to 1.5 g/night at weekly intervals (maximum dose: 9 g/night, split across two doses).

During the subsequent 2-week SDP, all participants took their individually optimized dose of LXB. At the end of SDP, participants were randomized 1:1 to continue LXB treatment or take placebo during the 2-week DBRWP. Randomization was performed based on a code prepared by a statistician who was not involved in the analysis of the study. Investigators randomized participants by accessing an interactive response system.

Among participants who enrolled in the OLE, those in the re-entry group initiated LXB at 4.5 g/night or, if taking SXB during rescreening, transitioned to LXB gram-for-gram. Any additional non-SXB anticataplectics were required to be tapered during the initial 12 weeks of the OLE.

Participants who rolled over directly after completing the DBRWP re-initiated LXB at a dose that was ≤ 50% of their prior stable dose to decrease the potential for TEAEs in those participants who had been randomized to placebo during DBRWP. Regardless of their mode of entry to the OLE, participants titrated according to the same schedule (up to 1.5 g/night/week) to a maximum of 9 g/night (split across two doses).

2.4 Statistical Analyses

This article reports the results of analyses performed over two time periods: a week-by-week analysis of TEAEs during the 12-week OLOTTP (while other anticataplectics were tapered/discontinued) and subsequent 2-week SDP, and a second month-by-month analysis of TEAEs during the 24-week OLE. In both analyses, TEAEs were evaluated in the safety population as of database lock (participants who took one or more study drug dose). TEAEs of interest were defined for each analysis as those occurring in ≥ 5% of the total study population during the specified timeframe. For TEAEs identified, incidence of a new occurrence or increased severity (worsening) over time was calculated within each time period (weeks for OLOTTP/SDP; months for OLE). For the first analysis, TEAEs were summarized weekly by treatment group at study entry as described above (i.e., SXB alone, SXB with other anticataplectics, other anticataplectics alone, or anticataplectic-treatment naive) for OLOTTP and SDP. TEAE duration was defined as time from TEAE start to end date (or end of SDP, if TEAE end date was unrecorded). For the second analysis (OLE), TEAEs

were summarized monthly according to the mode of entry to the OLE (re-entry or rollover). TEAE duration was defined as time from TEAE start to end date (or end of OLE, if TEAE end date was unrecorded). Sample size was based on a power calculation for the primary endpoint in the main study (change in mean weekly cataplexy attacks from SDP to DBRWP).

3 Results

3.1 Participant Disposition

Overall, the safety population comprised 201 participants (SXB alone, $n = 52$; SXB with other anticataplectics, $n = 23$; other anticataplectics alone, $n = 36$; anticataplectic-treatment naive $n = 90$) assessed between 14 March 2017 and 10 July 2019. The median (range) age was 36 (18–70) years, 61% were female, and 88% were White. Participants had a mean (SD) body mass index (BMI) of 28.8 (6.1) kg/m^2 ($n = 199$; baseline BMI values could not be determined for two participants due to missing height measurements). Full demographics and baseline disease characteristics for the safety population have been reported previously [10].

Seventy-four participants enrolled in the subsequent OLE (Table 1); 27 re-entered (after a median (range) of 15.0 (4.0–33.0) days), and 47 rolled over. The median (range) age was 38.0 (18–70) years; most were female (66.2%) and White (91.9%). The majority (97.3%) of participants in the OLE had been taking twice-nightly, equally divided doses of LXB during the SDP in the main study.

3.2 Timing and Duration of Treatment-Emergent Adverse Events (TEAEs) During the Open-Label Optimized Treatment and Titration Period (OLOTTP) and the Stable Dose Period (SDP)

Overall, although TEAEs varied by treatment at study entry, new TEAEs were most common during the initial weeks of the OLOTTP, had a short median duration (Table 2), and decreased in frequency as the study progressed. Few participants had TEAEs of fall ($n = 2$ (1%)) or enuresis ($n = 7$ (3%)). Participants previously taking SXB alone (Fig. 2a) reported TEAEs including headache (18 events; $n = 8$ (15%); median (range) duration = 1 (1–112) day) and diarrhea (4 events; $n = 4$ (8%); median (range) duration = 41 (2–131) days). Peak headache incidence was week 4 ($n = 4/52$, 8%) in this group, whereas diarrhea had no peak incidence.

Three participants previously taking SXB with other anticataplectics ($n = 3$ (13%)) reported three headache events, one each in weeks 1, 2, and 4 (Fig. 2b); one reported nausea (4%) persisting from week 1 to week 8. This group had the

Table 1 Baseline characteristics in the OLE (safety population)

Characteristics	Re-entry ($n = 27$)	Rollover ($n = 47$)	Total ($N = 74$)
Age (years)			
Mean (SD)	42.2 (11.79)	35.0 (12.45)	37.6 (12.63)
Median (range)	41.0 (23–68)	33.0 (18–70)	38.0 (18–70)
Sex, *n* (%)			
Female	20 (74.1)	29 (61.7)	49 (66.2)
Male	7 (25.9)	18 (38.3)	25 (33.8)
Race, *n* (%)			
White	26 (96.3)	42 (89.4)	68 (91.9)
Black or African American	0	5 (10.6)	5 (6.8)
Missing	1 (3.7)	0	1 (1.4)
Region, *n* (%)			
Europe	24 (88.9)	17 (36.2)	41 (55.4)
North America	3 (11.1)	30 (63.8)	33 (44.6)
Days from end of main study to OLE day 1			
Mean (SD)	16.6 (7.33)	1.0 (0)	6.7 (8.75)
Median (range)	15.0 (4.0–33.0)	1.0 (1.0–1.0)	1.0 (1.0–33.0)
Division of dosing during SDP, *n* (%)			
Unequal nighttime dosing	0	2 (4.3)	2 (2.7)
Equal nighttime dosing	27 (100.0)	45 (95.7)	72 (97.3)

OLE open-label extension, *SD* standard deviation, *SDP* stable-dose period

Table 2 Incidence and duration of TEAEs occurring in ≥ 5% of participants during the OLOTTP and SDP (safety population)[a,b]

TEAE Term	SXB alone ($n = 52$)		SXB + other anticataplectics ($n = 23$)		Other anticataplectics ($n = 36$)		Anticataplectic-treatment naive ($n = 90$)	
	Number of events	Median duration of events (range), d	Number of events	Median duration of events (range), d	Number of events	Median duration of events (range), d	Number of events	Median duration of events (range), d
Headache	18	1 (1–112)	3	1 (1–1)	14	1 (1–94)	36	1 (1–147)
Nausea	2	34 (14–54)	1	54 (54–54)	9	3 (1–16)	19	9 (1–37)
Dizziness	1	54 (54–54)	1	4 (4–4)	9	4 (1–29)	15	10 (1–117)
Cataplexy	–	–	12	9 (1–99)	6	39 (12–50)	3	1 (1–1)
Nasopharyngitis	2	6 (4–8)	1	10 (10–10)	4	7 (4–8)	6	4 (2–13)
Decreased appetite	–	–	1	3 (3–3)	2	68 (42–93)	13	58 (2–358)
Influenza	6	8 (3–14)	3	12 (7–38)	3	8 (7–39)	4	6 (5–17)
Diarrhea	4	41 (2–131)	–	–	–	–	9	2 (1–64)
Vomiting	1	2 (2–2)	–	–	5	1 (1–2)	5	1 (1–16)

[a]TEAE duration was defined as time from TEAE start to end date (or end of SDP, if TEAE end date was unrecorded). [b]Forty-three out of 520 (8%) TEAEs had a missing end date

OLOTTP open-label optimized treatment and titration period, *SDP* stable-dose period, *SXB* sodium oxybate, *TEAE* treatment-emergent adverse event

highest rate of cataplexy, which persisted throughout the duration of the OLOTTP and SDP.

Participants previously taking other anticataplectics alone (Fig. 2c) reported TEAEs including headache (14 events; $n = 7$ (19%); median (range) duration = 1 (1–94) day), nausea (9 events; $n = 7$ (19%); median (range) duration = 3 (1–16) days), and dizziness (9 events; $n = 6$ (17%); median (range) duration = 4 (1–29) days). Peak incidence was week 1 ($n = 3/36$, 8%) for headache, week 6 ($n = 2/32$, 6%) for nausea, and week 4 ($n = 2/33$, 6%) for dizziness among this group.

Anticataplectic-treatment-naive participants reported the highest number of TEAEs (Fig. 2d), most commonly headache (36 events; $n = 24$ (27%); median (range) duration = 1 (1–147) day), nausea (19 events; $n = 16$ (18%); median (range) duration = 9 (1–37) days), and dizziness (15 events; $n = 13$ (14%); median (range) duration = 10 (1–117) days). Peak incidence was week 2 ($n = 8/89$, 9%) for headache, week 3 ($n = 3/88$, 3%) for dizziness, and week 1 ($n = 6/90$, 7%) for nausea. Several anticataplectic-treatment-naive participants (13 events; $n = 12$ (13%)) also reported decreased appetite, with a relatively long median duration (58 (2–358) days).

Across the entire study, 22 severe TEAEs were reported by 15 participants, 12 of whom were taking LXB at the time the severe TEAE occurred. During the OLOTTP and SDP, most TEAEs reported were mild to moderate in severity; nine participants (4%) reported 16 severe TEAEs during these periods. Severe TEAEs reported in participants taking LXB were cataplexy ($n = 3$, four events), headache ($n = 2$, two events), accidental overdose, adverse drug reaction (doxycycline), adverse drug reaction (nitrofurantoin), anxiety, back pain, confusional state, hyperhidrosis, insomnia, nausea, and viral cardiomyopathy ($n = 1$, one event each). In total, seven participants reported nine serious TEAEs during the entire study. In the OLOTTP and SDP, serious TEAEs were reported by four participants (three during OLOTTP; one during SDP). One participant experienced a serious TEAE of confusion and hallucinations after accidentally taking the second dose of 4.5 g of LXB shortly after the first dose of 4.5 g; this serious TEAE was deemed to be related to LXB treatment. The participant was hospitalized and discharged after symptoms resolved. The other three participants experienced serious TEAEs of peripheral nerve paresis, viral cardiomyopathy (which led to study discontinuation), and bile duct stone, none of which were determined to be related to the study drug.

3.3 Timing and Duration of Treatment-Emergent Adverse Events (TEAEs) During the Open-Label Extension (OLE)

The majority of participants reported ≥ 1 TEAE during the OLE (overall, 58%; re-entry, 59%; rollover, 57%). Although the number of participants with ≥ 1 TEAE during the OLE was similar between groups split by study entry, there were some differences in the most common TEAEs between the re-entry and rollover participants (Table 3). Figure 3 shows new and continuing TEAEs during the OLE across the total safety population. Overall the most commonly reported TEAEs, in terms of the total remaining participants at each month, were headache (14 events; $n = 7$, 9%; peak incidence

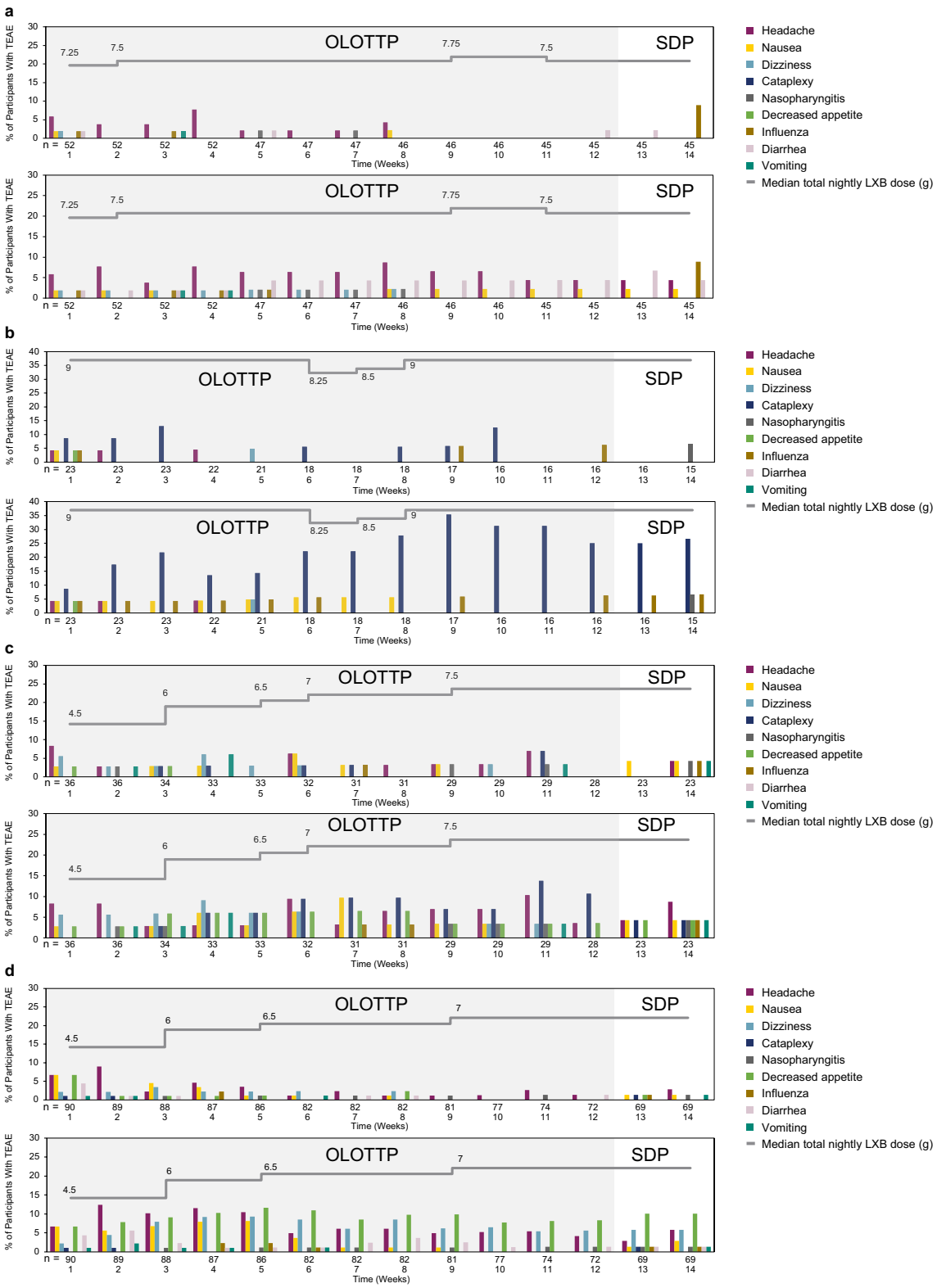


Fig. 2 New (top) and Continuing[a] (bottom) TEAEs at each week during the OLOTTP and SDP in participants taking SXB alone (**a**), SXB with other anticataplectics (**b**), other anticataplectics alone (**c**), and no prior anticataplectic treatment (**d**) (safety population). *LXB* low-sodium oxybate, *OLOTTP* open-label optimized treatment and titration period, *SDP* stable-dose period, *SXB* sodium oxybate, *TEAE* treatment-emergent adverse event. [a]Includes all participants experiencing a TEAE at each study time point, regardless of the week of TEAE onset

Table 3 TEAEs occurring in two or more participants during the OLE (safety population)

TEAE, *n* (%)	Re-entry (*n* = 27)	Rollover (*n* = 47)	Total (*N* = 74)
Headache	4 (14.8)	3 (6.4)	7 (9.5)
Nasopharyngitis	3 (11.1)	3 (6.4)	6 (8.1)
Dizziness	3 (11.1)	2 (4.3)	5 (6.8)
Influenza	0	4 (8.5)	4 (5.4)
Upper respiratory tract infection	1 (3.7)	3 (6.4)	4 (5.4)
Anxiety	1 (3.7)	2 (4.3)	3 (4.1)
Dysmenorrhea	2 (7.4)	1 (2.1)	3 (4.1)
Rhinitis	1 (3.7)	2 (4.3)	3 (4.1)
Abdominal pain	0	2 (4.3)	2 (2.7)
Diarrhea	2 (7.4)	0	2 (2.7)
Fatigue	1 (3.7)	1 (2.1)	2 (2.7)
Nasal congestion	0	2 (4.3)	2 (2.7)
Oropharyngeal pain	1 (3.7)	1 (2.1)	2 (2.7)
Urinary tract infection	1 (3.7)	1 (2.1)	2 (2.7)

OLE open-label extension, *TEAE* treatment-emergent adverse event

was month 3 (*n* = 5/72); median (range) duration = 1 (1−25) day), dizziness (eight events; *n* = 5, 7%; peak incidence was month 1 (*n* = 3/74); median (range) duration = 26 (1−181) days), and nasopharyngitis (six events; *n* = 6, 8%; peak incidence was month 6 (*n* = 2/69); median (range) duration = 9 (1−24) days). TEAEs were most prevalent in month 3 (*n* = 11/72 (15%) reporting a TEAE). No participant reported TEAEs of fall or enuresis; one reported a TEAE of nausea (rollover). Most TEAEs were mild or moderate; two participants had severe TEAEs, both unrelated to study drug (invasive ductal carcinoma (IDC), *n* = 1; dizziness, *n* = 1). One participant had a serious TEAE (IDC) and was therefore discontinued from the study. Few participants (14.9%) had LXB-related TEAEs, most frequently dizziness (overall, 5%; re-entry, 7%; rollover, 4%). LXB-related TEAEs were more common in participants who re-entered (re-entry, 22%; rollover, 11%).

3.4 Study Discontinuations

Forty-six (23%) participants discontinued early from the OLOTTP (SXB alone, *n* = 7/52, 13%; SXB with other anticataplectics, *n* = 9/23, 39%; other anticataplectics alone, *n* = 10/36, 28%; anticataplectic-treatment naive, *n* = 20/90, 22%). TEAEs were the primary reason for study discontinuation during the OLOTTP (18 participants overall, including two (4%), five (22%), five (14%), and six (7%) in participants taking SXB alone, SXB with other anticataplectics, other anticataplectics alone, and those who were anticataplectic-treatment naive, respectively). Common TEAEs leading to discontinuation during the OLOTTP included cataplexy (eight events), somnolence (four events), nausea (three events), depression (four events), sleep disturbances (two events), headache (two events), and anxiety (two events). Other reasons included protocol deviation (*n* = 8), withdrawal by participant (*n* = 6), noncompliance (*n* = 4), investigator decision (*n* = 3), lost to follow-up (*n* = 3), sponsor decision (*n* = 2), lack of efficacy (*n* = 1), and other (*n* = 1; without additional information). An additional 21 participants discontinued prior to receiving randomized study drug in the DBRWP, including six who completed the OLOTTP but did not enter the SDP; five who discontinued early from the SDP [for reasons including protocol deviation (*n* = 3), TEAE (*n* = 1), and lost to follow-up (*n* = 1)]; eight who completed the SDP but did not enter the DBRWP; and two who entered the DBRWP but did not take the study drug due to randomization errors. Across the entire main study period (defined as on or after the first dose of study drug up to the first day of the OLE for rollover participants, or the day of the last dose of study drug in the DBRWP + 30 days (whichever was the earliest) for re-entry participants), common TEAEs that led to discontinuation included cataplexy (*n* = 7), headache (*n* = 2), nausea (*n* = 3), and psychiatric disorders such as anxiety (*n* = 2), depression (*n* = 2), depressed mood (*n* = 2), and irritability (*n* = 2).

Seven participants discontinued from the OLE (re-entry, *n* = 2; rollover, *n* = 5), three of which were because of TEAEs (IDC, *n* = 1; apathy, *n* = 1; sleep apnea syndrome, *n* = 1). Among these TEAEs, only apathy was considered treatment related.

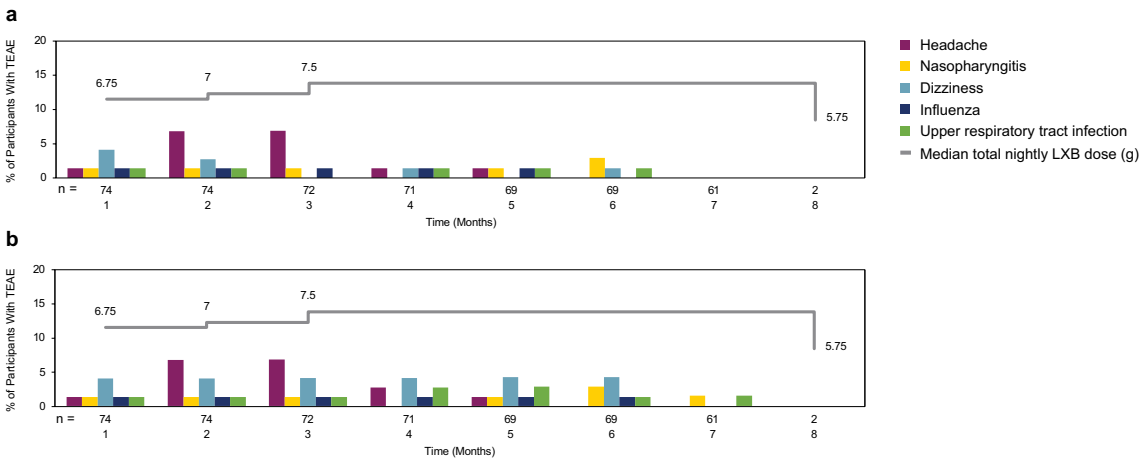


Fig. 3 New (**a**) and continuing[a] (**b**) TEAEs at each month during the OLE (safety population). *LXB* low-sodium oxybate, *OLE* open-label extension, *TEAE* treatment-emergent adverse event. [a]Includes all participants experiencing a TEAE at each study time point, regardless of the month of TEAE onset

4 Discussion

This analysis of TEAEs during a phase 3 clinical trial and OLE of LXB in participants with narcolepsy confirmed the safety and tolerability profile of long-term, open-label LXB use. During the OLOTTP and SDP phases, the pattern of new-onset TEAEs varied by treatment at study entry but decreased as the trial progressed across all four participant groups. The treatment-naive group reported the highest number of TEAEs of the four study groups.

Broadly, the most common TEAEs across all participants were headache, nausea, and dizziness; however, headache was less frequent in participants previously taking SXB. Most TEAEs were of short duration during this portion of the study. Among the participants who enrolled in the optional OLE, headache and dizziness remained relatively common (≥ 5% of participants), but nausea was no longer commonly reported. TEAE prevalence was highest in the first half of the OLE period and diminished over the duration of the extension period. The majority of TEAEs in all periods were mild to moderate.

TEAEs of worsening cataplexy were most common among participants who had previously been taking SXB with other anticataplectics and were also observed in a smaller number of participants who had previously been taking other anticataplectics alone. Participants previously taking SXB with other anticataplectics likely represent those with the most severe disease and were the only group in which the median LXB dose reached the maximum 9 g/night. TEAEs of cataplexy may have been related to discontinuation of prior anticataplectics during the OLOTTP. Indeed, in the primary analysis, weekly cataplexy attacks increased in participants randomized to placebo during the DBRWP but remained stable in those who continued LXB treatment [10]. However, beyond this worsening specific to narcolepsy, analysis of TEAEs during the DBRWP did not identify evidence of clinically significant withdrawal signs or symptoms. In contrast to participants taking SXB and other anticataplectics at study entry, treatment-naive participants did not report any incidences of worsening cataplexy, and instead experienced the more common TEAEs of headache, nausea, and dizziness. This could indicate that cataplexy was controlled with LXB in treatment-naive participants. During the OLOTTP and SDP, the majority of TEAEs were short-lived, with the exception of decreased appetite, which was noted to be of particularly long duration among some participants. One participant had an LXB-related TEAE of decreased appetite lasting 358 days. Because this TEAE was treatment related, follow-up was conducted with the affected participant until resolution. Although the relationship between decreased appetite and weight loss was not assessed in the present study, SXB treatment previously has been reported to be associated with lasting weight loss in participants with NT1 [27]. The authors of that study suggested that this effect may be particularly pronounced in those with a high BMI at baseline and that BMI decrease was generally beneficial.

The initial TEAEs observed in the OLOTTP and SDP had largely resolved by the time participants enrolled in the OLE; this finding was particularly true of cataplexy and decreased appetite. In the OLE, headache, nasopharyngitis, and dizziness were the most reported TEAEs, whereas nausea was reported in only one participant. Headache largely subsided by the latter half of the OLE, although a small number of participants continued to report dizziness into month 6. Headache and dizziness were both more common in re-entry than rollover participants and, given their higher frequency early in the OLE, may have been related

to restarting treatment among those who had discontinued LXB before re-enrolling. Dizziness was also the most common LXB-related TEAE (i.e., assessed by the investigator to be related or possibly related to study drug). However, dizziness did not result in any discontinuations during any study period. LXB-related TEAEs were infrequent overall, particularly among the rollover group.

With regard to other TEAEs of interest, falls have previously been reported when patients rise from bed after administering oxybate at night [14]. In this study where participants were taking LXB, there were no reports of falls during the 24-week OLE, and reports of TEAEs of falls during the main study period were uncommon. These findings suggest that falls may be infrequent among patients with baseline and disease characteristics similar to those of the representative study population. Falls may also be age-related, and thus may not be expected in this younger study population. Further, enuresis is a common adverse event associated with SXB treatment [9, 28]. In the 24-week OLE with open-label LXB treatment, no TEAEs of enuresis were reported, whereas only 3.5% of participants reported a TEAE of enuresis during the main study period [10]. It is possible that the significantly reduced sodium load of LXB relative to higher-sodium oxybate formulations may explain the infrequent reports of enuresis in this study [10, 28, 29]. The lower rates of enuresis observed with LXB in this study may have resulted in fewer instances of rising from bed at night to go to the bathroom, thus decreasing the likelihood of falls.

Almost one-quarter of participants in the safety population discontinued early from the OLOTTP, followed by an additional 10% prior to receiving the study drug during DBRWP; 4% of participants discontinued during the OLE. TEAEs were the most common reason for study discontinuation during OLOTTP (39% of discontinuations) and OLE (43%). The higher incidence of TEAE-related discontinuations could be attributed to the fact that re-entry participants re-entered the study after a period of time and rollover participants could have been on placebo during the prior DBRWP. These treatment gaps could have made these participants more vulnerable to experiencing adverse effects during the OLE. This pattern of discontinuations was similar to that observed in the subsequent phase 3 trial for LXB in participants with idiopathic hypersomnia (open-label titration, 20%; SDP, 5%; OLE, 10%) [30]. Additionally, discontinuations in the present study due to TEAEs were highest among participants previously naive to oxybate during the OLOTTP and SDP. This may be because the active moiety is conserved between SXB and LXB [14], so that participants who had already experienced acceptable tolerability with SXB were likely to have a similar experience with LXB.

This analysis has several strengths, including the stratification of participants by prior treatment at study entry; in addition, the 38-week duration of the analysis period allowed for a detailed assessment of the timing and duration of TEAEs across the study. Furthermore, doses were individually optimized for each participant, which more closely matches real-world practice than forced titration or fixed dosing. These findings therefore provide useful information that may guide patient and clinician decisions regarding treatment with LXB.

Several limitations should also be noted, however. First, the open-label nature of LXB treatment during the study periods assessed could have impacted participants' expectations about the treatment and their experience of TEAEs [31]. Second, no information was collected on the timing of TEAEs relative to the time of day at which participants took their LXB dose, so the short-term timescales around participants' experiences of TEAEs could not be examined. Third, the division of participants by treatment at study entry left few participants in the "other anticataplectics alone" and "SXB with other anticataplectics" groups relative to the "SXB alone" and "anticataplectic-treatment naive" groups. This may have made it more difficult to detect consistent patterns of TEAE incidence and prevalence across the groups. Fourth, data on the exact frequency of cataplexy at study entry were not collected; instead, participants were required to have experienced at least 14 attacks within a 2-week period before receiving any narcolepsy treatment. As such, subgroup analyses on the basis of cataplexy frequency could not be performed. We also note that the study design was not designed to measure or analyze blood pressure as an outcome. Blood pressure was evaluated during routine clinical visits but this evaluation was not standardized or controlled across sites and participants. Finally, more than 90% of the participants in this study were White; further research is needed in more diverse populations.

5 Conclusion

In conclusion, in this long-term study, the safety and tolerability profile of LXB was generally consistent with the known safety profile of SXB [9, 17–20]. During the OLOTTP and SDP, most TEAEs occurred early on and were generally of short duration. TEAEs were typically mild or moderate in severity for the duration of the study, and their frequency decreased during the OLE. Of note, TEAEs of cataplexy were absent during the OLE, reports of nausea were infrequent, and no TEAEs of falls or enuresis were reported in this 24-week open-label period. Study discontinuations occurred at a similar frequency to that observed in another study of LXB in participants with idiopathic

hypersomnia [30]. Together, these findings highlight the long-term safety and tolerability profile of LXB for patients with narcolepsy, and provide useful information that may help clinicians make informed decisions related to long-term treatment with LXB.

Acknowledgements The authors would like to thank the patients, study investigators, and study staff for their contributions to this research. Medical writing and editorial support at all stages of manuscript development, as directed by the authors, were provided by Sean Anderson, PhD, and Michael J. Theisen, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Jazz Pharmaceuticals.

Declarations

Funding This work and its open access publication were supported by Jazz Pharmaceuticals. The authors, including the Jazz Pharmaceuticals authors, were involved with designing the study, collecting, analyzing, interpreting the data, and writing the manuscript. Although Jazz Pharmaceuticals was involved in the review of the manuscript, the content of this article, the ultimate interpretation, and the decision to submit it for publication in CNS Drugs was made by the authors independently.

Conflict of interest RK Bogan has served on the speakers' bureau and participated in advisory boards for Jazz Pharmaceuticals. N Foldvary-Schaefer has served on an advisory committee for Jazz Pharmaceuticals and participated in clinical trials supported by Jazz Pharmaceuticals, Suven, and Takeda. R Skowronski and A Chen are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. MJ Thorpy has received research/grant support and consultancy fees from Jazz Pharmaceuticals, Harmony Biosciences, Balance Therapeutics, Axsome Therapeutics, and Avadel Pharmaceuticals.

Ethics approval The study was approved by institutional review boards or ethics committees at all sites and was performed in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki.

Consent to participate All participants provided written informed consent. ClinicalTrials.gov identifier: NCT03030599 (25 January 2017).

Consent for publication Not applicable.

Availability of data and material All relevant data are provided within the article and supporting files. Jazz has established a process to review requests from qualified external researchers for data from Jazz-sponsored clinical trials in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on Jazz Pharmaceuticals data sharing criteria and process for requesting access can be found at: https://www.jazzpharma.com/science/clinical-trial-data-sharing/.

Code availability Not applicable.

Author contributions Study design: R Skowronski. Participated in the study: RK Bogan, N Foldvary-Schaefer, R Skowronski, MJ Thorpy. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical review and revision of the manuscript: All authors. Statistical analysis: A Chen. Final approval of manuscript: All authors. All authors had full access to the data and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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