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ORIGINAL RESEARCH ARTICLE

Assessing Early Efficacy After Initiation of Once-Nightly Sodium Oxybate (ON-SXB; FT218) in Participants with Narcolepsy Type 1 or 2: A Post Hoc Analysis from the Phase 3 REST-ON Trial

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Abstract

Background Once-nightly sodium oxybate (LUMRYZ™; ON-SXB; FT218) significantly improved narcolepsy symptoms in the phase 3 REST-ON trial. The objective of this post hoc analysis was to investigate the early efficacy of ON-SXB at weeks 1 (4.5-g dose) and 2 (6-g dose).

Methods In REST-ON, participants (≥ 16 years) with narcolepsy type 1 or 2 were randomized 1:1 to ON-SXB (4.5 g, 1 week; 6 g, 2 weeks; 7.5 g, 5 weeks; 9 g, 5 weeks) or placebo. Protocol-prespecified efficacy assessments were conducted at weeks 3 (6-g dose), 8 (7.5-g dose), and 13 (9-g dose). A post hoc analysis was conducted to assess the early efficacy of ON-SXB, defined as efficacy at weeks 1 (4.5-g dose) and 2 (6-g dose) on Epworth Sleepiness Scale (ESS) score, visual analog scale (VAS) sleep quality, and VAS refreshing nature of sleep. Least squares mean differences (LSMD) in change from baseline to weeks 1 and 2, 95% confidence intervals (CIs), and *P* values were calculated using mixed-effects models for repeated measures.

Results In the modified intent-to-treat population ($n = 190$; ON-SXB, $n = 97$; placebo, $n = 93$), baseline ESS scores were 16.6 and 17.5, sleep quality scores were 53.8 and 55.9, and refreshing nature of sleep scores were 46.5 and 49.9 with ON-SXB and placebo, respectively. At week 1 (4.5 g), numerical improvement in ESS score (LSMD [95% CI], −0.7 [−1.6 to 0.2]) and significant improvements in sleep quality (3.6 [1.1–6.1]; $P < 0.01$) and refreshing nature of sleep (3.2 [0.5–5.9]; $P < 0.05$) were observed with ON-SXB versus placebo. At week 2 (6 g), significant improvements with ON-SXB versus placebo were observed for ESS score (−1.3 [−2.4 to −0.2]; $P < 0.02$), sleep quality (7.0 [3.8–10.1]; $P < 0.001$), and refreshing nature of sleep (5.8 [2.3–9.4]; $P = 0.001$).

Conclusions ON-SXB improved daytime sleepiness, sleep quality, and refreshing nature of sleep, with observable benefits beginning in the first week of treatment. These data may help clinicians set expectations with patients.

Clinical Trial ID NCT02720744.

Key Points

Participants who took once-nightly sodium oxybate (ON-SXB) experienced significant improvements in their daytime sleepiness, sleep quality, and refreshing nature of their sleep as early as 2 weeks after starting ON-SXB.

These data may help clinicians to set expectations that patients taking ON-SXB may experience transient tolerability effects, coupled with some degree of symptom relief after 1–2 weeks and increasing improvement from week 3 onward, with the goal to improve medication adherence for people with narcolepsy.

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1 Introduction

Narcolepsy is a rare, chronic disease characterized by the symptom pentad of excessive daytime sleepiness (EDS), cataplexy, disrupted nighttime sleep, sleep paralysis, and hypnagogic/hypnopompic hallucinations [1, 2]. Current treatments for narcolepsy often provide partial improvement, target a limited range of symptoms, or require treatment regimens that may impact patient adherence [3–5]. Sodium oxybate (SXB) is an established standard-of-care treatment for adults with narcolepsy that effectively treats multiple narcolepsy symptoms, including EDS and cataplexy [6, 7]. Two currently approved formulations of immediate-release oxybates (SXB and calcium/magnesium/potassium/sodium [mixed-salt] oxybates) require twice-nightly dosing, with a second dose taken 2.5–4 h after the first, bedtime dose [8, 9]. However, treatment adherence is often suboptimal in people with narcolepsy [10, 11], and in a study examining patient preference for overall product choice, SXB dosing frequency was the most important attribute considered, with patients preferring once-nightly over twice-nightly treatment [12]. Likewise, clinicians show preference for once-nightly oxybate dosing to promote patient quality of life and to reduce patient anxiety when asked about taking the medication [13]. Suboptimal treatment adherence, such as taking half of the therapeutic dose, could decrease the effectiveness of EDS and/or cataplexy control.

The challenges associated with currently available medications highlight a need for effective treatments that provide improved adherence. Once-nightly SXB (ON-SXB; LUMRYZ™; FT218) is an extended-release formulation of SXB for the treatment of patients 7 years of age and older with narcolepsy [14, 15]. The phase 3 REST-ON clinical trial evaluated the efficacy and safety of ON-SXB relative to placebo in individuals with narcolepsy type 1 and 2 [14]. Significant improvements were observed for the 6-g (week 3), 7.5-g (week 8), and 9-g (week 13) doses of ON-SXB for the three coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness test, Clinical Global Impression of Improvement rating, and mean number of weekly cataplexy episodes, as well as the secondary endpoints Epworth Sleepiness Scale (ESS) score and patient-reported sleep quality and refreshing nature of sleep on visual analog scales (VAS) (all $P < 0.001$) [14, 16]. A post hoc analysis revealed that ON-SXB 4.5 g significantly reduced the number of weekly cataplexy episodes compared with placebo at week 1 of treatment (least squares mean difference [LSMD], −2.7; 95% CI −4.9 to −0.5; $P < 0.05$) [14]. To better understand whether early onset of effectiveness was achieved for other narcolepsy symptoms in participants from REST-ON, this post hoc analysis evaluated ESS score, sleep quality, and refreshing nature of sleep with ON-SXB at weeks 1 (4.5-g dose) and 2 (6-g dose).

2 Patients and Methods

2.1 Study Design

REST-ON (NCT02720744) was a phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial (Fig. 1). Participants were randomized 1:1 to ON-SXB (4.5 g, 1 week; 6 g, 2 weeks; 7.5 g, 5 weeks; 9 g, 5 weeks) or placebo. Protocol-prespecified efficacy assessments were conducted at weeks 3 (6-g dose), 8 (7.5-g dose), and 13 (9-g dose), and the earliest data available were collected at week 1. Early efficacy of ON-SXB, defined as efficacy at weeks 1 (4.5-g dose) and 2 (6-g dose), on ESS score and VAS sleep quality and refreshing nature of sleep was analyzed post hoc.

Institutional review board or independent ethics committee approval was obtained for each study center. REST-ON was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, International Council for Harmonisation guidelines, and any applicable regulatory requirements at the local and national level. Written informed consent was provided by all adult participants (≥ 18 years old); consent was obtained from both the participant and their legally authorized representative for participants 16 and 17 years of age. Full study details and full inclusion/exclusion criteria have been reported previously [14].

2.2 Participants

Individuals ≥ 16 years of age with a documented diagnosis of narcolepsy type 1 or type 2 as defined by the International Classification of Sleep Disorders-3 criteria were eligible [17]. Continuing presence of EDS, as defined by patient report for the past 3 months and ESS > 10, and current continuing presence of cataplexy, as defined by patient report for the last 3 months (narcolepsy type 1 only), were required for enrollment. Confirmation of EDS as defined by baseline ESS score > 10 and baseline mean sleep latency < 11 min on the Maintenance of Wakefulness Test was required for randomization. Key exclusion criteria included prior use of SXB (except use of SXB ≤ 4.5 g for ≤ 2 weeks and ≥ 1 year before study entry) and diagnosis of sleep apnea (apnea–hypopnea index ≥ 15) or any other sleep disorder known to cause EDS as determined by polysomnography findings and sleep history.

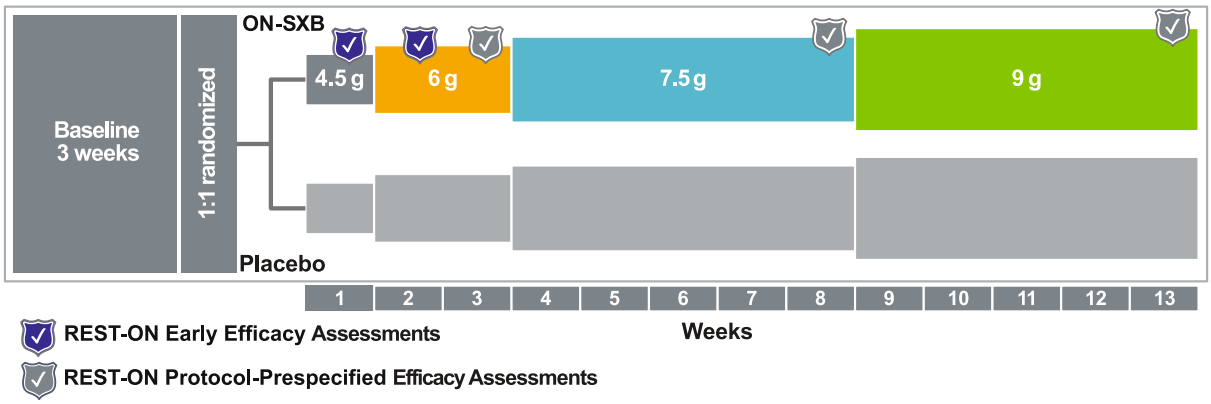

Fig. 1 Study design. ON-SXB, once-nightly sodium oxybate. Protocol-prespecified efficacy assessments were conducted at weeks 3 (6 g), 8 (7.5 g), and 13 (9 g). Early efficacy was assessed post hoc at weeks 1 (4.5 g) and 2 (6 g)

2.3 Assessments

The ESS score was calculated from a questionnaire that evaluates the extent of sleepiness in everyday situations [18]; participants were asked to rate their likelihood of dozing during eight activities on a scale from 0 ("never") to 3 ("high"). Higher total scores were indicative of a greater tendency toward sleepiness. Sleep quality and refreshing nature of sleep were assessed using a VAS from 1 to 100, with 1 indicating poor sleep quality/unrefreshing sleep and 100 indicating good sleep quality/refreshing sleep. Mean VAS responses to the quality of sleep questions were recorded. ESS score, VAS sleep quality, and VAS refreshing nature of sleep were recorded daily by the participants in an electronic diary. Baseline review of the electronic diary data occurred before randomization and at all study time points except the first after randomization. Adverse events (AEs) were assessed at all study visits. Adverse drug reactions (ADRs) were defined as those AEs assessed by the investigator to be related or possibly related to the study drug. Any event that resulted in death, was life-threatening or required hospitalization, or resulted in disability was considered a serious AE (SAE) and was required to be reported to the sponsor by the investigator within 24 h.

2.4 Statistical Analysis

Participant demographics, baseline characteristics, and safety information were tabulated for the safety population, defined as all randomized participants who took ≥ 1 dose of the study drug. All post hoc analyses reported herein were conducted in the modified intent-to-treat (mITT) population, defined as all participants with ≥ 1 efficacy measurement after receiving the 6-g dose of ON-SXB or placebo. LSMDs in change from baseline to weeks 1 and 2, associated 95% CIs, and *P* values were calculated post hoc using a mixed-effects model for repeated measures, with change from baseline as the response variable, fixed effects of treatment, time, treatment by time, site, covariate of baseline ESS score, and participants as random effects, and unstructured variance–covariance structure. If week 1 or 2 had < 3 days of diary entries, data from that week were excluded from the analysis.

3 Results

3.1 Participant Disposition and Demographics

A total of 190 participants were included in the mITT population (ON-SXB, $n = 97$; placebo, $n = 93$). The safety population included 212 participants (ON-SXB, $n = 107$; placebo, $n = 105$). Full participant demographics and disposition information have been previously published [14].

3.2 ESS

Baseline mean (SD) ESS scores were similar for participants receiving ON-SXB (16.6 [3.8]) and placebo (17.5 [4.1]). Numerical improvement with ON-SXB treatment compared with placebo was seen at week 1 with the 4.5-g dose (LSMD, −0.7 [95% CI −1.6 to 0.2]; $P = 0.143$; Fig. 2). A significant improvement in ESS score with ON-SXB treatment compared with placebo was observed at week 2 with the 6-g dose (LSMD, −1.3 [95% CI −2.4 to −0.2]; $P < 0.02$).

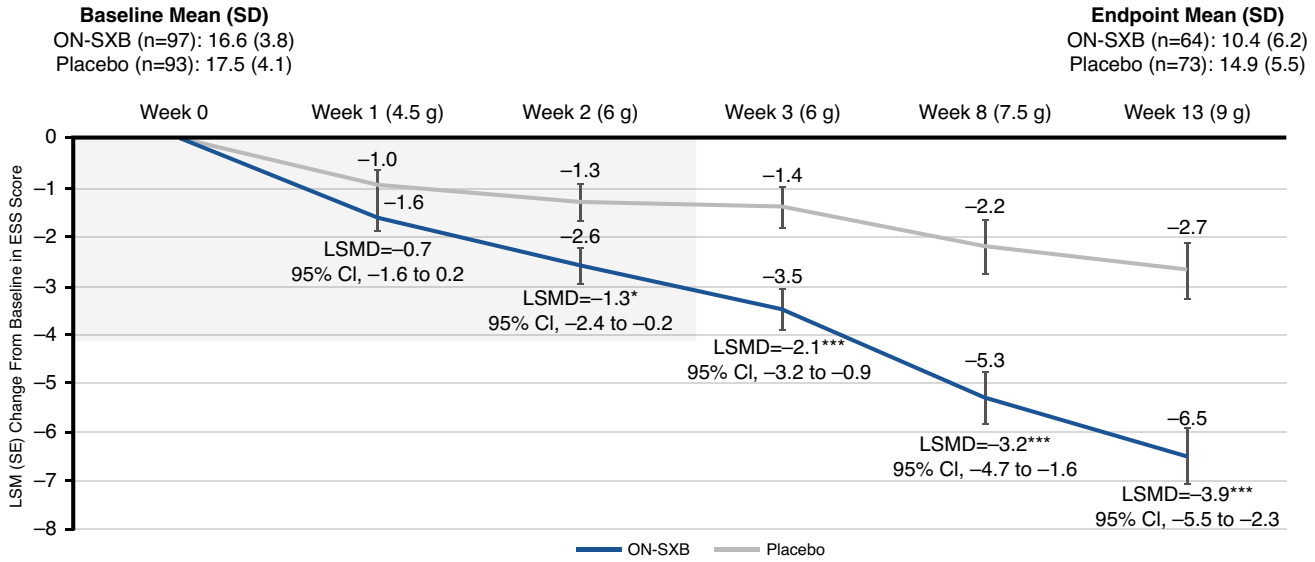

Fig. 2 Change from baseline in ESS score. ESS, Epworth Sleepiness Scale; LSM, least squares mean; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate (FT218). *$P < 0.05$; ***$P < 0.001$. Note: data for weeks 3–13 have been previously published [14]

3.3 Sleep Quality

For participants receiving ON-SXB and placebo, baseline mean (SD) sleep quality on the VAS was 53.8 (20.8) and 55.9 (22.6), respectively. Significantly greater improvement in sleep quality was observed with ON-SXB treatment relative to placebo at week 1 (LSMD, 3.6 [95% CI 1.1–6.1]; $P < 0.01$; Fig. 3) with the 4.5-g dose and at week 2 (LSMD, 7.0 [95% CI 3.8–10.1]; $P < 0.001$) with the 6-g dose.

3.4 Refreshing Nature of Sleep

Baseline mean (SD) refreshing nature of sleep on the VAS was 46.5 (21.8) and 49.9 (23.3) in the ON-SXB and placebo arms, respectively. Significantly greater improvement in the refreshing nature of sleep was observed with ON-SXB treatment relative to placebo at week 1 (LSMD, 3.2 [95% CI 0.5–5.9]; $P < 0.05$; Fig. 4) with the 4.5-g dose and at week 2 (LSMD, 5.8 [95% CI 2.3–9.4]; $P = 0.001$) with the 6-g dose.

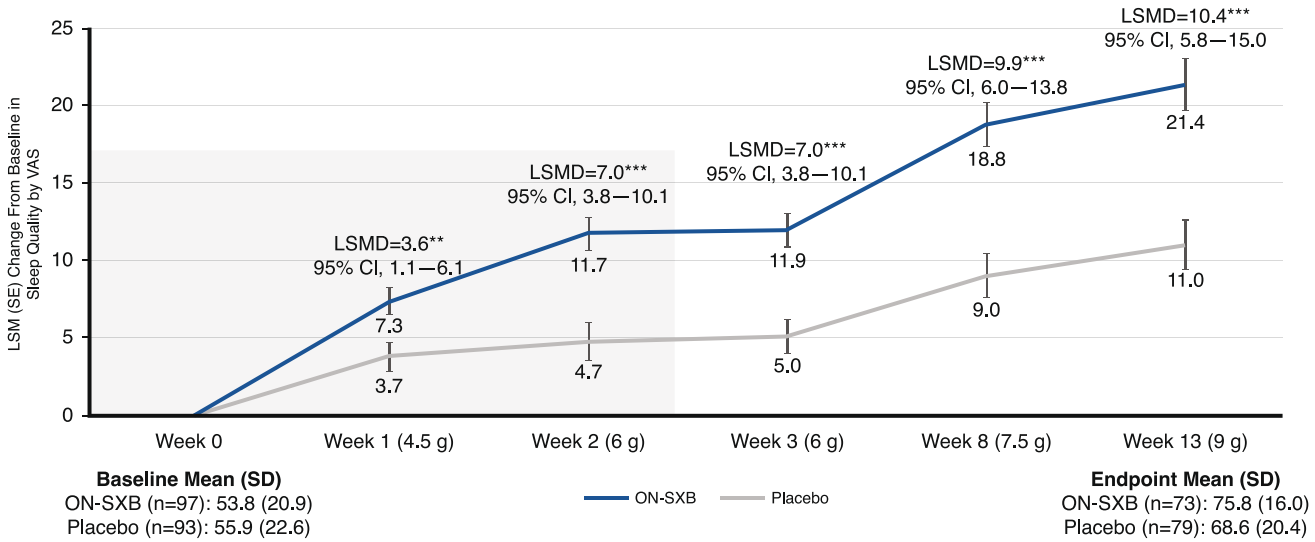

Fig. 3 Change from baseline in sleep quality. LSM, least squares mean; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate (FT218); VAS, visual analog scale. **$P < 0.01$; ***$P < 0.001$. Note: data for weeks 3–13 have been previously published [14]

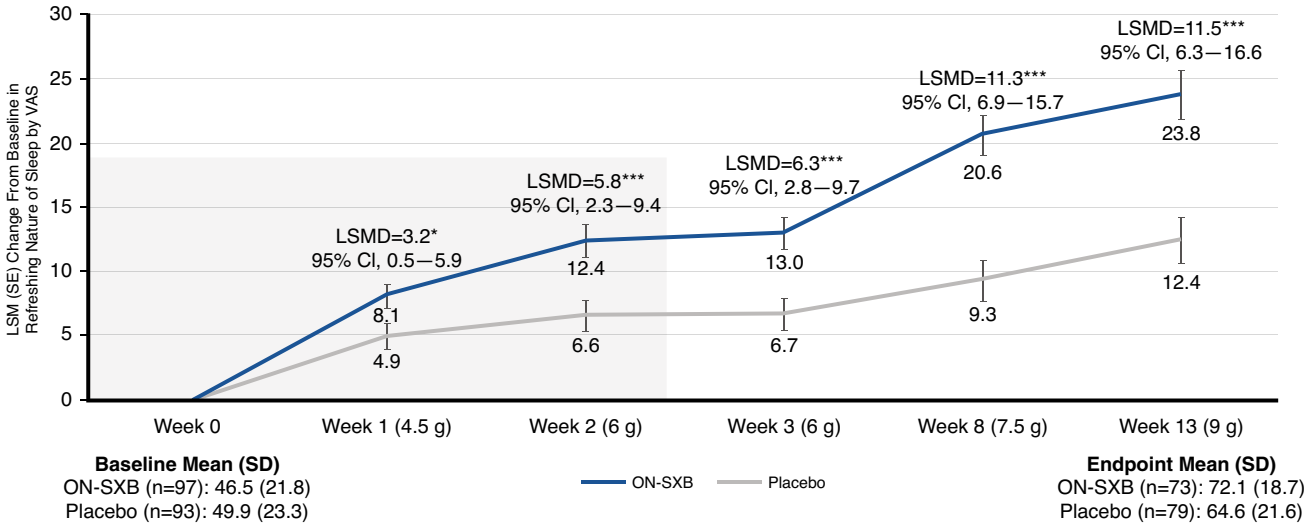

Fig. 4 Change from baseline in refreshing nature of sleep. LSM, least squares mean; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate (FT218); VAS, visual analog scale. $^{*}P < 0.05$; $^{***}P \leq 0.001$. Note: data for weeks 3–13 have been previously published [14]

3.5 Safety

At week 1 (4.5-g ON-SXB), the most common ADRs (≥ 5% of participants over time) among participants receiving ON-SXB ($n = 107$) were headache (6.5%), nausea (5.6%), dizziness (5.6%), decreased appetite (3.7%), vomiting (2.8%), anxiety (2.8%), and enuresis (1.9%) [14]. One participant per treatment arm experienced one SAE (ON-SXB, 0.9%, inadequate control of diabetes mellitus; placebo, 1.0%, drug hypersensitivity; both not related to study drug). Among the seven (6.5%) participants who discontinued ON-SXB owing to an AE at week 1 (4.5-g dose), the reported AEs included dizziness, anxiety, painful respiration, dysphagia, inadequately controlled diabetes mellitus, and delirium. Additionally, one (1.0%) participant receiving placebo discontinued at week 1 owing to an AE, which was identified as an allergic reaction to amoxicillin. At week 2 (6-g ON-SXB), the most common ADRs (≥ 5% of participants over time) in the ON-SXB treatment arm ($n = 104$) were nausea (5.8%), dizziness (3.8%), headache (3.8%), enuresis (3.8%), vomiting (2.9%), and decreased appetite (2.9%). One participant experienced an SAE of paresthesia (ON-SXB, 1.0%; not related to study drug). Three (3.1%) participants discontinued ON-SXB at week 2 (6-g dose) owing to an AE, which included nausea, enuresis, dyspnea, dizziness, headache, and restlessness. In the placebo group, one (1.0%) participant discontinued at week 2 owing to nausea, anxiety, and vomiting.

4 Discussion

Participants receiving ON-SXB experienced improvements in subjective measures of daytime sleepiness, sleep quality, and refreshing nature of sleep relative to placebo as early as week 1 with the 4.5-g starting dose, with even greater benefit at week 2 after starting the therapeutic 6-g dose. Safety analyses performed at weeks 1 and 2 provide further support for the tolerability of ON-SXB during early phases of treatment. ADRs, which are generally related to issues of tolerability, are most frequent when SXB therapy is first initiated and when doses are increased. In the REST-ON clinical trial, ADRs were mostly rated mild or moderate in severity, occurred more frequently when initiating medication or increasing the dose, and decreased over time with stable dosing [14]. The highest rate of ADRs occurred with the 4.5-g dose at week 1 (all < 7%); a slight and then marked decrease in most ADRs was observed after increasing the dose to 6 g at week 2 and week 3, respectively. Consistent with this decrease in ADRs, discontinuations due to ADRs were highest during the first week of treatment and decreased over time [14]. The ability for clinicians to set expectations that patients taking ON-SXB may experience transient tolerability effects (e.g., headache, nausea, and dizziness), coupled with some degree of symptom relief after 1–2 weeks and increasing improvement from week 3 onward, may be important for adherence to the prescribed regimen. While the rate of enuresis was only 1.9% in week 1 and 3.8% in week 2, during the 5-week dosing periods of 7.5 g and 9 g, the reported rate of enuresis was 9.1%. As with other adverse reactions, enuresis was transient and decreased after participants were on these doses; moreover,

only one subject discontinued owing to enuresis. While not part of the protocol, counseling patients to consider limiting fluid intake prior to bed, and to void immediately before bed, may be pragmatic approaches to lessen this known oxybate side effect.

Therapies that provide early symptom improvement are beneficial to individuals with narcolepsy; however, the efficacy of immediate-release oxybate formulations at early timepoints during dose escalation, particularly for measures of EDS, is not well established in published reports. Immediate-release SXB has been studied in multiple trials; however, the earliest its effect was assessed on measures of EDS [19–21] and disrupted nighttime sleep [22] was at week 4 (6-g dose). The current analysis provides evidence of symptom relief for measures of EDS and disrupted nighttime sleep with ON-SXB early in treatment (weeks 1 and 2), with 4.5- and 6-g doses. Although the greatest improvements in ESS, sleep quality, and refreshing nature of sleep with ON-SXB treatment during REST-ON were observed at week 13 with the 9-g dose, these post hoc analyses at weeks 1 and 2 suggest that some people with narcolepsy may experience symptom improvements with ON-SXB treatment shortly after initiating therapy [14, 16].

Individuals with narcolepsy often have suboptimal treatment adherence, which can negatively affect clinical outcomes. Additionally, some people with narcolepsy may not receive timely or adequate symptom relief owing to delayed diagnosis or treatment with therapies that target a limited range of symptoms [23–25]. A treatment that provides early efficacy may provide improved adherence by patients, thus improving clinical outcomes. The improvements in ESS score exceeded the ≥ 2-point reduction from baseline established by the American Academy of Sleep Medicine as a clinical significance threshold (CST) [26] at week 2 with ON-SXB and approached it at week 1, suggesting that some individuals may experience a noticeable benefit within 2 weeks of treatment. Because minimal clinically important differences and CSTs for improvements in sleep quality and refreshing nature of sleep measured by VAS have not been established, it is difficult to predict the magnitude of change that will be clinically relevant for patients. However, the early improvements—particularly when compared with baseline, as would occur in clinical practice—support the idea that patients may experience benefits in their perception of both sleep quality and the refreshing nature of sleep early in treatment. These data may help clinicians in setting expectations, particularly in the first few weeks after initiation, when there is a greater likelihood of AEs associated with oxybates but effectiveness may not yet be fully realized. Counseling patients that early improvements may be observed after 1–2 weeks of therapy and that these improvements are expected to continue increasing over subsequent weeks on ON-SXB is necessary for promoting treatment adherence and improving outcomes.

The primary limitations of this study are that it reports data from secondary endpoints that were not powered for a multiplicity analysis and that all analyses were conducted post hoc. The statistical significance of the changes reported in this analysis should be interpreted with consideration for these limitations. However, the data are pertinent, as they provide insight into early efficacy during treatment initiation with ON-SXB.

5 Conclusions

ON-SXB demonstrated significant improvement compared with placebo in subjective measures of sleep quality and refreshing nature of sleep as early as week 1 (4.5-g dose) and week 2 (6-g dose); significant improvement in daytime sleepiness was achieved at week 2, with a numerical improvement in the ESS score at week 1. ON-SXB was generally well tolerated, and no new safety signals were observed. ON-SXB is a once-at-bedtime treatment option that may provide early relief of symptoms for some individuals with narcolepsy.

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Declarations

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Conflict of interest L.K. is a consultant for and/or has served on advisory boards for Avadel Pharmaceuticals, Harmony Biosciences, and Takeda. A.R. has received grant/research support from Jazz Pharmaceuticals, Suven, Inspire, Nyxoah, LivaNova, and Avadel Pharmaceuticals; is a consultant for Jazz Pharmaceuticals, Suven, Inspire, and Avadel Pharmaceuticals; and has served on speakers' bureaus for Jazz Pharmaceuticals and Eisai. J.W.W. has received consultation fees from Avadel Pharmaceuticals, Emalex Biosciences, Noctrix Health, Disc Medicine, and Idorsia Pharmaceuticals; and research support from Merck & Co., American Regent, NIDA, the RLS Foundation, and the Baszucki Brain Research Fund. J.W.W. is an Editorial Board member of *CNS Drugs*. J.W.W. was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. A.M.M. has served as a consultant, speaker, and/or on advisory boards for Avadel Pharmaceuticals, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, Alkermes, and Takeda Pharmaceutical Co; has received grant funding from National Institutes of Health, UCB Pharmaceuticals, Jazz Pharmaceuticals, ResMed Foundation, Coverys Founda-

tion, Harmony Biosciences, and Geisinger Health Plan; is the CEO of DAMM Good Sleep, LLC; and serves as an advisor for Neura Health and Floraworks. J.G. is an employee of Avadel Pharmaceuticals.

Ethics approval Institutional review board or independent ethics committee approval was obtained for each study center.

Consent to participate Written informed consent was provided by all adult participants (≥ 18 years old); consent was obtained from both the participant and their legally authorized representative for participants 16 and 17 years of age.

Consent for publication Not applicable

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions L.K.: writing—review and editing, and formal analysis. A.R.: writing—review and editing, and formal analysis. J.W.W.: writing—review and editing, and formal analysis. A.M.M.: writing—review and editing, and formal analysis. J.G.: writing—review and editing, and formal analysis. All authors have read and approved the final submitted manuscript and have agreed to be accountable for the work.

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