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ORIGINAL RESEARCH ARTICLE

Efficacy of Once-Nightly Sodium Oxybate in Patients with Narcolepsy: Post Hoc Analyses of Sensitivity, Effect Size, and Numbers Needed to Treat from the Phase 3 REST-ON Trial

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Abstract

Background Once-nightly sodium oxybate (ON-SXB; LUMRYZ™; FT218) treatment significantly improved the coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness Test (MWT), Clinical Global Impression of Improvement (CGI-I) rating, and number of weekly cataplexy episodes versus placebo in a randomized, placebo-controlled trial (REST-ON). The objective of these post hoc sensitivity analyses was to evaluate the robustness of treatment with ON-SXB, while accounting for missing participant data. Number needed to treat (NNT) and effect size analyses were conducted to quantify the treatment benefits.

Methods Participants ≥ 16 years of age with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (4.5 g [week 1]; 6 g [weeks 2–3]; 7.5 g [weeks 4–8]; or 9 g [weeks 9–13]) or placebo. Sensitivity analyses included completer population, placebo-based multiple imputation (MI) with a missing-not-at-random assumption, analysis of covariance (ANCOVA), and tipping-point–based MI of worsening values until $P > 0.05$. Mean differences and *P*-values were calculated for the MWT and number of cataplexy episodes. For CGI-I, odds ratios and *P*-values were calculated for completers; mean differences (1–7 points; lower values indicate greater improvement) and *P*-values were calculated using ANCOVA. Effect sizes were calculated using Cohen's *d*; NNTs were calculated as the inverse of the absolute risk reduction.

Results In the completer population (ON-SXB, $n = 69$; placebo, $n = 79$), all ON-SXB doses demonstrated significant improvements versus placebo for all coprimary endpoints ($P < 0.001$). All ON-SXB doses demonstrated significant improvements ($P < 0.001$) versus placebo for all coprimary endpoints when missing values in both treatment arms were imputed from observed values in the placebo arm (i.e., missing data were replaced with placebo data) and when analyzed using ANCOVA. Tipping-point–based analysis on the change from baseline in mean sleep latency on the MWT demonstrated that implausible or nearly implausible baseline MWT assumptions were needed to render the differences between ON-SXB and placebo no longer statistically significant. All doses of ON-SXB had NNTs of three and effect sizes of 0.7–0.9 for MWT response. For the response in terms of number of cataplexy episodes, NNT was six for the 6 g dose and three for the 7.5 g and 9 g doses; the effect sizes were between −0.7 and −0.8. For the Epworth Sleepiness Scale (ESS) response, NNTs ranged from three to six, with a dose–response effect. Effect sizes were between −0.5 and −0.7 for all doses.

Conclusions These post hoc results demonstrate the robustness of the REST-ON clinical trial efficacy data.

Clinical Trial ID: NCT02720744.

1 Introduction

Narcolepsy is a rare, chronic, neurologic sleep disorder [1–3]. Sodium oxybate (SXB) is strongly recommended in the USA and Europe for the treatment of excessive daytime sleepiness (EDS) and cataplexy in adults with narcolepsy [4, 5]. Once-nightly SXB (ON-SXB [LUMRYZ™] extended-release for oral suspension CIII; FT218) is approved by the US Food and Drug Administration for the treatment of EDS or cataplexy in patients 7 years of age and older with

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Key Points

This analysis confirms the statistically significant improvements in ability to stay awake, overall improvement, and number of cataplexy episodes with once-nightly sodium oxybate (ON-SXB) as demonstrated in the REST-ON trial, using multiple methods to account for missing data.

The medium to large effect sizes and minimal number needed to treat indicate clinically impactful effects on the ability to stay awake, number of cataplexy episodes, and daytime sleepiness with ON-SXB.

The results of these analyses confirm the robust efficacy of ON-SXB for the treatment of narcolepsy.

narcolepsy [6]. Clinical efficacy for all three evaluated ON-SXB dose levels (6 g, 7.5 g, and 9 g) was demonstrated in the 13-week, phase 3, pivotal REST-ON clinical trial [7, 8]. Statistically significant and clinically meaningful improvements were observed in all three REST-ON primary endpoints—mean sleep latency on the Maintenance of Wakefulness Test (MWT), Clinical Global Impression of Improvement (CGI-I) rating, and weekly number of cataplexy episodes—as well as the secondary endpoints of sleep stage shifts and nocturnal arousals measured by polysomnography and subjective assessments of sleep quality, refreshing nature of sleep, and EDS measured using the Epworth Sleepiness Scale (ESS) [7, 8].

In total, 222 participants enrolled in REST-ON. The primary efficacy analysis was conducted in the 190 participants of the modified intent-to-treat (mITT) population—participants with ≥ 1 efficacy measurement following receipt of either the 6 g dose of ON-SXB or placebo [7, 8]. Missing data for clinical trial participants are not uncommon and can result in biased treatment estimates [9–11]. In REST-ON, approximately 30% of participants discontinued the study early [7], similar to other oxybate trials [12], resulting in missing data for these participants. Therefore, the robustness of the results of REST-ON were evaluated using stringent statistical techniques to account for these missing data. Although no analysis methods can completely compensate for the effects of missing data, sensitivity analyses can be employed to assess the robustness of findings with respect to assumptions about the missing data [13, 14]. Moreover, additional context for interpreting treatment effect sizes provides information for clinical decision-making [15].

The primary objective of these post hoc sensitivity analyses was to assess the robustness of the results for the three coprimary endpoints from the REST-ON trial using a reduced participant population and widely accepted, rigorous statistical methods to account for missing data. Further context for the clinical efficacy of ON-SXB was provided via calculation of effect sizes and numbers needed to treat (NNT) for treatment response in the primary endpoints of mean sleep latency on the MWT and number of weekly cataplexy episodes, and the secondary endpoint, EDS, was measured using the ESS.

2 Methods

2.1 Study Design and Participants

The full details of REST-ON (NCT02720744), a double-blind, placebo-controlled, multicenter clinical trial evaluating the efficacy and safety of ON-SXB for the treatment of narcolepsy, have been reported previously [7]. Briefly, participants aged ≥ 16 years and stratified by narcolepsy type were randomly assigned to receive ON-SXB or placebo in a 1:1 ratio. After a 3-week screening period, participants received treatment with ON-SXB or placebo over 13 weeks (4.5 g for week 1, 6 g during weeks 2–3, 7.5 g during weeks 4–8, and 9 g during weeks 9–13) and were followed for 1 additional week. The study design allowed for the assessment of efficacy and safety of each dose level within the same participant [7].

Eligible participants had a diagnosis of either narcolepsy type (NT) 1 (narcolepsy with cataplexy) or NT2 (narcolepsy without cataplexy), according to the International Classification of Sleep Disorders (Third edition) [7, 16]. Key inclusion criteria were the continued presence of EDS for the preceding 3 months and an ESS score > 10, as well as the continuing presence of cataplexy (participants with NT1 only) for the previous 3 months. Participants using concomitant alerting agents must have had stable dosing for ≥ 3 weeks prior to screening, and the medication regimen was required to remain the same for the duration of the trial. Individuals were initially excluded from REST-ON if they had previously used SXB. The protocol was later amended to allow prior use of SXB ≤ 4.5 g per night for < 2 weeks and ≥ 1 year before entering the study [7].

The REST-ON trial was approved by the institutional review board or ethics committee at each study center and conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, International Council for Harmonisation guidelines, and applicable regulatory requirements at the national and local level. Written informed consent was obtained from all adult participants (≥ 18 years old); participants aged 16 or 17 years provided assent with written informed consent provided by their legal representative [7].

2.2 Assessments

In REST-ON, efficacy endpoints were assessed at baseline and at weeks 3 (6 g dose), 8 (7.5 g dose), and 13 (9 g dose) [7]. Mean sleep latency on the MWT was assessed as the average of five 30-min trials, with each trial terminating immediately after sleep onset or at 30 min in the case of no sleep. The CGI-I assessed the proportion of participants whose overall condition was rated by the clinician as "much improved" or "very much improved" from baseline, measured on a 7-point Likert scale, with a score of 1 indicating "very much improved" and a score of 7 indicating "very much worse." The mean weekly number of cataplexy episodes was determined for participants with NT1 using the cataplexy item from the Sleep and Symptom Daily Diary. Subjective evaluation of EDS was performed using the ESS, in which participants rated their likelihood of dozing off during eight daily activities on a 4-point scale ranging from 0 (never) to 3 (high), with a higher total score indicating greater sleepiness.

2.3 Statistical Analysis

Methods for the primary analysis of the REST-ON trial have been reported previously [7]. In brief, all primary efficacy analyses were conducted in the mITT population (n = 190), which included all randomized participants who had ≥ 1 efficacy measurement after receiving the 6 g dose of ON-SXB or placebo. MWT, cataplexy, and ESS data were analyzed with a mixed-effects model for repeated measures (MMRM). A logistic regression model for binomial data with logit link was used to analyze CGI-I data.

The post hoc sensitivity analyses for handling missing data reported here include evaluation of the coprimary endpoints of mean sleep latency on the MWT, the proportion of participants who were "much" or "very much" improved on the CGI-I, and the mean weekly number of cataplexy episodes. These endpoints were evaluated in an analysis of all participants who completed the 13-week REST-ON trial (completer population) and in the mITT population via the following analyses: placebo-based multiple imputation (MI) with a missing-not-at-random assumption, analysis of covariance (ANCOVA), and tipping-point–based MI of worsening values. Analyses of the MWT and number of cataplexy episodes evaluated changes from baseline at weeks 3 (6 g), 8 (7.5 g), and 13 (9 g); CGI-I analysis evaluated the proportion of participants with CGI-I ratings of "much" or "very much" improved at the same three time points and dose levels. All analyses that assessed the endpoint regarding number of cataplexy episodes included only those participants with NT1.

For the completer analysis, least squares mean differences (LSMDs), 95% confidence intervals (CIs), and P-values were calculated for change from baseline in mean sleep latency on the MWT and mean weekly number of cataplexy episodes. Odds ratios (OR), 95% CIs, and P-values for the proportion of participants who were "much" or "very much" improved on the CGI-I were also calculated.

In the placebo-based MI analysis, missing values in both treatment groups were imputed from values observed in the placebo group by assuming values were missing not at random. All ANCOVA models included the response variable associated with the endpoint, the fixed effects of treatment visit, treatment by visit, site (US or non-US), and the covariate of the baseline value for the response variable. The tipping-point MI analysis was performed to identify the outcome value at which the statistical significance of the model would be overturned (i.e., $P > 0.05$). For the placebo-based MI analysis, LSMDs for ON-SXB versus placebo, 95% CIs, and P-values were calculated for the MWT and cataplexy endpoints; ORs, 95% CIs, and P-values were calculated for the CGI-I endpoint. For the ANCOVA, LSMDs for ON-SXB versus placebo, 95% CIs, and P-values were calculated for all three coprimary endpoints. P-values were generated using Rubin's formula with 100 imputations for the three coprimary endpoints evaluated with the tipping-point–based MI analysis. Statistical significance was assessed using a two-sided α test at a 5% significance level.

Effect size analysis [17] was performed by calculating Cohen's d from the LSMDs for response of ON-SXB versus placebo in the mITT population on the endpoints of mean sleep latency on the MWT, mean weekly number of cataplexy episodes, and ESS score. All ON-SXB doses (6, 7.5, and 9 g) were assessed and compared with placebo. NNTs were calculated for response of ON-SXB versus placebo in the mITT population on the three coprimary endpoints of REST-ON, identifying the number of participants who need to be treated to obtain one additional responder.

For this post hoc analysis, participants were considered responders if their mean sleep latency increased from baseline by ≥ 5 min on the MWT, their ESS score was ≤ 10, or their mean weekly number of cataplexy episodes declined from baseline by ≥ 50% (participants with NT1). Thresholds were chosen before running the analysis.

3 Results

3.1 Patient Disposition and Demographics

In REST-ON, 66.6% of participants (148/222 randomized) completed the trial (week 13, ON-SXB 9 g dose) [7]; these 148 participants are included in the completer analysis (Fig. 1). The mITT population, in which the placebo-based MI, tipping-point MI, and ANCOVA analyses were conducted, included 190 participants (ON-SXB, n = 97 [NT1, n = 73]; placebo, n = 93 [NT1, n = 72]). Baseline

characteristics were well balanced in the safety population of 212 participants (ON-SXB, $n = 107$; placebo, $n = 105$) who received ≥ 1 dose of the study drug (Table 1). Most participants were white ($n = 160$; 75.5%), were female ($n = 144$; 67.9%), and had NT1 ($n = 162$; 76.4%). The mean age was 31.2 years. Concomitant medication use was reported by 171 (80.7%) participants, with alerting agents being the most frequently used concomitant medication. Of the 190 participants in the mITT population, 66 (34.7%) in the ON-SXB group and 53 (27.9%) in the placebo group were taking an alerting agent at baseline. One participant had prior exposure to SXB. Full patient demographics and disposition information have been previously published [7]. Results of the coprimary endpoints from the REST-ON primary analysis [7] are presented in Figs. 2A, 3A, and 4A.

Table 1 Participant clinical and demographic characteristics*

Characteristic	ON-SXB $N = 107$	Placebo $N = 105$
Mean (range) age, years	30.9 (16–72)	31.6 (16–69)
Female, *n* (%)	69 (64.5)	75 (71.4)
Race		
White	80 (74.8)	80 (76.2)
Black/African American	21 (19.6)	15 (14.3)
Asian	3 (2.8)	8 (7.6)
Other†	3 (2.8)	2 (1.9)
NT1, *n* (%)	80 (74.8)	82 (78.1)

*Table adapted from Kushida CA, et al. *Sleep*. 2022;45(6):zsab200

†Egyptian ($n = 2$); white/American Indian/Alaska Native ($n = 1$); half Asian, half white ($n = 1$); and multiracial (white, African American/Native American, $n = 1$)

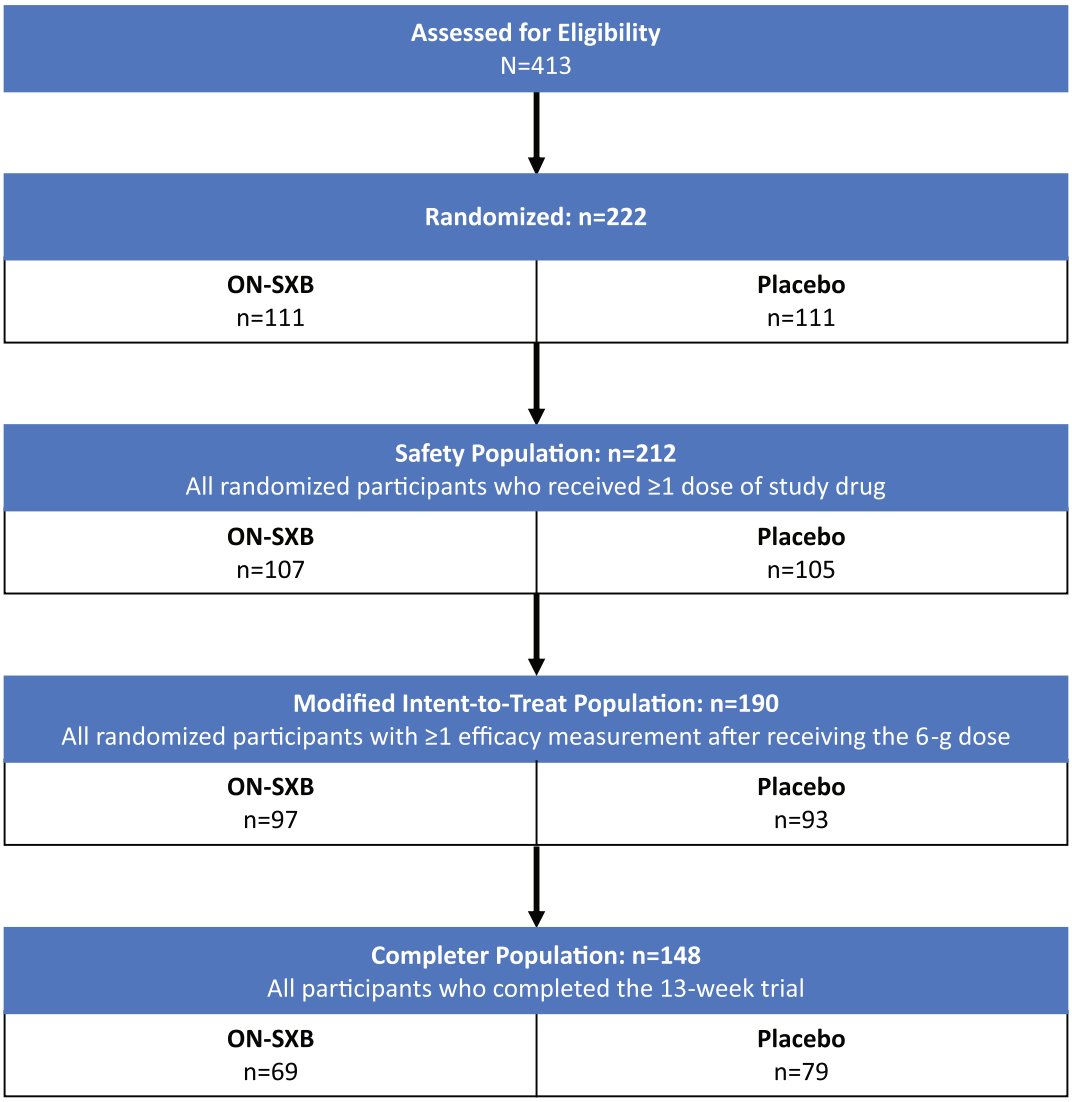

Fig. 1 REST-ON participant populations

3.2 Completer Population Analysis

In the completer population (ON-SXB, $n = 69$; placebo, $n = 79$), all doses of ON-SXB (6, 7.5, and 9 g) demonstrated significant improvements versus placebo for all coprimary endpoints ($P < 0.001$). With the 9-g dose, LSMD (95% CI) was 6.0 min (3.3–8.7) for the MWT (Fig. 2B), CGI-I responder proportions for ON-SXB and placebo were 72.3% and 31.6% (OR, 5.7 [95% CI: 2.8–11.6]; Fig. 3B), and LSMD (95% CI) was −6.6 (−9.6 to −3.6) for the number of cataplexy episodes (Fig. 4B).

3.3 Placebo-Based MI (Missing Not at Random)

All ON-SXB doses demonstrated significant improvements for all coprimary endpoints compared with placebo ($P < 0.001$), even if missing values in both arms were imputed from observed values in the placebo arm. With the 9-g dose, LSMD (95% CI) was 5.4 min (2.8–8.0) for the MWT (Fig. 2C), CGI-I responder proportions for ON-SXB and placebo were 63.0% and 28.5% (OR, 4.3 [95% CI: 2.3–8.0]; Fig. 3C), and LSMD (95% CI) was −6.4 (−9.0 to −3.7) for the number of cataplexy episodes (Fig. 4C).

3.4 ANCOVA

All ON-SXB doses demonstrated significant improvements for all coprimary endpoints compared with placebo ($P < 0.001$) when analyzed using ANCOVA. With the 9-g dose, LSMD (95% CI) was 6.0 min (3.6–8.5) for the MWT (Fig. 2D), −1.0 (−1.3 to −0.7) for CGI-I (Fig. 3D), and −6.4 (−9.0 to −3.7) for number of cataplexy episodes (Fig. 4D).

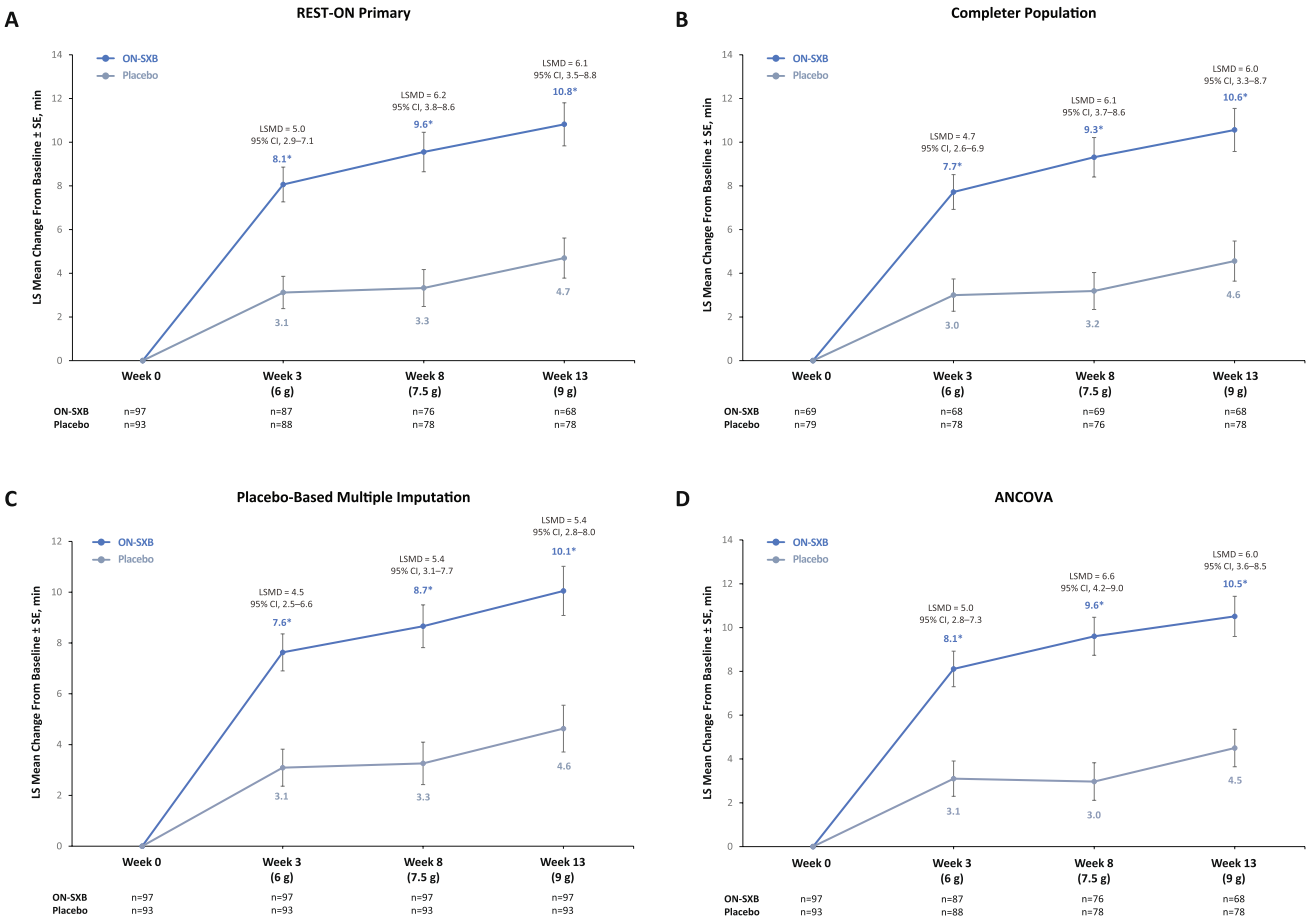

Fig. 2 Least squares mean change from baseline in mean sleep latency on the Maintenance of Wakefulness Test for participants receiving ON-SXB or matching placebo. **A** REST-ON primary analysis, **B** completer population analysis, **C** placebo-based multiple imputation sensitivity analysis, and **D** ANCOVA. ANCOVA, analysis of covariance; CI, confidence interval; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate; SE, standard error. *$P < 0.001$. †Figure adapted from Kushida CA, et al. *Sleep*. 2022;45(6):zsab200

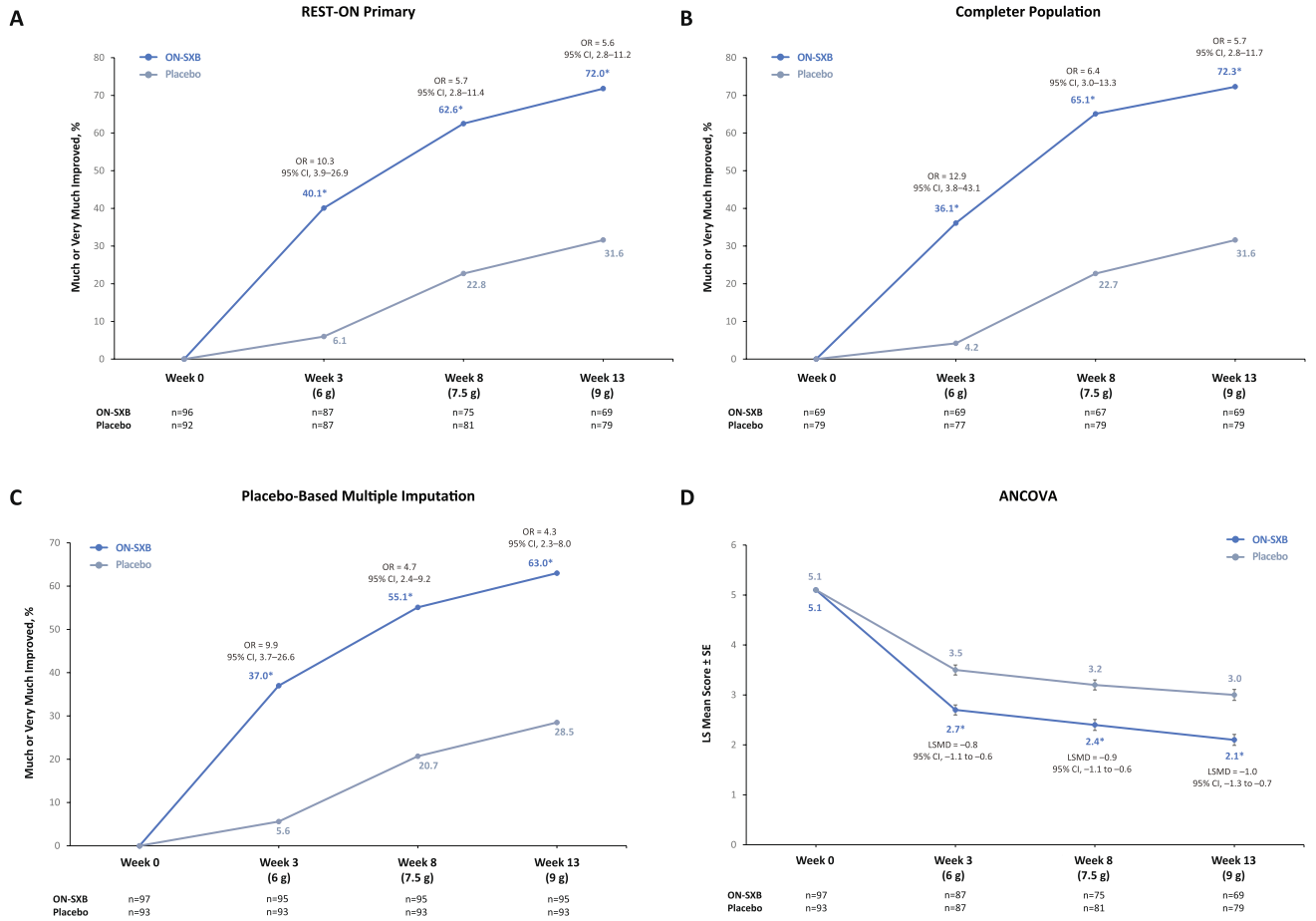

Fig. 3 Clinical Global Impression of Improvement. **A** REST-ON primary analysis, **B** completer population analysis, **C** placebo-based multiple imputation sensitivity analysis, and **D** ANCOVA. ANCOVA, analysis of covariance; CI, confidence interval; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate; OR, odds ratio. *$P < 0.001$. †Figure adapted from Kushida CA, et al. *Sleep*. 2022;45(6):zsab200

3.5 Tipping-Point–Based MI

For the MWT, the difference between ON-SXB and placebo lost significance with worsening of 7.0, 5.2, and 4.3 min from baseline for each of the three ON-SXB doses (6, 7.5, and 9 g), respectively. CGI-I remained significant ($P < 0.001$) for all ON-SXB doses versus placebo when participants who withdrew from the ON-SXB arm were imputed as "not improved" (i.e., minimally improved or worse on the 7-point scale). The number of cataplexy episodes remained significant for ON-SXB doses of 6, 7.5, and 9 g versus placebo when participants who withdrew from the ON-SXB arm were assigned worsening trajectories of up to 7.1 ($P < 0.001$), 8.8 ($P < 0.001$), and 9.4 ($P < 0.05$) additional weekly cataplexy episodes, respectively.

3.6 Effect Sizes

Effect sizes ranged from 0.7 to 0.9 for the MWT (Fig. 5A), −0.7 to −0.8 (a decrease in score denotes a response) for number of cataplexy episodes (Fig. 5B), and −0.5 to −0.7 (a decrease in score denotes a response) for the ESS (Fig. 5C).

3.7 NNT Analysis

The NNT was 3–6 for ON-SXB 6 g (week 3), 3–4 for ON-SXB 7.5 g (week 8), and 3 for ON-SXB 9 g (week 13) (Fig. 6).

4 Discussion

These post hoc analyses reveal the strengths of the efficacy data from the REST-ON clinical trial. Aligned with results of other clinical studies [10, 11], premature

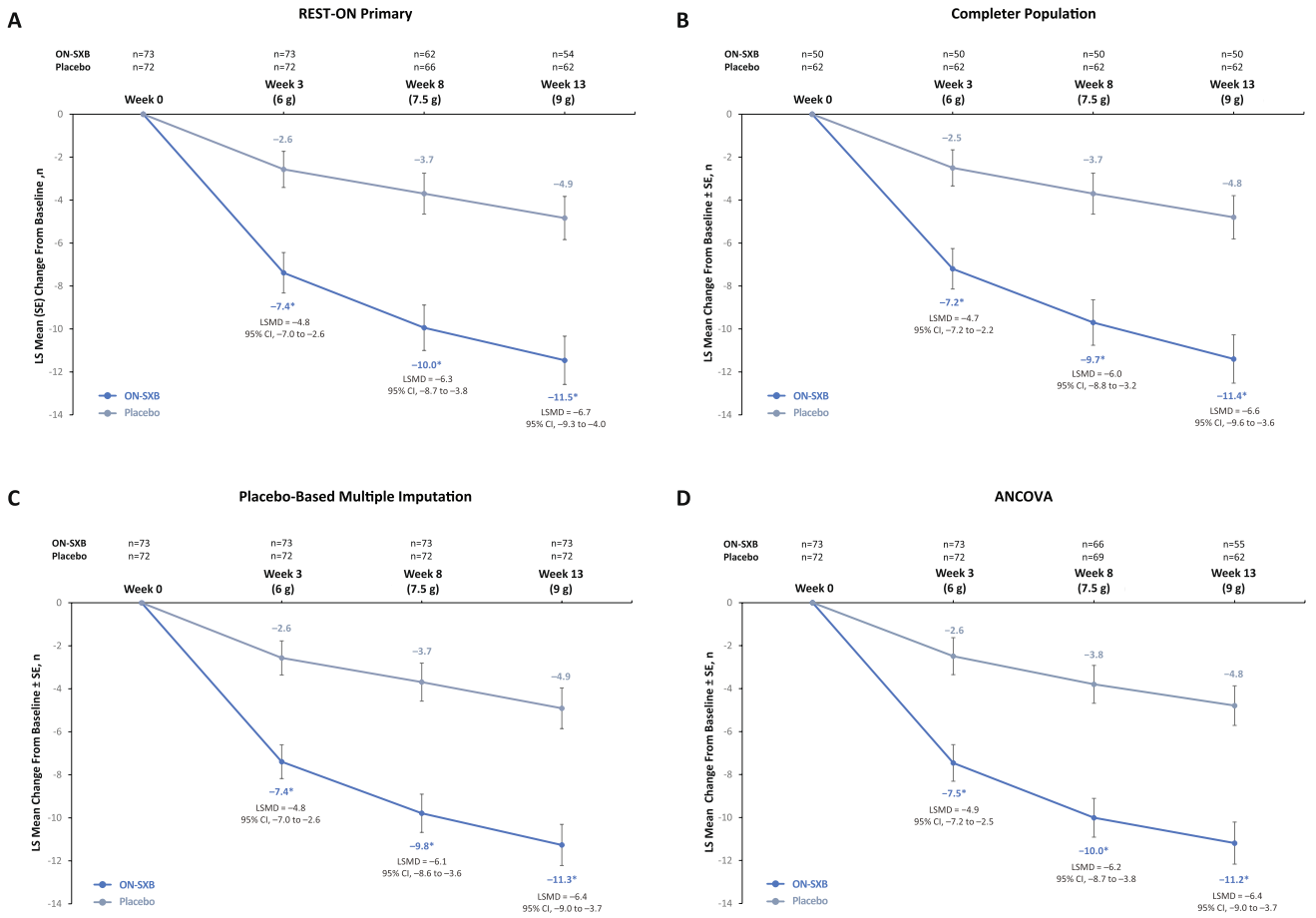

Fig. 4 Least squares mean change from baseline in mean weekly number of cataplexy episodes. **A** REST-ON primary analysis, **B** completer population analysis, **C** placebo-based multiple imputation sensitivity analysis, and **D** ANCOVA. ANCOVA, analysis of covariance; CI, confidence interval; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate; SE, standard error. *$P < 0.001$. †Figure adapted from Kushida CA, et al. *Sleep*. 2022;45(6):zsab200

discontinuations are not uncommon in oxybate trials; in the calcium/magnesium/potassium/sodium oxybates (mixed-salt oxybates) randomized withdrawal trial, 32% of subjects discontinued during the open-label titration phase and stable-dosing period [12]. Similarly, there was a 30% discontinuation rate in the REST-ON trial. Sensitivity analyses are useful to address potential bias associated with missing data [18]. Employing MI techniques in these analyses aids in reducing bias by accounting for variability between data [13, 18]. The completer population approach simply analyzed the subset (70%) of the REST-ON population that finished the entire 13-week trial; all endpoints remained statistically significant [7]. The second sensitivity analysis applied placebo values for the ~ 30% of the population that did not complete the trial; again, all endpoints remained statistically significant. The third method applied, ANCOVA, detected a difference in means of treatment groups while controlling for covariates (i.e., variables such as baseline score, which are not of primary interest); all endpoints remained statistically significant. The last sensitivity analysis identified hypothetical data points for the missing data at which the difference between ON-SXB and placebo would "tip" and no longer significantly favor ON-SXB treatment [19]. As described in the results, the MWT worsening is implausible, given that it is either greater than baseline (for the lower doses) or approximately the baseline MWT for the 9 g dose. For cataplexy, the tipping point of losing statistical significance would be based upon all missing values increasing by approximately 50% from the baseline values. Collectively, the results from the sensitivity analyses support the robust positive findings of REST-ON, assuaging concerns that may exist owing to the discontinuation rate.

The effect size using Cohen's *d* metric relies upon the standard deviation to express the extent of clinical response following treatment; an effect size of 0.5 or more is generally regarded as a moderate effect and 0.8 as a large effect [15, 17]. Effect sizes for the MWT, number of cataplexy

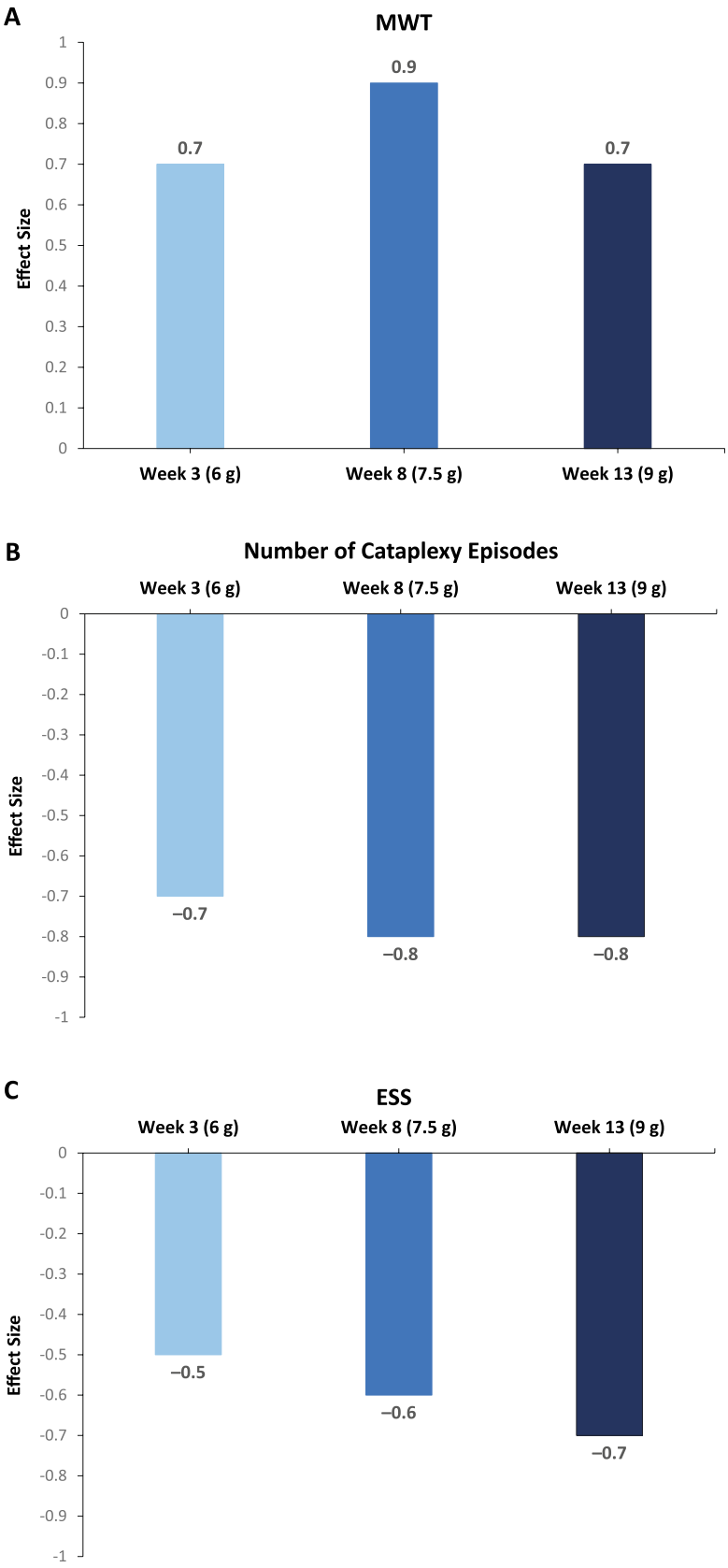

Fig. 5 Effect sizes with ON-SXB. **A** The MWT, **B** number of weekly cataplexy episodes, and **C** the ESS. ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; ON-SXB, once-nightly sodium oxybate

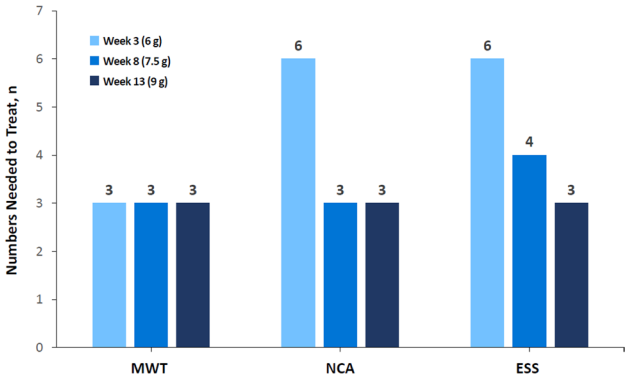

Fig. 6 Numbers needed to treat with ON-SXB for improvement in terms of the MWT, number of weekly cataplexy episodes, and the ESS. ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; NCA, number of cataplexy episodes; ON-SXB, once-nightly sodium oxybate

episodes, and the ESS indicate a medium to large effect for all ON-SXB doses compared with placebo (i.e., greater improvements versus placebo). NNTs provide a useful interpretation of the expected effectiveness of a medication; values less than 10 are generally considered to demonstrate a robust effect size difference [15]. NNT results for the MWT, number of cataplexy episodes, and the ESS suggest that only three to six individuals need to be treated with ON-SXB to achieve ≥ 5 min of increased sleep latency on the MWT or an ESS score of ≤ 10, with the same number needed to achieve a 50% or greater reduction in cataplexy. There was also a potential dose-dependent effect, with the 9-g dose requiring the fewest number of participants ($n = 3$); however, time on therapy may also have affected the therapeutic response, as efficacy with the 6-g dose was assessed at week 3.

The potential clinical benefit of a treatment should also be balanced with safety considerations. In the REST-ON trial, ON-SXB was generally well tolerated, with participants experiencing mostly mild to moderate severity treatment-emergent adverse events (TEAEs) [7]. TEAEs considered by investigators to be related to treatment with an incidence of ≥ 5% and greater than placebo included nausea, dizziness, enuresis, headache, and vomiting [7]; these adverse events (AEs) are in line with the known safety profile of oxybate products [20, 21]. Of the seven participants who experienced a serious TEAE during REST-ON, one event in the 9-g ON-SXB dose group was considered treatment-related (suicidal ideation) [7]. This participant discontinued study treatment, was treated in a psychiatric facility, and was subsequently seen by the investigator who considered the serious TEAE resolved.

These analyses have several limitations. Sensitivity analyses rely on assumptions about missing data that cannot be tested or verified [13, 14]; imputation of missing data, though useful and illustrative, cannot completely account for potential biases arising as an effect of missing data (i.e., discontinuation related to the perception of lack of efficacy or experience with side effects). A survey of published randomized controlled trials reported missing some primary outcome data for 75% of published trials, with 24% of trials missing > 10% of responses for the primary outcome [22]. As some level of missing outcome data is likely [23], efforts should be made by investigators to obtain data on treatment and outcomes of interest for discontinued participants, and thus preserve the benefits of initial randomization and minimize biases in treatment group comparisons to the extent possible [13, 14]. Despite these limitations, the results of these multiple post hoc sensitivity analyses, as well as the effect sizes and NNTs, support the primary results of the REST-ON trial [7].

5 Conclusions

The results of these post hoc analyses demonstrate the robustness of the REST-ON clinical trial data and further confirm the efficacy of ON-SXB for the treatment of narcolepsy. ON-SXB provides a once-at-bedtime oxybate treatment option for patients with this chronic and debilitating neurologic sleep disorder.

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Declarations

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Conflicts of Interest/Competing Interests TR is a consultant for Jazz Pharmaceuticals, Takeda Pharmaceutical Co., Orexo, Avadel Pharmaceuticals, Eisai, Merck & Co., and Idorsia. MJT is the guest editor of this supplement and played no part in the peer review or decision making of this article at the editorial level and contributed solely as an author. He has served as a consultant or on advisory boards for Axsome Therapeutics, Balance Therapeutics, Eisai, Avadel Pharmaceuticals, Harmony Biosciences, Jazz Pharmaceuticals, NLS Pharmaceuticals, Suven Life Sciences Ltd, and Takeda Pharmaceutical Co. CAK is a consultant for Avadel Pharmaceuticals and XW Pharma. JG 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 Contribution Thomas Roth: Writing – review and editing, formal analysis. Michael J. Thorpy: Writing – review and editing, formal analysis. Clete A. Kushida: Writing – review and editing, formal analysis. Jennifer Gudeman: Writing – review and editing, formal analysis.

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