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Effectiveness and Safety of Low-Sodium Oxybate in Participants With Narcolepsy: Results From the DUET Study

DUET STUDY 407

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Introduction

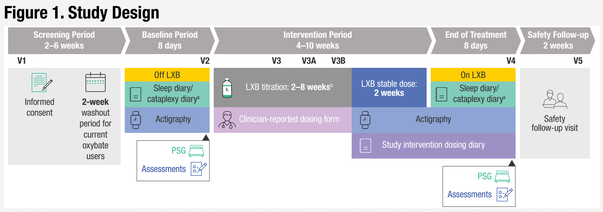
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat excessive daytime sleepiness (EDS) or cataplexy in patients ≥7 years of age with narcolepsy or idiopathic hypersomnia in adults[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, multicenter, single-arm, multiple-cohort, open-label study (NCT05875974)
- This patient-centric study evaluated the effectiveness of LXB on daytime and nighttime-related symptoms and functional outcomes in participants with narcolepsy (type 1 [NT1] or 2 [NT2]) or idiopathic hypersomnia
  - For effectiveness and safety results in the idiopathic hypersomnia cohort, please refer to **Poster 413**

Objective

- To evaluate the effectiveness and safety of LXB on daytime and nighttime-related symptoms in participants with narcolepsy

Methods

Figure 1. Study Design



[a]Cateplexy diary in narcolepsy type 1 only. [b]Weekly titration visits were by teleconference. Visit 3 occurred on titration day 14. Titration could take between 2 and 8 weeks. Additional in-clinic visits were scheduled for day 35 (visit 3A) and day 56 (visit 3B), as needed. Investigator could optimize participant dosage and move participant to stable dose at visit 3, 3A, or 3B but not during intervening weekly teleconferences.
EOT, end of treatment; LXB, low-sodium oxybate; PSG, polysomnography; V, visit.

- DUET comprised a screening period (with a 2-week washout for current oxybate users), an 8-day baseline (BL) period (ending with an overnight BL polysomnography [PSG] visit with additional assessments), a 2- to 8-week LXB titration period, a 2-week stable-dose period (SDP), an 8-day end-of-treatment (EOT) assessment period while participants are taking their optimized stable dose of LXB (ending with an overnight EOT PSG with additional assessments), an optional pharmacokinetic EOT visit (narcolepsy cohort only), and a 2-week safety follow-up
  - All participants with narcolepsy took LXB twice nightly (per the US prescribing label)[1]
- Eligible participants were adults 18 to 75 years of age with a primary diagnosis of NT1 or NT2 (meeting the *International Classification of Sleep Disorders – Third Edition* [ICSD-3][5] or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[6] criteria)
- Participants were required to have an Epworth Sleepiness Scale (ESS) score >10 at screening visit 1 or an ESS score >10 after the washout period, if taking an oxybate medication
- Participants were allowed to continue taking concomitant anticataplectics or alerting agents (stimulants or wake-promoting agents) but had to have been taking the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study period
- Exclusion criteria included the following:
  - Untreated or inadequately treated sleep-disordered breathing (ie, apnea-hypopnea index >10, with hypopnea definition including a ≥4% desaturation as per *The AASM Manual for the Scoring of Sleep and Associated Events*),[7] as assessed during the BL PSG visit
  - History or presence of an unstable or clinically significant medical condition or behavioral or psychiatric disorder (including active suicidal ideation or a current or past [within 1 year] major depressive episode), or another neurologic disorder or surgical history that could affect the participant's safety or interfere with the conduct of the study, as determined by the investigator
- The primary endpoint was change in ESS score from BL to EOT
- Key secondary endpoints for the narcolepsy cohort included change in 3 PSG parameters from BL to EOT: total number of shifts from deeper to lighter stages of sleep per night (from stage N1/N2/N3/ rapid eye movement [REM] to wake and from stage N2/N3/REM to N1; from the onset of persistent sleep to lights on), stage N3 sleep duration (in minutes, per night; from the first epoch of sleep [any stage] to lights on), and number of awakenings per night (defined as ≥2 consecutive wake epochs, separated by an epoch of stage N2, N3, or REM; from lights off to lights on)
- Additional secondary endpoints included the Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C), both assessing overall narcolepsy disease
- Safety endpoints included incidence and severity of treatment-emergent adverse events (TEAEs)
- The safety analysis set includes all participants who enrolled in the study and took their prescribed LXB regimen for ≥1 night after the BL period (narcolepsy cohort: N=55); 13 participants in the narcolepsy cohort transferred to a different study cohort; the completer analysis set includes all participants who enrolled in the study, took their prescribed LXB regimen for ≥1 night after the BL period, completed the SDP, and completed the PSG EOT visit (narcolepsy cohort: n=34)
- Details on statistical methodology and centralized PSG scoring definitions are available through the QR code on the bottom right corner of this poster

Results

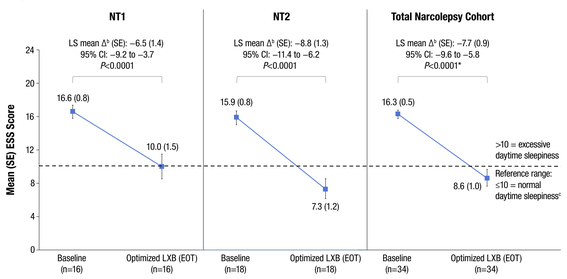
Table 1. Demographics and Baseline Characteristics for Enrolled Participants With Narcolepsy[a]

Characteristic	NT1 (n=26)	NT2 (n=29)	Total Narcolepsy Cohort (N=55)
Age (years)			
Mean (SD)	34.6 (12.6)	32.4 (13.2)	33.4 (12.9)
Median (min, max)	31.5 (18, 68)	28.0 (20, 75)	29.0 (18, 75)
Sex at birth, n (%)			
Male	7 (26.9)	8 (27.6)	15 (27.3)
Female	19 (73.1)	21 (72.4)	40 (72.7)
Gender identity, n (%)			
Male (including transgender man)	7 (26.9)	8 (27.6)	15 (27.3)
Female (including transgender woman)	19 (73.1)	21 (72.4)	40 (72.7)
Nonbinary	0	0	0
Other	0	0	0
Declined to state	0	0	0
Participant of childbearing potential, n (%)	14 (73.7)	19 (90.5)	33 (82.5)
Race, n (%)			
White	19 (73.1)	25 (86.2)	44 (80.0)
Black or African American	4 (15.4)	3 (10.3)	7 (12.7)
American Indian or Alaska Native	0	0	0
Asian	2 (7.7)	0	2 (3.6)
Native Hawaiian or other Pacific Islander	0	0	0
Multiple[b]	0	1 (3.4)	1 (1.8)
Unknown	1 (3.8)	0	1 (1.8)
Ethnicity, n (%)			
Hispanic or Latino	1 (3.8)	2 (6.9)	3 (5.5)
Not Hispanic or Latino	25 (96.2)	27 (93.1)	52 (94.5)
Body mass index (kg/m²)			
Mean (SD)	30.3 (6.9)	28.7 (6.6)	29.5 (6.7)
Median (min, max)	31.8 (20, 42)	25.5 (21, 44)	27.5 (20, 44)
Oxybate type at study entry, n (%)			
Naive[c]	18 (69.2)	24 (82.8)	42 (76.4)
Low-sodium oxybate	3 (11.5)	3 (10.3)	6 (10.9)
Sodium oxybate	3 (11.5)	2 (6.9)	5 (9.1)
Once-nightly sodium oxybate	2 (7.7)	0	2 (3.6)
Oxybate total nightly dosage at screening[d] (g)			
Mean (SD)	7.1 (1.4)	8.0 (1.2)	7.4 (1.4)
Median (min, max)	6.5 (5.6, 9.0)	8.0 (7.0, 9.0)	7.0 (5.6, 9.0)

[a]Safety analysis set. [b]Participant reported >1 race. [c]No oxybate use within 2 weeks of entering the study. [d]For the 13 participants who were taking an oxybate at screening and prior to washout; n=8 (NT1) and n=5 (NT2).
BL, baseline; LXB, low-sodium oxybate; max, maximum; min, minimum; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

- Fifty-five participants with narcolepsy enrolled in the study and took their prescribed LXB regimen for ≥1 night after the BL period; most were female (72.7%) and White (80.0%)

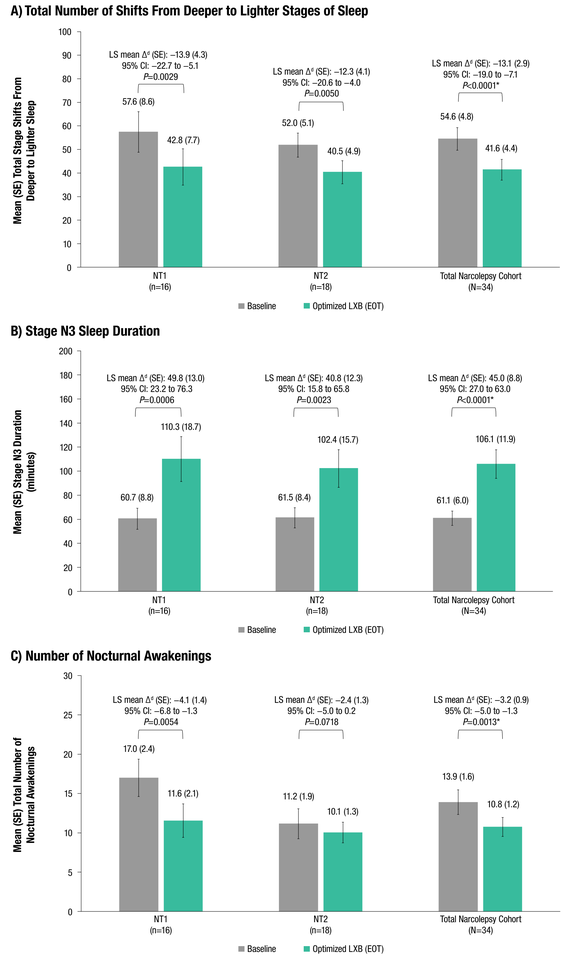
Figure 2. Epworth Sleepiness Scale Scores[a]



[a]Completer analysis set. [b]Difference between BL and EOT. [c]Established categories consider scores up to 10 normal. *The MCID for ESS was defined as 2 points according to an AASM systematic review and meta-analysis. [a]An ESS score >10 at screening was required for study inclusion. *Controlled for multiplicity.
AASM, American Academy of Sleep Medicine; BL, baseline; CI, confidence interval; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; MCID, minimal clinically important difference; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SE, standard error.

- Participants with narcolepsy taking LXB showed a statistically significant reduction in ESS score from BL to EOT (all cohorts, mean [SE]: total narcolepsy cohort, −7.7 [0.9]; NT1 cohort, −6.5 [1.4]; NT2 cohort, −8.8 [1.3])

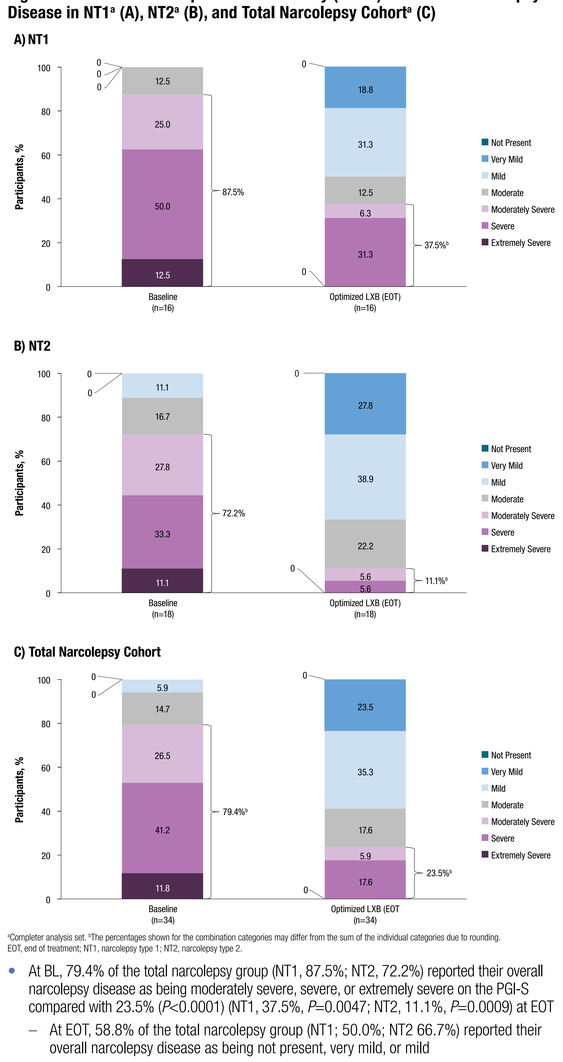
Figure 3. Total Number of Shifts From Deeper to Lighter Stages of Sleep[a,b] (A), Stage N3 Sleep Duration[a] (B), and Number of Nocturnal Awakenings[a,c] (C)



[a]Completer analysis set. [b]Sleep stage shifts included N1/N2/N3/REM to wake and N2/N3/REM to N1. [c]Defined as ≥2 consecutive wake epochs; awakenings must have been separated by an epoch of stage N2, N3, or REM. [d]Difference between BL and EOT. *Controlled for multiplicity.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N1 , non-REM stage 1; N2, non-REM stage 2; N3, non-REM stage 3; NT1, narcolepsy type 1; NT2, narcolepsy type 2; REM, rapid eye movement; SE, standard error.

- Participants with narcolepsy taking LXB experienced a reduction in the total number of shifts from deeper to lighter sleep stages, an increase in the duration of stage N3 sleep, and a reduction in the number of nocturnal awakenings from BL to EOT; all 3 assessments were statistically significant for the total narcolepsy cohort
- In the total narcolepsy cohort, the mean (SE) percentage of time spent in stage N3 sleep was 13.7 (1.4) minutes at BL and 24.0 (2.8) minutes at EOT

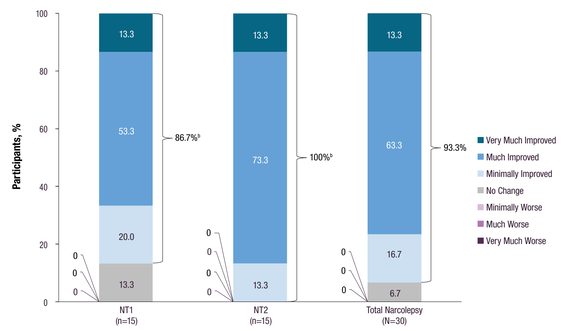
Figure 4. Patient Global Impression of Severity (PGI-S) for Overall Narcolepsy Disease in NT1[a] (A), NT2[a] (B), and Total Narcolepsy Cohort[a] (C)



[a]Completer analysis set. [b]The percentages shown for the combination categories may differ from the sum of the individual categories due to rounding.
EOT, end of treatment; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

- At BL, 79.4% of the total narcolepsy group (NT1, 87.5%; NT2, 72.2%) reported their overall narcolepsy disease as being moderately severe, severe, or extremely severe on the PGI-S compared with 23.5% (*P*<0.0001) (NT1, 37.5%, *P*=0.0047; NT2, 11.1%, *P*=0.0009) at EOT
  - At EOT, 58.8% of the total narcolepsy group (NT1; 50.0%; NT2 66.7%) reported their overall narcolepsy disease as being not present, very mild, or mild

Figure 5. Patient Global Impression of Change at End of Treatment for Overall Narcolepsy Disease[a]



[a]Completer analysis set. [b]The percentages shown for the combination categories may differ from the sum of the individual categories due to rounding.
NT1, narcolepsy type 1; NT2, narcolepsy type 2.

- At EOT, 93.3% (95% CI: 77.9–99.2) of the total narcolepsy group reported improvement (very much, much, or minimal) on the PGI-C for overall narcolepsy disease
  - Similarly, 86.7% (95% CI: 59.5–98.3) of participants with NT1 and 100% (95% CI: 78.2–100) with NT2 reported improvement (very much, much, or minimal) on the PGI-C for overall narcolepsy disease

Table 2. Mean Nightly LXB Dosage During Stable-Dose Period[a]

Mean (SD), grams	NT1 (n=16)	NT2 (n=20)	Total Narcolepsy Cohort (N=36[b])
Total nightly LXB dosage	7.3 (1.2)	6.9 (1.9)	7.0 (1.6)
First nightly LXB dose	3.8 (0.7)	3.6 (1.0)	3.7 (0.9)
Second nightly LXB dose	3.5 (0.6)	3.3 (1.1)	3.4 (0.9)

[a]Includes all participants from the safety analysis set who reached the SDP. Once a participant reached an optimized dosage, they continued this dosage as a stable regimen during the SDP and EOT period.
EOT, end of treatment; LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; SDP, stable-dose period.

- For the total narcolepsy cohort, the average optimized twice-nightly total dosage was 7.0 g/night
- Seven (12.7%) participants took LXB 9.0 g/night

Table 3. Concomitant Alerting Medications for Enrolled Participants With Narcolepsy[a]

Alerting Agent, n (%)	NT1 (n=26)	NT2 (n=29)	Total Narcolepsy Cohort (N=55)
Any alerting agent[b,c,d]	16 (61.5)	15 (51.7)	31 (56.4)
Centrally acting sympathomimetics			
Amphetamine aspartate, amphetamine sulfate, dexamphetamine saccharate, dexamphetamine sulfate	5 (19.2)	9 (31.0)	14 (25.5)
Methylphenidate	4 (15.4)	1 (3.4)	5 (9.1)
Solriamfetol hydrochloride	4 (15.4)	1 (3.4)	5 (9.1)
Lisdexamfetamine dimesylate	1 (3.8)	3 (10.3)	4 (7.3)
Armodafinil	1 (3.8)	0	1 (1.8)
Dexmethylphenidate	1 (3.8)	0	1 (1.8)
Modafinil	1 (3.8)	0	1 (1.8)
Other antidepressants			
Bupropion hydrochloride	2 (7.7)	1 (3.4)	3 (5.5)
Other nervous system drugs			
Pitolisant hydrochloride	3 (11.5)	5 (17.2)	8 (14.5)

[a]Safety analysis set. [b]Participants could have been taking multiple different alerting medications. [c]It is not known whether these agents were prescribed for excessive sleepiness, narcolepsy, and/or another condition. [d]Concomitant medications were started prior to the first dose of LXB and were ongoing throughout the study or could have been stopped after the first dose of LXB.
LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

- At study entry, 31 participants (56.4%) were taking alerting agents, with amphetamines being the most common (25.5%)

Table 4. Treatment-Emergent Adverse Events[a]

Participants, n (%)	NT1 (n=26)	NT2 (n=29)	Total Narcolepsy Cohort (N=55)
With ≥1 TEAE	16 (61.5)	18 (62.1)	34 (61.8)
With ≥1 TEAE related to treatment	15 (57.7)	14 (48.3)	30 (54.5)
With ≥1 TEAE leading to discontinuation	0	4 (13.8)	4 (7.3)
TEAEs occurring in ≥5% of participants			
Nausea	6 (23.1)	7 (24.1)	13 (23.6)
Dizziness	5 (19.2)	3 (10.3)	8 (14.5)
Headache	2 (7.7)	5 (17.2)	7 (12.7)
Somnolence	0	6 (20.7)	6 (10.9)
Vomiting	3 (11.5)	3 (10.3)	6 (10.9)
Anxiety	1 (3.8)	3 (10.3)	4 (7.3)
Nasal congestion	1 (3.8)	3 (10.3)	4 (7.3)
Oropharyngeal pain	2 (7.7)	2 (6.9)	4 (7.3)
Brain fog	0	3 (10.3)	3 (5.5)
Cough	0	3 (10.3)	3 (5.5)
Decreased appetite	1 (3.8)	2 (6.9)	3 (5.5)
Enuresis	3 (11.5)	0	3 (5.5)
Hypoesthesia	2 (7.7)	1 (3.4)	3 (5.5)

[a]Safety analysis set.
NT1, narcolepsy type 1; NT2, narcolepsy type 2; TEAE, treatment-emergent adverse event.

- The overall TEAE rate was 61.8% in the narcolepsy cohort; there were no serious TEAEs
- TEAEs were mild or moderate in severity; 4 participants with narcolepsy discontinued treatment due to a TEAE
  - TEAEs that led to discontinuation included nausea (n=1), anxiety (n=1), dysphoria (n=1), and irritability (n=1)

Conclusions

- Participants with NT1 and NT2 taking open-label LXB showed improvements in EDS (reduction of ESS scores), improvements in disrupted nighttime sleep (fewer shifts from deeper to lighter sleep stages, increased stage N3 sleep duration, and a reduction in the number of awakenings), and a reduced symptom burden (improved PGI-S and PGI-C ratings)
- This study provides prospective data on LXB treatment of narcolepsy
  - Limitations of the study include the open-label and single-arm design; causality cannot be established
  - Analyses were based on the completer analysis set of participants who reached a stable LXB dosage and may not represent the experience of all individuals starting LXB treatment
- TEAEs were consistent with the known safety profile of LXB
- These findings highlight the significant symptom burden experienced by individuals with narcolepsy, and reinforce the established effectiveness of LXB as a treatment for this condition

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Szarfman A, et al. *N Engl J Med.* 1995;333(19):1291. **3.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **4.** US Food and Drug Administration. Quantitative labeling of sodium, potassium, and phosphorus for human over-the-counter and prescription drug products. Guidance for industry. 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **5.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders–Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **6.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Publishing; 2013. **7.** Berry RB, et al. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 3.* Darien, IL: American Academy of Sleep Medicine; 2023. **8.** Johns MW. *Sleep.* 1991;14(6):540-545. **9.** Maski K, et al. *J Clin Sleep Med.* 2021;17(9):1895-1945.

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Supplemental Statistical Methods

- Formal hypothesis testing was conducted using the completer analysis set for the following endpoints:
  1. Epworth Sleepiness Scale (ESS) score (decrease from baseline [BL])
  2. Total sleep stage shifts from N1/N2/N3/rapid eye movement [REM] to wake and N2/N3/REM to N1 (decrease from BL)
  3. Duration of N3 sleep (increase from BL)
  4. Total number of nocturnal awakenings (decrease from BL)
- Decreases or increases from BL were estimated using an analysis of covariance (ANCOVA) model adjusted for the BL value. The parameter of interest for each endpoint, the least-squares mean difference at the end-of-treatment (EOT) visit, was compared against a null hypothesis value of 0.
- Multiplicity control was achieved using a sequential testing strategy conducted separately for each cohort. Listed endpoints were tested in the order shown above. The Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) endpoints were not controlled for multiplicity. Hypothesis tests with 2-sided $P<0.05$ in the expected direction were considered statistically significant. If any ordered endpoint failed to reject the null hypothesis, subsequent hypothesis tests were considered nominal. Hypothesis tests for endpoints not included in the sequential testing procedure were considered nominal.
- *P* values for comparisons of proportions of participants at BL versus EOT reporting "moderately severe/severe/extremely severe" on the PGI-S assessments were obtained from the McNemar test. Exact 95% CIs were obtained using the Clopper-Pearson method for the proportion of participants rating "minimal/much/very much" improvement at EOT on the PGI-C assessments.

Centralized Polysomnography Scoring Definitions: The following sleep stage definitions were adapted from *The AASM Manual for the Scoring of Sleep and Associated Events:*

- **Epoch:** a standard 30-second duration of the sleep recording that is assigned a sleep stage value.
- **Stage W:** corresponds to the waking state ranging from full alertness through the early stages of drowsiness; characterized by alpha activity in the electroencephalogram (EEG): trains of sinusoidal 8–13 Hz activity recorded over the occipital region with eye closure, attenuating with eye opening; any epoch between lights off and lights on during which a participant is out of bed is scored as Stage W.
- **Stage N1:** a relatively low amplitude, mixed frequency (LAMF) EEG with a majority of activity in the 4–7 cps range; vertex sharp waves may occur and are distinguishable from background EEG activity, maximal over the central region; slow eye movements typically are present; rapid eye movements are absent; tonic electromyographic (EMG) levels are usually below those of relaxed wakefulness.
- **Stage N2:** the presence of sleep spindles and/or K complexes (maximal over the central region) and the absence of sufficient high-amplitude, slow activity to define the presence of stage N3 sleep
- **Stage N3:** an EEG (epoch) with ≥20% of an epoch consisting of slow, high amplitude waveforms of 0.5–2 Hz and peak-to-peak amplitude of >75mV.
- **Stage R:** rapid eye movement (REM) sleep is defined by the concomitant appearance of LAMF EEG activity and episodic REMs; sawtooth waves (2–6 Hz waves maximal over the central region) may be present; chin EMG activity is typically low, and REM sleep is not scored in the presence of relatively elevated tonic mental-submental EMG activity.
- **Awakening:** 2 consecutive epochs of Wake.
- **Latency to onset of Persistent Sleep:** reported in minutes, defined as latency from lights off to the first epoch of 20 consecutive epochs of non-Wake.