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Long-term Safety and Timing of Adverse Events With Low-Sodium Oxybate in a Phase 3 Idiopathic Hypersomnia Study

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Introduction

- Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by chronic excessive daytime sleepiness; additional symptoms may include severe sleep inertia as well as prolonged, nonrestorative nighttime sleep, cognitive impairment, and long and unrefreshing naps[1,2]
- Low-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates; LXB; Xywav®) is approved by the US Food and Drug Administration for the treatment of idiopathic hypersomnia in adults and cataplexy or excessive daytime sleepiness in patients ≥7 years of age with narcolepsy[3-6]
- The efficacy and safety of LXB in adults with idiopathic hypersomnia were established in a placebo-controlled, double-blind, randomized withdrawal study (NCT03533114)[7]

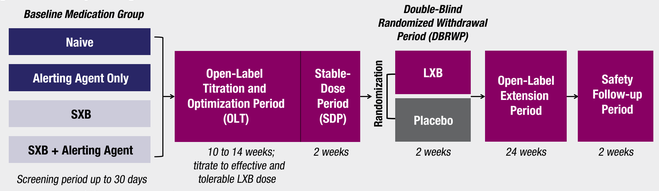
Objective

- To evaluate time of onset and duration of treatment-emergent adverse events (TEAEs) in a post hoc analysis of the phase 3, double-blind, placebo-controlled, randomized withdrawal trial of LXB in adults with idiopathic hypersomnia[7]

Methods

- Eligible participants were adults (18–75 years of age) diagnosed with idiopathic hypersomnia per *International Classification of Sleep Disorders*, version 2 (ICSD-2)[8] or version 3 (ICSD-3)[9] criteria, and with average nocturnal sleep time of ≥7 hours
- Participants could be taking medications for idiopathic hypersomnia symptoms, including high-sodium oxybate (SXB), alerting agents (stimulants or wake-promoting agents), or both, or could be treatment naive at study entry
  - Individuals treated with alerting agents were required to have been taking the same dose and regimen for ≥2 months before study entry and agreed to take the same dose throughout the study
  - Alerting agents include traditional stimulants (amphetamines and methylphenidates) and wake-promoting agents (modafinil, armodafinil, pitolisant, and solriamfetol)
  - The 6 participants who were taking SXB at study entry were excluded from these analyses
- Participants began LXB treatment during an open-label titration and optimization period (OLT; 10–14 weeks), during which LXB dosing was titrated to optimize efficacy and tolerability, followed by a 2-week stable-dose period (SDP), a 2-week double-blind randomized withdrawal period (DBRWP), a 24-week open-label extension (OLE), and a 2-week safety follow-up
- TEAEs were defined as any AEs that started or worsened in severity on or after the first dose of study drug, including AEs that occurred until 30 days after the last dose date, and were analyzed across all study periods in the analysis population (oxybate-naive participants who took ≥1 dose of study drug)
  - TEAEs that occurred during the DBRWP for participants randomized to placebo were excluded
- Onset, recurrence (quantified as 0 [never occurred], 1 [occurred once], etc), and duration (defined as the time from when a TEAE started until it was reported as ended) of common TEAEs (≥5% of the total population) were reported in the total population and by baseline medication group
- Results are presented using descriptive statistics; TEAEs are organized by System Organ Class

Figure 1. Study Design



LXB, low-sodium oxybate; SXB, high-sodium oxybate.

Results

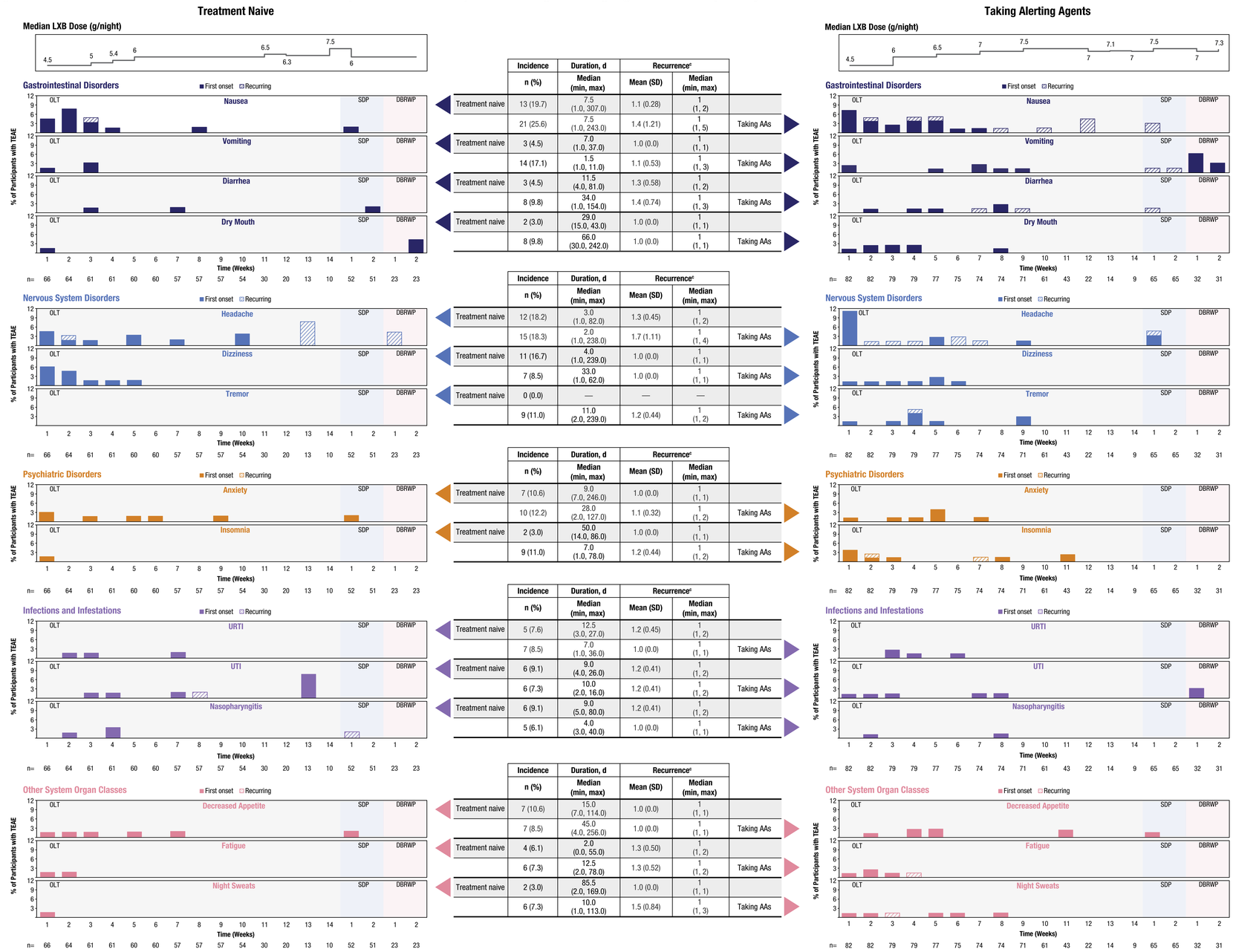
- The analysis population (N=148) included 82 participants taking alerting agents and 66 treatment-naive participants; there were no notable imbalances between these subgroups in terms of demographics or disease characteristics, except for percentage of females (75.6% and 60.6%, respectively) and North Americans (81.7% and 53.0%, respectively)

Table 1. Common TEAE (≥5%) Incidence, Duration, and Recurrence Across All Study Periods[a,b]

Preferred Term	Incidence, n (%)	Duration, d, median (min, max)	Recurrence, mean (SD)	Recurrence, median (min, max)
Nausea	34 (23.0)	7.5 (1.0, 307.0)	1.3 (0.97)	1 (1, 5)
Headache	27 (18.2)	2.5 (1.0, 238.0)	1.5 (0.89)	1 (1, 4)
Dizziness	18 (12.2)	9.5 (1.0, 239.0)	1.0 (0.00)	1 (1, 1)
Anxiety	17 (11.5)	21.0 (2.0, 246.0)	1.1 (0.24)	1 (1, 2)
Vomiting	17 (11.5)	2.0 (1.0, 37.0)	1.1 (0.49)	1 (1, 3)
Decreased appetite	14 (9.5)	36.0 (4.0, 256.0)	1.0 (0.00)	1 (1, 1)
Upper respiratory tract infection	12 (8.1)	8.0 (1.0, 36.0)	1.1 (0.29)	1 (1, 2)
Urinary tract infection	12 (8.1)	9.5 (2.0, 26.0)	1.2 (0.39)	1 (1, 2)
Diarrhea	11 (7.4)	16.0 (1.0, 154.0)	1.4 (0.67)	1 (1, 3)
Insomnia	11 (7.4)	11.0 (1.0, 86.0)	1.2 (0.40)	1 (1, 2)
Nasopharyngitis	11 (7.4)	8.5 (3.0, 80.0)	1.1 (0.30)	1 (1, 2)
Dry mouth	10 (6.8)	49.5 (15.0, 242.0)	1.0 (0.00)	1 (1, 1)
Fatigue	10 (6.8)	9.0 (0.0, 78.0)	1.3 (0.48)	1 (1, 2)
Tremor	9 (6.1)	11.0 (2.0, 239.0)	1.2 (0.44)	1 (1, 2)
Night sweats	8 (5.4)	10.0 (1.0, 169.0)	1.4 (0.74)	1 (1, 3)

[a]Recurrence included initial report of TEAE and any subsequent reports (ie, TEAE that occurred once had recurrence value of 1).
[b]5.7% (15/265) of TEAE end dates are unrecorded; missing dates are imputed from the date the individual participant ended the study.
d, day; max, maximum; min, minimum; SD, standard deviation; TEAE, treatment-emergent adverse event.

Figure 2. TEAEs Over Time in Treatment-Naive Participants and Participants Taking Alerting Agents at Study Entry[a,b]



[a]As OLT duration could vary from 10 to 14 weeks, sample size at later time points in that period was lower than at earlier time points.
[b]Participants reporting >1 TEAE of a given type per week were counted only once within that week; percentage is based on number of participants in study group in corresponding week.
[c]Recurrence included initial report of TEAE and any subsequent reports (ie, TEAE that occurred once had recurrence value of 1).
AA, alerting agent; d, day; DBRWP, double-blind randomized withdrawal period; LXB, low-sodium oxybate; OLT, open-label titration period; SD, standard deviation; SDP, stable-dose period; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

- There were 15 common TEAEs (≥5% of participants) in the analysis population
  - Nine of these TEAEs (nausea, headache, dizziness, anxiety, decreased appetite, upper respiratory tract infection, urinary tract infection, nasopharyngitis, fatigue) were reported in ≥5% of treatment-naive participants; the other 6 TEAEs (vomiting, diarrhea, insomnia, dry mouth, tremor, night sweats) were reported in <5% of treatment-naive participants
  - All 15 of these TEAEs were reported in ≥5% of participants taking alerting agents
- The majority of these TEAEs occurred within the first 5 weeks after study onset
- Overall, TEAEs were ≤21 days in duration, with the exception of decreased appetite (36.0 days) and dry mouth (49.5 days)
- On average, TEAEs recurred infrequently. Headache, diarrhea, night sweats, nausea, and fatigue were most likely to recur, with their mean (SD) recurrence being, respectively, 1.5 (0.89), 1.4 (0.67), 1.4 (0.74), 1.3 (0.97), and 1.3 (0.48)
- All common TEAEs (≥5%) were of mild or moderate severity
- TEAEs that led to discontinuation in >1 participant were anxiety (4/148, 2.7%), insomnia (3/148, 2.0%), and nausea (3/148, 2.0%)
- Nine serious TEAEs occurred in 4/148 (2.7%) participants; none were severe, considered related to study drug, or led to study discontinuation
  - Serious TEAEs were non-cardiac chest pain, rhabdomyolysis, and syncope (1 participant each) and, in 1 participant, nephrolithiasis (5 occurrences) and pyelonephritis (1 occurrence)

Conclusions

- In this post hoc analysis of LXB in participants with idiopathic hypersomnia, TEAEs (≥5% of participants) were consistent with the known safety profile of oxybate, generally occurred within the first 5 weeks after study onset, and were mild to moderate in severity in both treatment-naive participants and participants taking alerting agents
- The higher incidence of TEAEs early in the OLT period compared with later time points suggests that it is particularly important to monitor patients during initiation and titration of LXB treatment
- This analysis was limited in that measurement of TEAE duration relied on participant recall and sampling interval; additionally, average duration may lack accuracy for TEAEs with very low incidence
- These findings demonstrating the safety profile of LXB may help in managing expectations and guiding dosing optimization based on efficacy and tolerability

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