005 Minimal Clinically Important Difference for the Visual Analog Scale for Sleep Inertia Using Data From a Phase 3 Trial of Low-Sodium Oxybate for Idiopathic Hypersomnia

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Introduction

- Sleep inertia (difficulty awakening), a common symptom in people with idiopathic hypersomnia, can significantly impair functioning and quality of life[1-3]
- The visual analog scale for sleep inertia (SI-VAS) is a useful measure for monitoring the severity of sleep inertia[4]
- Calcium, magnesium, potassium, and sodium oxybates (low-sodium oxybate [LXB]) is approved in the United States for the treatment of idiopathic hypersomnia in adults[5]
  - The SI-VAS was used to assess sleep inertia in the phase 3 trial of LXB in participants with idiopathic hypersomnia (NCT03533114)[4]
  - To date, however, the minimal clinically important difference (MCID) for SI-VAS has not been determined

Objective

- Propose an MCID for SI-VAS using an anchor-based method and Patient Global Impression of Change (PGIc) data from a phase 3 trial of LXB in participants with idiopathic hypersomnia

Methods

- Eligible participants (18–75 years of age with a diagnosis of idiopathic hypersomnia) began LXB treatment in an open-label treatment titration and optimization period (10–14 weeks); a 2-week stable-dose period (SDP) followed; subsequently, participants were randomized to placebo or to continued LXB treatment for a 2-week, double-blind, randomized withdrawal period (DBRWP)[4]
- Using the SI-VAS, participants rated their difficulty awakening in the morning on a 100-mm line anchored at 0 (very easy) and 100 (very difficult)
- Using the PGIc, participants rated changes in their overall idiopathic hypersomnia symptoms on a 7-point Likert-type scale anchored at 1 (very much improved) and 7 (very much worse)
- Participants completed the SI-VAS at baseline, end of SDP, and end of DBRWP, and the PGIc throughout titration, at end of SDP, and at end of DBRWP
- The MCID was estimated using nonmissing data pairs (screening vs SDP, or SDP vs DBRWP) by assessing the relationship between change in SI-VAS and PGIc scores via the Kruskal-Wallis test and a linear mixed model (LMM) with repeated measurements

Results

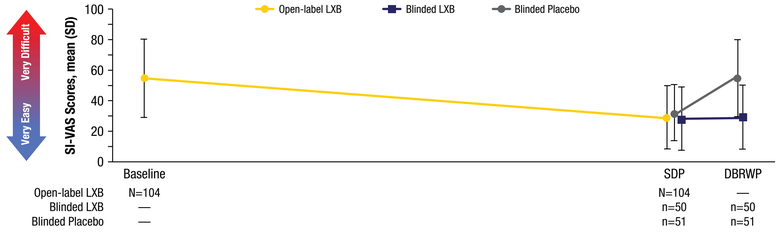
Table 1. Participant Demographics and Baseline Characteristics

Characteristic	Participants (N=109[a])
Age, years, mean (SD)	40.8 (14.1)
Female, n (%)	76 (69.7)
Race, n (%)	
Black or African American	6 (5.5)
Native Hawaiian or other Pacific Islander	1 (0.9)
White	89 (81.7)
Declined to answer	12 (11.0)
Multiple	1 (0.9)
BMI, kg/m^2, mean (SD)	27.8 (8.1)
Baseline CGIs, n (%)[b]	
Normal, not at all ill	0
Borderline ill	1 (0.9)
Mildly ill	4 (3.7)
Moderately ill	43 (39.5)
Markedly ill	38 (34.9)
Severely ill	22 (20.2)
Among the most extremely ill	1 (0.9)

[a]Includes all participants with nonmissing data pairs used in the MCID analysis (screening vs SDP, or SDP vs DBRWP).
[b]Due to rounding, percentages do not sum to 100.
BMI, body mass index; CGIs, Clinical Global Impression of Severity; DBRWP, double-blind, randomized withdrawal period; MCID, minimal clinically important difference; SD, standard deviation; SDP, stable-dose period.

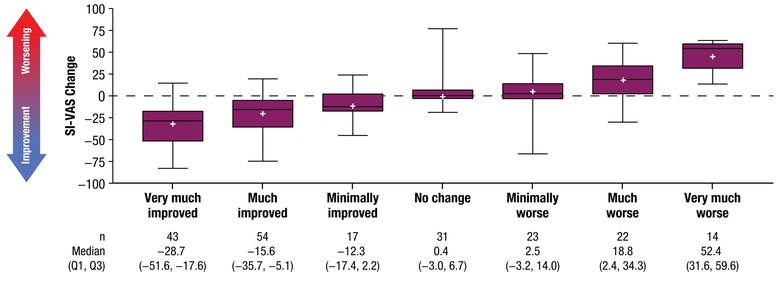
- Most (95%) participants were at least moderately ill on the Clinical Global Impression of Severity at baseline

Figure 1. Change in SI-VAS Scores During Open-Label Treatment, Stable Dosing, and Randomized Withdrawal[a]



[a]Includes all participants with nonmissing data pairs used in the MCID analysis (screening vs SDP, or SDP vs DBRWP).
Dash (—) represents absence of subgroup, per study design, at given time point.
DBRWP, double-blind randomized withdrawal period; LXB, low-sodium oxybate; MCID, minimal clinically important difference; SDP, stable-dose period; SI-VAS, visual analog scale for sleep inertia.

Figure 2. Change in SI-VAS Scores by PGIc Level: Descriptive

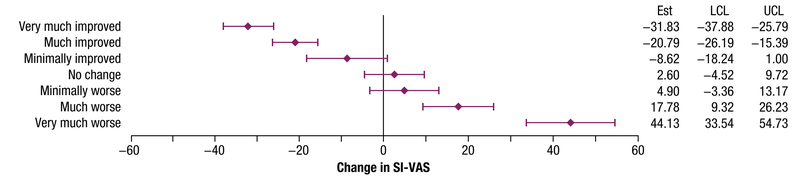


Data represent all nonmissing data pairs in the safety population. PGIc was assessed at end of SDP and end of DBRWP and compared; change in SI-VAS was calculated from SDP week 2 to end of DBRWP. Horizontal lines within boxes represent median values; + signs represent mean values; lower bounds of boxes represent Q1; upper bounds of boxes represent Q3; whiskers represent minimum and maximum values.
DBRWP, double-blind randomized withdrawal period; PGIc, Patient Global Impression of Change; Q1, quartile 1; Q3, quartile 3; SDP, stable-dose period; SI-VAS, visual analog scale for sleep inertia.

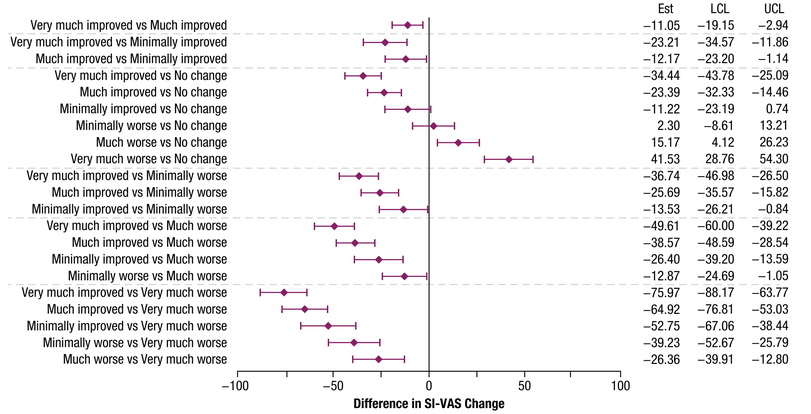
- Change in SI-VAS score was strongly associated with change in PGIc level (Kruskal-Wallis test statistic, 110.2; $P<0.0001$)

Figure 3. Change in SI-VAS Scores by PGIc Level: LMM With Repeated Measurements

A) Change in SI-VAS by PGIc Response



B) Pairwise PGIc Differences in Change in SI-VAS



PGIc was assessed at end of SDP and end of DBRWP; change in SI-VAS was calculated from study baseline to SDP week 2, and again from SDP week 2 to end of DBRWP. Data represent all nonmissing data pairs in the safety population. Estimates were obtained from an LMM of change in SI-VAS with PGIc as a categorical factor and random subject effect to account for repeated measurements.
DBRWP, double-blind randomized withdrawal period; Est, estimate; LCL, lower 95% confidence limit; LMM, linear mixed model; PGIc, Patient Global Impression of Change; SDP, stable-dose period; SI-VAS, visual analog scale for sleep inertia; UCL, upper 95% confidence limit.

- The estimated mean (standard error) difference in SI-VAS scores between consecutive PGIc levels was 10.9 (0.8) mm
- On that basis, an MCID of 10–12 mm is suggested for the SI-VAS

Conclusions

- The suggested MCID of 10–12 mm for the SI-VAS is based on change in PGIc scores using an anchor-based approach in this phase 3 clinical trial of LXB for patients with idiopathic hypersomnia
- This MCID for the SI-VAS may help clinicians identify clinically meaningful change in their management of sleep inertia, a common and debilitating symptom of idiopathic hypersomnia[1]

References: 1. Evangelista E, et al. *Sleep.* 2022;45(1):zsab220. **2.** Arnulf I, et al. *Sleep Med Rev.* 2023;69:101766. **3.** *International Classification of Sleep Disorders – Third Edition, Text Revision* (ICSD-3-TR). Darien, IL: American Academy of Sleep Medicine; 2023. **4.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. **5.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.

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