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Weight Changes During Treatment With Lower-Sodium Oxybate in a Phase 3 Clinical Study in Patients With Idiopathic Hypersomnia

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Yves Dauvilliers, MD, PhD[1,2]; Patricia Chandler, MD[3]; Luke Hickey, MSc[4]; Abby Chen, MS[3]; Teresa Steininger, PhD[3]; Nancy Foldvary-Schaefer, DO, MS[5]

[1]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France; [2]University of Montpellier, INSERM Institute Neuroscience Montpellier (INM), Montpellier, France; [3]Jazz Pharmaceuticals, Palo Alto, CA, USA; [4]Jazz Pharmaceuticals, Philadelphia, PA, USA; [5]Sleep Disorders Center, Department of Neurology, Cleveland Clinic, Cleveland, OH, USA

Introduction

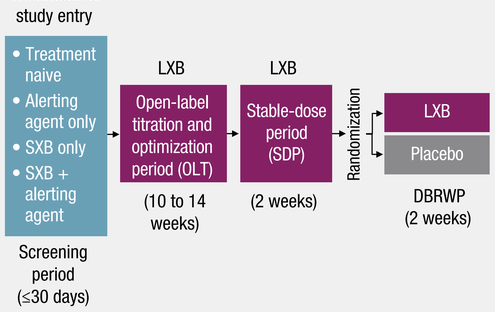
- Treatment with sodium oxybate (SXB; Xyrem®) has been associated with weight loss in narcolepsy[1-4]
- Lower-sodium oxybate (LXB; Xywav®) contains the same active moiety as SXB, with 92% less sodium, and is approved in the United States for the treatment of idiopathic hypersomnia in adults and previously approved for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy[5,6]
- The efficacy and safety of LXB for the treatment of idiopathic hypersomnia were established in a phase 3, double-blind, randomized withdrawal study (NCT03533114)[7]

Objective

- This analysis assessed weight changes after 12 to 16 weeks of open-label LXB treatment in adults with idiopathic hypersomnia in the phase 3 clinical study

Methods

Figure 1. Study Design

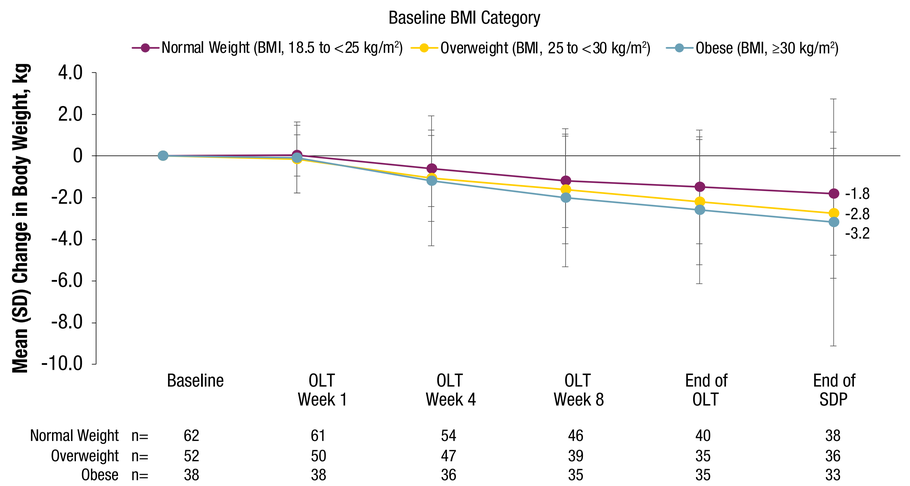


DBRWP, double-blind randomized withdrawal period; LXB, lower-sodium oxybate; SXB, sodium oxybate.

- Eligible participants were 18 to 75 years of age with a primary diagnosis of idiopathic hypersomnia according to *International Classification of Sleep Disorders*, 2nd or 3rd Edition criteria and an average nocturnal total sleep time of at least 7 hours
  - Participants were either treatment naive or taking medications for idiopathic hypersomnia symptoms, including SXB and/or alerting agents (stimulants or wake-promoting agents)
  - Participants taking alerting agents were required to have been taking the same dose and regimen for ≥2 months before screening and to take the same dose throughout the study
- Participants began LXB treatment in a 10- to 14-week, open-label, optimized treatment and titration period (OLT), followed by a 2-week stable-dose period (SDP) on their optimized dose of LXB
- *P* values for changes in weight from baseline are from a linear mixed model with weight as the response variable, baseline weight and baseline body mass index (BMI) subgroup as covariates, and visit as the random effect
  - Due to no adjustments for multiplicity, the *P* values presented are nominal

Results

Figure 2. Mean Decrease in Body Weight Over Time Based on Baseline BMI Categories[a,b]



		Baseline	OLT Week 1	OLT Week 4	OLT Week 8	End of OLT	End of SDP
Normal Weight	n=	62	61	54	46	40	38
Overweight	n=	52	50	47	39	35	36
Obese	n=	38	38	36	35	35	33

Note: n's represent the number of participants with vital signs collected at the indicated time point.
BMI, body mass index; OLT, open-label titration and optimization period; SD, standard deviation; SDP, stable-dose period.
[a]Safety population includes all participants who took ≥1 dose of study drug.
[b]Underweight category (BMI, <18.5 kg/m²) not shown; at baseline, 2 (1.3%) participants were underweight.

- At the end of the SDP, mean (SD) change in body weight in the safety population (n=108) was –2.5 (4.1) kg
- Mean (SD) decreases in body weight at the end of the SDP were numerically greater in participants with higher baseline BMI (overweight, –2.8 [3.1] kg, *P*=0.3407; obese, –3.2 [5.9] kg, *P*=0.3253) compared with normal baseline BMI (–1.8 [3.0] kg)
- Mean (SD) decreases in body weight at the end of the SDP were similar in participants taking idiopathic hypersomnia medications at baseline (–2.3 [2.8] kg) compared with treatment-naive participants (–2.8 [5.5] kg)

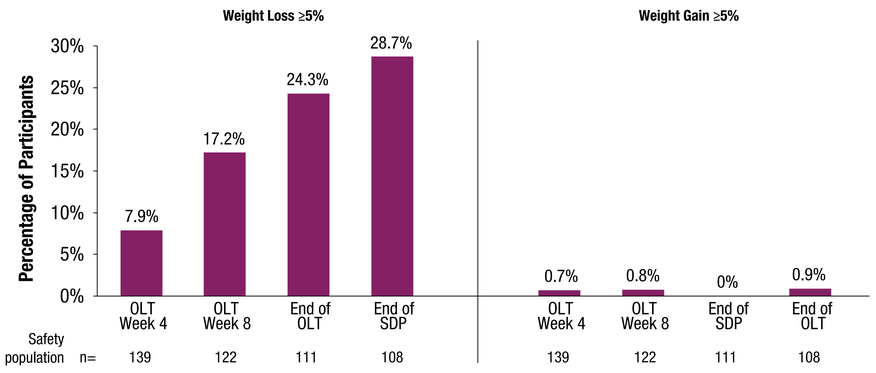
Table 1. Demographics and Baseline Disease Characteristics

Characteristic	Taking Idiopathic Hypersomnia Medication[a] (n=88)	Treatment Naive[b] (n=66)	Safety Population[c] (N=154)
Age, years, mean (SD)[d]	41.0 (13.4)	39.4 (14.3)	40.3 (13.7)
Female, n (%)	65 (73.9)	40 (60.6)	105 (68.2)
Race, n (%)			
White	76 (86.4)	53 (80.3)	129 (83.8)
Black or African American	5 (5.7)	4 (6.1)	9 (5.8)
Other[e]	7 (8.0)	9 (13.6)	16 (10.4)
Weight, mean (SD), kg	75.0 (19.0)	79.4 (17.9)	76.9 (18.6)
BMI, mean (SD), kg/m²	26.5 (5.9)	27.9 (5.8)	27.1 (5.9)
BMI category, n (%)			
Underweight (<18.5 kg/m²)	2 (2.3)	0 (0.0)	2 (1.3)
Normal weight (18.5 to <25 kg/m²)	39 (44.3)	23 (34.8)	62 (40.3)
Overweight (25 to <30 kg/m²)	28 (31.8)	24 (36.4)	52 (33.8)
Obese (≥30 kg/m²)	19 (21.6)	19 (28.8)	38 (24.7)
Treatment at study entry, n (%)			
Treatment naive	0 (0.0)	66 (100.0)	66 (42.9)
Alerting agent only	82 (93.2)	0 (0.0)	82 (53.2)
SXB only	2 (2.3)	0 (0.0)	2 (1.3)
SXB + alerting agent	4 (4.5)	0 (0.0)	4 (2.6)

BMI, body mass index; SD, standard deviation; SXB, sodium oxybate.
[a]Includes participants who were taking an alerting agent (stimulant or wake-promoting agent) at study entry. [b]Includes participants not taking SXB or an alerting agent (stimulant or wake-promoting agent) at study entry. [c]Includes all participants who took ≥1 dose of study drug. [d]Participants ranged from 19 to 75 years of age. [e]Includes declined to state.

- Over half of the participants (58%) were overweight or obese at baseline

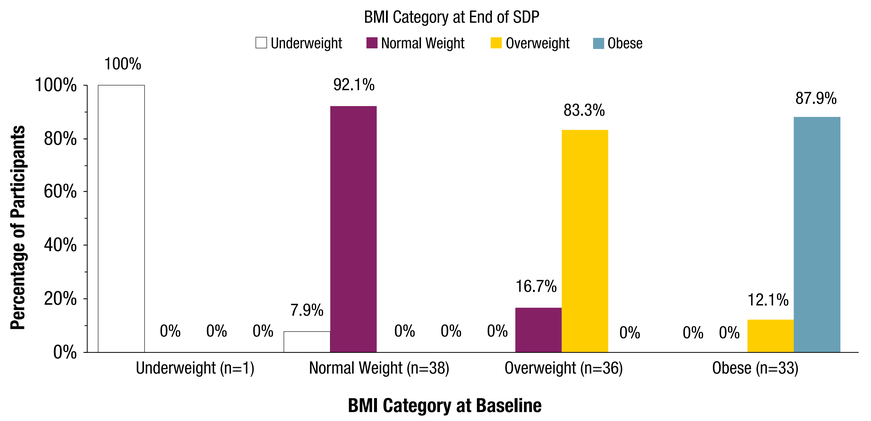
Figure 3. Substantial (≥5%) Weight Changes From Baseline[a]



Safety population	n=	OLT Week 4	OLT Week 8	End of OLT	End of SDP	OLT Week 4	OLT Week 8	End of SDP	End of OLT
		139	122	111	108	139	122	111	108

Note: n's represent the number of participants with vital signs collected at the indicated time point.
OLT, open-label titration and optimization period; SDP, stable-dose period.
[a]Safety population includes all participants who took ≥1 dose of study drug.

Figure 4. Most Participants Remained Within Their Baseline BMI Category at the End of SDP[a]



BMI, body mass index; SDP, stable-dose period.
[a]Includes participants in the safety population with available BMI data at the end of the SDP.

- Across all study periods, excluding placebo data, treatment-emergent adverse events (TEAEs) of decreased weight were reported by 5 (3.2%) participants
  - TEAEs of decreased weight occurred in 2 (2.3%) participants taking idiopathic hypersomnia medication at baseline and 3 (4.5%) treatment-naive participants
  - At the time of the TEAEs of decreased weight, 1 (0.6%) participant was underweight (BMI, 18.4 kg/m²), 1 (0.6%) participant was normal weight (BMI, 19.6 kg/m²), 1 (0.6%) participant was overweight (BMI, 25.7 kg/m²), and 2 (1.3%) participants did not have BMI recorded
- No TEAEs of decreased weight were severe or serious, or resulted in discontinuation

Conclusions

- Adults with idiopathic hypersomnia experienced weight loss during open-label LXB treatment, including substantial (≥5%) weight loss in 28.7% of participants
  - Mean weight loss was numerically greater in participants who were overweight or obese at baseline compared with those who were normal weight
- Most participants who were normal weight at baseline remained normal weight at the end of the SDP, whereas 16.7% of those who were overweight at baseline became normal weight, and 12.1% of those who were obese at baseline became overweight
- TEAEs of decreased weight were reported by 5 (3.2%) participants; none were severe or serious, or resulted in discontinuation

References: 1. Plazzi G, et al. *Lancet Child Adolesc Health.* 2018;2:483-94. **2.** Husain AM, et al. *Sleep Med.* 2009;10:661-3. **3.** Ponziani V, et al. *Sleep.* 2021;44:1-7. **4.** Schinkelshoek MS, et al. *J Sleep Res.* 2019;28:e12684. **5.** Bogan RK, et al. *Sleep.* 2021;44:zsaa206. **6.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **7.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21:53-65.

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Disclosures: Y Dauvilliers is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, UCB Pharma, Flamel Technologies, Theranexus, and Bioprojet. **P Chandler, L Hickey, A Chen,** and **T Steininger** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals. **N Foldvary-Schaefer** has served on an advisory committee for Jazz Pharmaceuticals and participated in clinical trials supported by Jazz Pharmaceuticals, Suven, and Takeda.

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