136

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

SLEEP 2022, the 36th Annual Meeting of the Associated Professional Sleep Societies (APSS)
June 4-8, 2022 • Charlotte, NC

Nancy Foldvary-Schaefer, DO, MS[1]; Roman Skowronski, MD, PhD[2]; Luke Hickey, MSc[3]; Abby Chen, MS[2]; Thomas J. Measey, PhD[3]; Yves Dauvilliers, MD, PhD[4,5]

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

Introduction

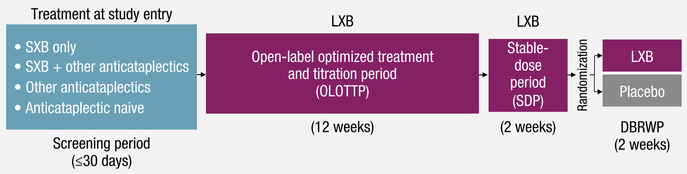
- In narcolepsy, treatment with sodium oxybate (SXB; Xyrem®) has been associated with weight loss[1-4]
- Lower-sodium oxybate (LXB; Xywav®) contains the same active moiety as SXB, with 92% less sodium, and is approved in the United States for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy, and idiopathic hypersomnia in adults[5,6]
  - LXB has been recognized by the US Food and Drug Administration in the narcolepsy population for its significant reduction in chronic sodium burden compared with SXB, which "will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated"[7]
- The efficacy and safety of LXB for the treatment of narcolepsy with cataplexy in adults were established in a phase 3, double-blind, randomized withdrawal study (NCT03030599)[5]

Objectives

- This analysis assessed weight changes after 14 weeks of open-label LXB treatment in adults with narcolepsy with cataplexy 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 18–70 years of age with a primary diagnosis of narcolepsy with cataplexy according to *International Classification of Sleep Disorders,* 3rd edition or *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition criteria
  - Participants may have been taking SXB and/or other anticataplectic medications (primarily antidepressants), or were cataplexy treatment naive
  - Participants taking medication(s) for the treatment of cataplexy were required to have been taking the same dose and regimen for ≥2 months before study entry
  - Participants taking stimulants and/or wake-promoting agents were required to take the same dose and regimen throughout the study
- Participants entered a 12-week, open-label, optimized treatment and titration period (OLOTTP) with initiation and titration of LXB occurring alongside tapering and discontinuation of any prior other anticataplectic treatments (tapering to begin after week 2 with discontinuation by the end of week 10), followed by ≥2 weeks of LXB alone (weeks 11 and 12) for all participants
  - Participants taking SXB (with or without other anticataplectics) at study entry transitioned from SXB to the same dose and regimen of LXB; after 2 weeks, the dose could be adjusted as needed
  - Participants not taking SXB at study entry initiated LXB treatment at 4.5 g/night and titrated to an optimal dose
  - The maximum total dose of LXB was 9 g/night; titration proceeded at ≤1.5 g/night/week
- The OLOTTP was followed by a 2-week stable-dose period (SDP) during which participants took their stable LXB dose, unchanged, for 2 weeks
- *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 subgroup as covariates, and visit as the random effect
  - The *P* values presented are nominal; no adjustments for multiplicity were made

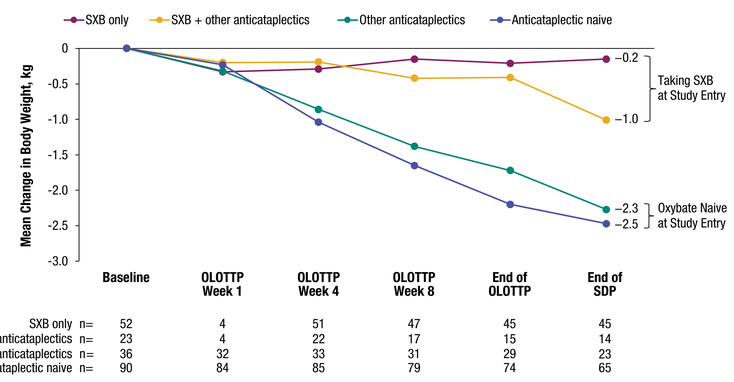
References: 1. Plazzi G, et al. *Lancet Child Adolesc Health.* 2018;2:483-94. **2.** Husain AM, et al. *Sleep Med.* 2009;10:661-3. **3.** Ponziani V, et al. *Sleep.* 2021;44:1-7. **4.** Schinkelshoek MS, et al. *J Sleep Res.* 2019;28:e12684. **5.** Bogan RK, et al. *Sleep.* 2021;44:zsaa206. **6.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **7.** Food and Drug Administration. Clinical superiority findings. 2021. Available at: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings.

Support and Acknowledgments: This study was supported by Jazz Pharmaceuticals. Under the direction of the authors, Karyn Liu, PhD, of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support for this poster, which was funded by Jazz Pharmaceuticals.

Disclosures: N Foldvary-Schaefer has served on an advisory committee for Jazz Pharmaceuticals and participated in clinical trials supported by Jazz Pharmaceuticals, Suven, and Takeda. **R Skowronski, L Hickey, A Chen, and TJ Measey** 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, plc. **Y Dauvilliers** is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, UCB Pharma, Flamel Technologies, Theranexus, and Bioprojet.

Results

Figure 2. Mean Decrease in Body Weight Over Time Based on Treatment at Study Entry

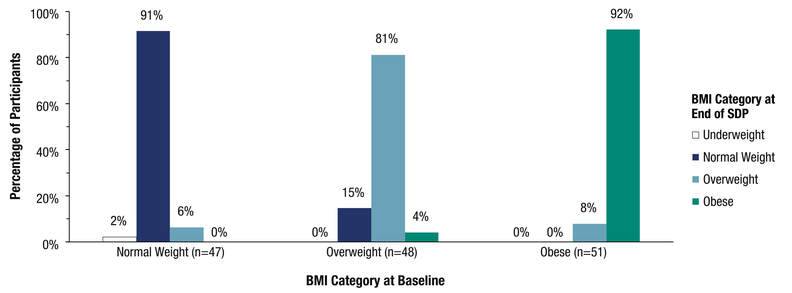


		Baseline	OLOTTP Week 1	OLOTTP Week 4	OLOTTP Week 8	End of OLOTTP	End of SDP
SXB only	n=	52	4	51	47	45	45
SXB + other anticataplectics	n=	23	4	22	17	15	14
Other anticataplectics	n=	36	32	33	31	29	23
Anticataplectic naive	n=	90	84	85	79	74	65

Note: n's represent the number of participants with vital signs collected at the indicated time point.
OLOTTP, open-label optimized treatment and titration period; SDP, stable-dose period; SXB, sodium oxybate.

- At the end of the SDP, in the safety population, mean (SD) change in body weight (n=147) was −1.6 (3.5) kg
- Mean (SD) decreases in body weight at the end of the SDP were numerically greater in participants who were oxybate naive at study entry (−2.4 [3.8] kg) compared with participants taking SXB at study entry (−0.3 [2.4] kg)
- Weight loss ≥5% at the end of SDP occurred in 6.7%, 0.0%, 21.7%, and 27.7% of participants in the SXB only, SXB + other anticataplectics, other anticataplectics, and anticataplectic-naive groups, respectively

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



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.
[b]No participants were underweight (BMI <18.5 kg/m²) at baseline.

Table 1. Demographics and Baseline Characteristics

	Pre-randomization Treatment Group				
Characteristic	SXB Only (n=52)	SXB + Other Anticataplectics (n=23)	Other Anticataplectics (n=36)	Anticataplectic Naive (n=90)	Safety Population[a] (N=201)
Age, mean (SD), y	39.4 (13.0)	39.0 (12.5)	35.7 (12.2)	36.0 (11.6)	37.2 (12.2)
Female, n (%)	27 (51.9)	11 (47.8)	23 (63.9)	61 (67.8)	122 (60.7)
Race, n (%)					
White	48 (92.3)	18 (78.3)	35 (97.2)	76 (84.4)	177 (88.1)
Black or African American	1 (1.9)	1 (4.3)	0 (0.0)	9 (10.0)	11 (5.5)
Other[b]	3 (5.8)	4 (17.4)	1 (2.8)	5 (5.6)	13 (6.5)
Weight, mean (SD), kg	83.2 (17.1)	90.4 (23.1)	83.4 (16.6)	82.5 (20.1)	83.7 (19.2)
BMI, mean (SD), kg/m²	28.5 (6.5)	29.8 (5.3)	29.0 (5.4)	28.5 (6.3)	28.8 (6.1)
BMI category, n (%)					
Underweight (<18.5 kg/m²)	0 (0.0)		0 (0.0)		0 (0.0)
Normal weight (18.5 to <25 kg/m²)	21 (28.0)		43 (34.1)		64 (31.8)
Overweight (25 to <30 kg/m²)	26 (34.7)		38 (30.2)		64 (31.8)
Obese (≥30 kg/m²)	26 (34.7)		45 (35.7)		71 (35.3)

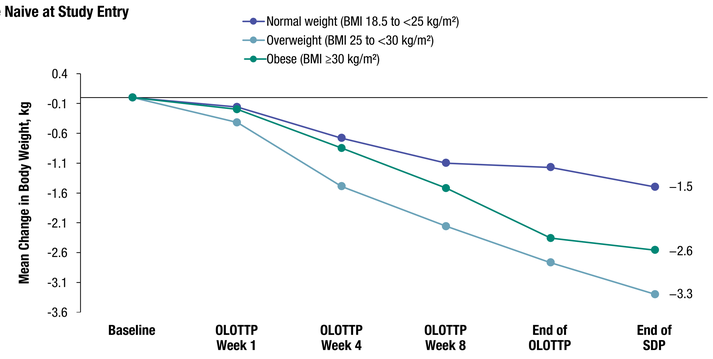
BMI, body mass index; SD, standard deviation; SXB, sodium oxybate.
[a]Includes all participants who took ≥1 dose of study drug.
[b]Includes not reported and multiple (>1 race).

- Two-thirds of the participants (67%) were overweight or obese at baseline

- There was a single, nonserious treatment-emergent adverse event of decreased weight, reported in a participant who was in the SXB + other anticataplectic pre-randomization treatment group; the event began and resolved during OLOTTP, was mild in severity, was not related to study drug, and did not result in discontinuation
  - The participant's weight was 79.5 kg and 76.0 kg at screening and day 1, respectively, and 74.0 kg at the end of SDP and DBRWP

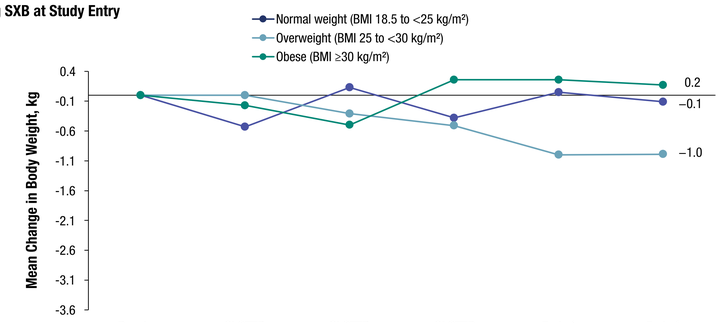
Figure 3. Mean Decrease in Body Weight Over Time Based on Treatment and Weight Category at Study Entry[a]

Oxybate Naive at Study Entry



		Baseline	OLOTTP Week 1	OLOTTP Week 4	OLOTTP Week 8	End of OLOTTP	End of SDP
Normal weight	n=	43	39	39	36	36	31
Overweight	n=	38	36	36	33	30	27
Obese	n=	45	41	43	41	37	30

Taking SXB at Study Entry



		Baseline	OLOTTP Week 1	OLOTTP Week 4	OLOTTP Week 8	End of OLOTTP	End of SDP
Normal weight	n=	21	3	19	18	16	16
Overweight	n=	26	1	26	22	21	21
Obese	n=	26	3	26	23	22	21

Note: n's represent the number of participants with vital signs collected at the indicated time point.
BMI, body mass index; OLOTTP, open-label optimized treatment and titration period; SDP, stable-dose period.
[a]No participants were underweight (BMI <18.5 kg/m²) at baseline.

- In oxybate-naive participants who were normal weight, overweight, and obese at study entry, mean (SD) decreases in body weight at the end of the SDP were −1.5 (3.1) kg (*P*=0.8904), −3.3 (3.5) kg (*P*=0.7596), and −2.6 (4.7) kg (*P*=0.8111), respectively
- In participants taking SXB at baseline who were normal weight, overweight, and obese at study entry, mean (SD) decreases in body weight at the end of the SDP were −0.1 (1.9) kg (*P*=0.9842), −1.0 (2.4) kg (*P*=0.8654), and 0.2 (2.8) kg (*P*=0.9735), respectively

Conclusions

- Adults with narcolepsy with cataplexy experienced weight loss during open-label LXB treatment
  - Mean weight loss was numerically greater in oxybate-naive participants compared with participants taking SXB at study entry
  - In oxybate-naive participants, mean weight loss was numerically greater among those 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 15% of those who were overweight at baseline became normal weight, and 8% of those who were obese at baseline became overweight
- A single TEAE of decreased weight was reported; it was mild in severity, was not related to study drug, and did not result in discontinuation

Scan this code to access this poster online. This code is not for promotional purposes.