256

Population Pharmacokinetic and Exposure-Response Analyses Supporting Individualized Dosing of Oxybate

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Introduction

- Narcolepsy and idiopathic hypersomnia are central disorders of hypersomnolence characterized by excessive daytime sleepiness (EDS)[1]
- Low-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates; LXB; Xywav®) and high-sodium oxybate (SXB; Xyrem®) are approved for the treatment of cataplexy or EDS in patients aged ≥7 years with narcolepsy[2-6]
  - For narcolepsy, LXB and SXB are administered twice nightly at a recommended total nightly dosage of 6–9 g in adults; the first and second doses may be equal or unequal to allow for treatment individualization and titration to effect (optimization) within the recommended dose range[2,3]
- LXB is also approved for idiopathic hypersomnia in adults[3]
  - For idiopathic hypersomnia, LXB may be administered once or twice nightly at a recommended total nightly dosage range of 6–9 g in adults; for twice-nightly dosing, the first and second doses may be equal or unequal to allow for treatment individualization and optimization within the recommended dose range[3]

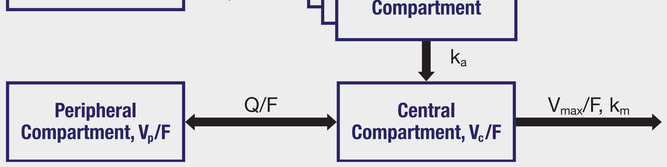
Objective

- To inform dosing individualization of LXB and SXB, population pharmacokinetic (PPK) and exposure-response analyses were conducted to identify factors influencing PK variability and assess relationships between exposure and efficacy and safety

Methods

- For narcolepsy, a 2-compartment PPK model with Michaelis-Menten clearance was fit to plasma concentration-time data from prior LXB and SXB clinical studies
  - Absorption was modeled as a first-order process with an absorption lag time modeled through a series of transit compartments
  - Food and formulation effects were evaluated for absorption rate constant (k_a), mean transit time (MTT) and relative bioavailability (F)

Figure 1. Schematic for the Narcolepsy PPK Structural Model



k_a, first-order absorption rate constant; k_m, concentration at half-maximal elimination; MTT, mean transit time; N, number of transit compartments; PPK, population pharmacokinetic; Q/F, apparent inter-compartmental clearance; V_c/F, apparent central distribution volume; V_{max}/F, apparent maximal saturable elimination rate; V_p/F, apparent peripheral distribution volume.

- Clinical judgment and mechanistic plausibility were used to determine which covariates should be tested on which parameters
- For idiopathic hypersomnia, an LXB PPK model was refined based on the narcolepsy model to replace the transit absorption compartments with a depot compartment for the absorption and elimination of LXB in patients with idiopathic hypersomnia, with fed/fasted state effect on k_a, lag time, and body weight effect on apparent maximal saturable elimination rate (V_{max}/F) and apparent central distribution volume (V_c/F)
- The PPK model-derived oxybate exposures (eg, area under the concentration-time curve; AUC) were employed in exposure-response analyses using response data from randomized parallel-group (SXB only; maintenance dose was not optimized) and randomized withdrawal (LXB and SXB; maintenance dose was optimized) studies

Table 1. Studies Included in PPK and/or Exposure-Response Analyses

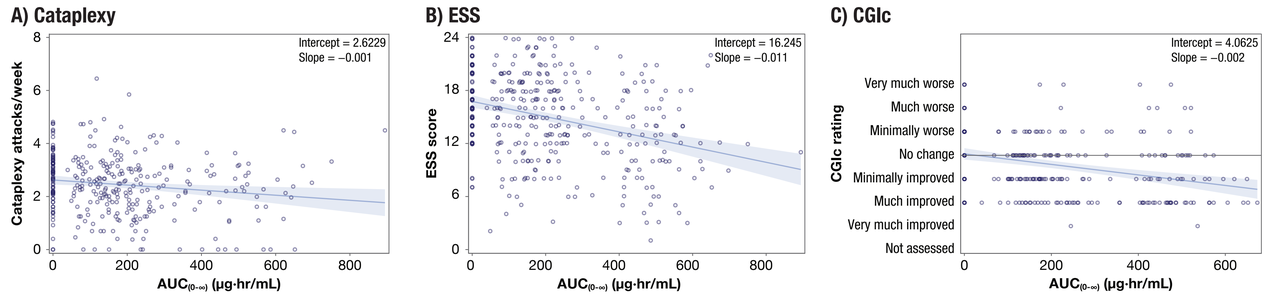
Study	Regimen	Endpoints Collected at Baseline and Throughout Treatment
Randomized parallel		
Study 1 of SXB in adults with narcolepsy[7]	SXB 0, 3, 6, and 9 g/night for 4 weeks	Cataplexy, ESS, CGIc Adverse events
Study 2 of SXB in adults with narcolepsy[8,9]	SXB 0, 4.5, 6, 7.5, and 9 g/night for up to 8 weeks	Cataplexy, ESS, CGIc, MWT, PSG Adverse events
Study 3 of SXB in adults with narcolepsy[10]	SXB 0, 6, and 9 g/night for up to 8 weeks	ESS, CGIc, MWT, PSG Adverse events
Randomized withdrawal		
Phase 2/3 study of SXB in adults with narcolepsy[11]	SXB stable dose for 2 weeks, then randomized to continue stable dose or placebo for 2 weeks	Cataplexy Adverse events
Phase 3 study of SXB in children and adolescents with narcolepsy[12]	SXB stable dose for 2–3 weeks, then randomized to continue stable dose or placebo for 2 weeks	Cataplexy, ESS-CHAD, CGIc for cataplexy severity, PSG Adverse events
Phase 3 study of LXB in adults with narcolepsy[13]	LXB dose titration/optimization for 12 weeks; LXB stable dose for 2 weeks; then randomized to continue stable dose or placebo for 2 weeks	Cataplexy, ESS, CGIc Adverse events
Phase 3 study of LXB in adults with idiopathic hypersomnia[a,14]	LXB dose titration/optimization for 10–14 weeks; LXB stable dose for 2 weeks; then randomized to continue stable dose or placebo for 2 weeks	ESS, CGIc Adverse events

[a]Included in idiopathic hypersomnia analyses only.
CGIc, Clinical Global Impression of Change; ESS, Epworth Sleepiness Scale; ESS-CHAD, Epworth Sleepiness Scale for Children and Adolescents; LXB, low-sodium oxybate; MWT, Maintenance of Wakefulness Test; PSG, polysomnography; SXB, high-sodium oxybate.

Results

- In the narcolepsy PPK model, the interindividual variabilities associated with key clearance and absorption parameters were 42.9%–83.8%, and in the idiopathic hypersomnia PPK model, the interindividual variabilities were 52.7%–57.9%
- In both PPK models, food delayed oxybate absorption; greater body weight was associated with wider distribution and higher clearance, as expected

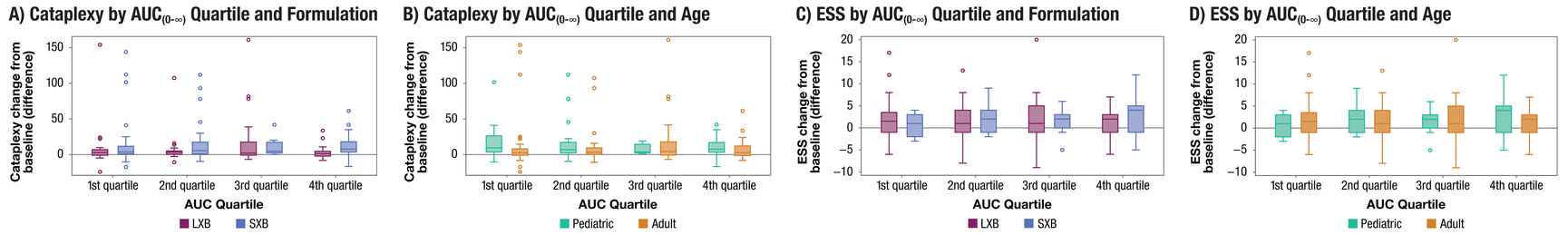
Figure 2. Exposure-Response Analyses of Parallel-Group Studies Demonstrate Interindividual Variability in Response to Oxybate Treatment, With Higher Exposures Associated With Higher Efficacy Responses



$AUC_{(0-\infty)}$, area under the plasma oxybate concentration-time curve from time 0 to infinity; CGIc, Clinical Global Impression of Change; ESS, Epworth Sleepiness Scale.

- In placebo- and baseline-corrected exposure-response analyses from randomized, parallel-group, narcolepsy studies in which participants either received fixed doses or were titrated to a specified stable oxybate dosage, higher oxybate exposure (AUC) was significantly associated ($P<0.05$) with:
  - Lower cataplexy frequency
  - Lower ESS score
  - Greater improvement as assessed by CGIc

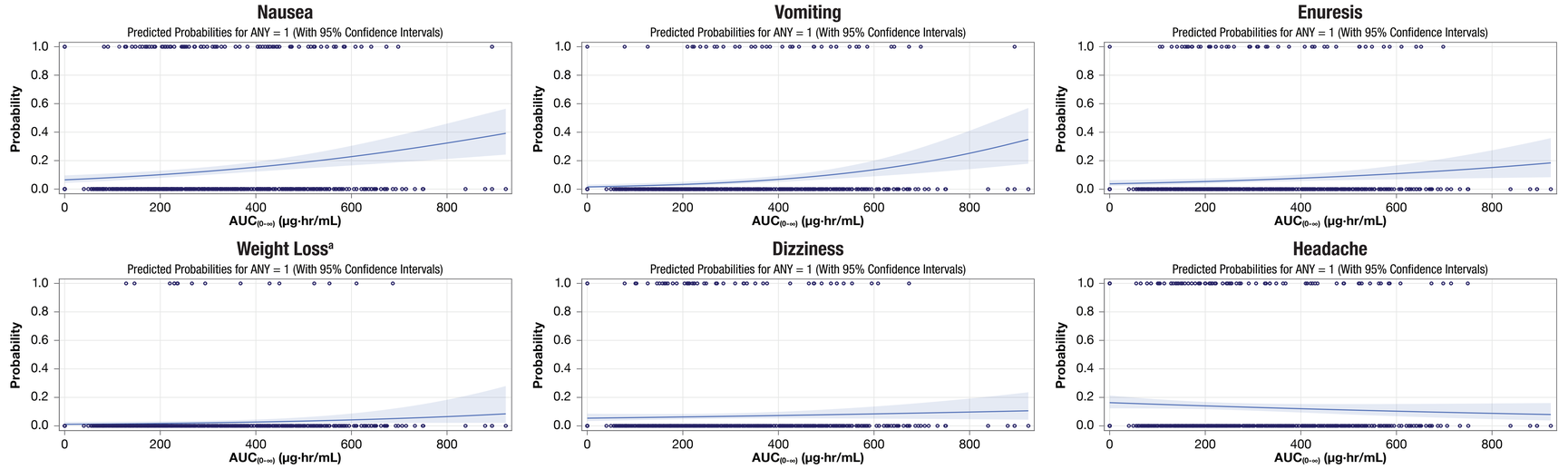
Figure 3. Exposure-Response Analyses of Randomized Withdrawal Studies Support Individualized Titration to Achieve an Optimal Oxybate Dose and Response



$AUC_{(0-\infty)}$, area under the plasma oxybate concentration-time curve from time 0 to infinity; ESS, Epworth Sleepiness Scale; LXB, low-sodium oxybate; SXB, high-sodium oxybate.

- In randomized withdrawal studies in narcolepsy (shown here) and idiopathic hypersomnia (**see QR code at bottom right for additional figure**), in which participants were titrated to their optimal dose during the open-label titration phase/prior to randomization, exposure-response relationships for cataplexy change and ESS score were flat, indicating that there is a range of effective concentrations and that different patients require specific doses to achieve an optimal response

Figure 4. Adverse Events Associated With Oxybate Exposure Included Nausea, Vomiting, and Enuresis but Not Weight Loss, Dizziness, or Headache



[a]It should be noted that weight loss is a known class effect of oxybate treatment.[15,16]
$AUC_{(0-\infty)}$, area under the plasma concentration-time curve from time 0 to infinity.

- Binomial (any event versus no event) logistic regression analyses from narcolepsy studies suggest nausea, vomiting, and enuresis were adverse events (AEs) associated with oxybate exposure, whereas dizziness, weight loss, and headache were not

Conclusions

- PPK analyses identified fed/fasting status and body weight as possible reasons for large interpatient variability of oxybate (LXB and SXB) PK in both narcolepsy and idiopathic hypersomnia populations
- Exposure-response analyses demonstrated that, despite interindividual variability in response to oxybate treatment, higher oxybate concentrations are associated with better efficacy (parallel-group studies) and a diverse range of concentrations or doses are equally effective for different patients when titrated to optimal dose
- Binomial logistic regression analysis suggested that AEs associated with oxybate exposure included nausea, vomiting, and enuresis but not weight loss, dizziness, or headache
- The PPK analysis is limited by the lack of LXB PK data in participants with narcolepsy to confirm the final PPK model's predictability, and the exposure-AE relationship may have been confounded by pooling of AEs from parallel-group (SXB) and non–parallel-group (SXB and LXB) studies
- Overall, these modeling analyses suggest the value of individually optimized oxybate dosing in narcolepsy or idiopathic hypersomnia to achieve the appropriate dose and associated exposure for an optimal clinical response

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition,* Text Revision (ICSD-3-TR). Darien, IL: American Academy of Sleep Medicine; 2023. **2.** Xyrem® (sodium oxybate) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **3.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **4.** Szarfman A, et al. *N Engl J Med.* 1995;333(19):1291. **5.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. Accessed: February 28, 2023. **6.** 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. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. Accessed: October 11, 2022. **7.** U.S. Xyrem Multicenter Study Group. *Sleep.* 2002;25(1):42-9. **8.** Xyrem International Study Group. *Sleep Med.* 2005;6(5):415-21. **9.** Xyrem International Study Group. *J Clin Sleep Med.* 2005;1(4):391-7. **10.** Black J, et al. *Sleep.* 2006;29(7):939-46. **11.** U.S. Xyrem Multicenter Study Group. *Sleep Med.* 2004;5(2):119-23. **12.** Plazzi G, et al. *Lancet Child Adolesc Health.* 2018;2(7):483-94. **13.** Bogan RK, et al. *Sleep.* 2021;44(3);zsaa206. **14.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. **15.** Dauvilliers Y, et al. *J Clin Sleep Med.* 2024;20(3):445-54. **16.** Schinkelshoek MS, et al. *J Sleep Res.* 2019;28(3):e12684.

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Disclosures: H Zhou, **LS Wu**, and **C Chen** 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.

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256

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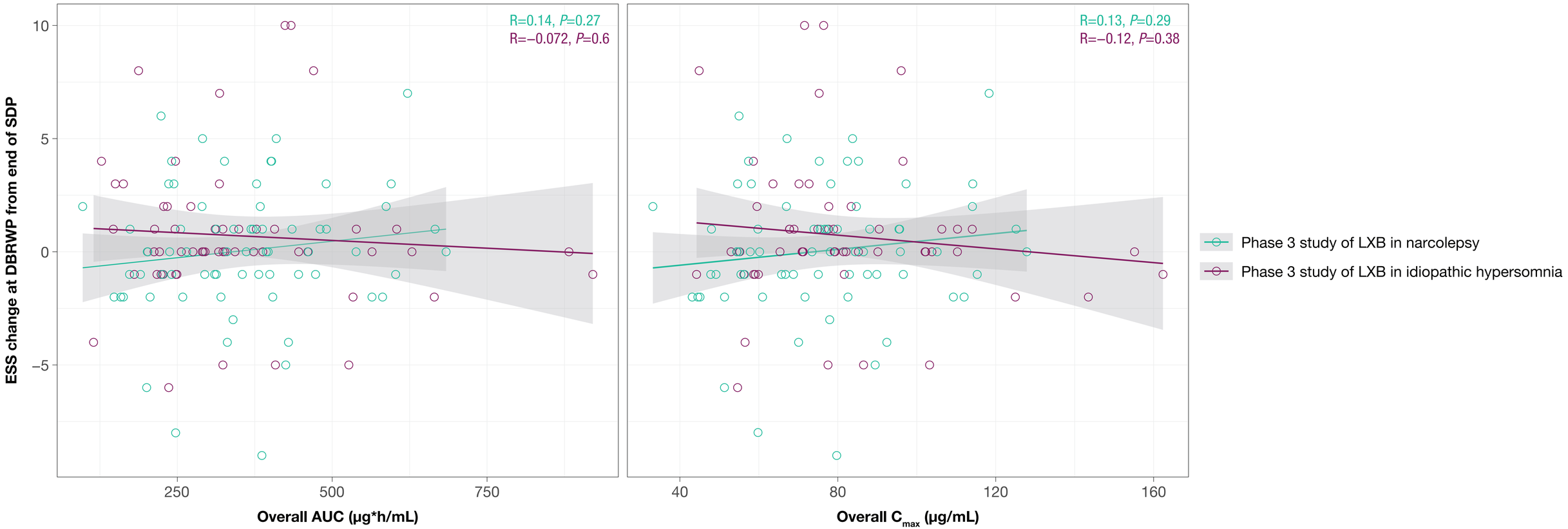
Supplementary Results

Supplemental Figure. Exposure-Response Analyses of Randomized Withdrawal Studies Support Individualization of LXB Dosing to Achieve an Optimal Dose and Response in Narcolepsy and Idiopathic Hypersomnia



AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; DBRWP, double-blind randomized withdrawal period; ESS, Epworth Sleepiness Scale; LXB, low-sodium oxybate; SDP, stable-dose period.

- In randomized withdrawal studies in narcolepsy[13] and idiopathic hypersomnia,[14] in which participants were titrated to their optimal dose during the open-label titration phase/prior to randomization, exposure-response relationships for ESS score were similar using either overall AUC or overall C_{max} as PK metrics
- These data indicate that there is a range of effective concentrations and that different patients require specific doses to achieve an optimal response