Evaluation of Drug-Drug Interactions of Sodium Oxybate with Ibuprofen: Results from a Pharmacokinetic/Pharmacodynamic Study

M. Eller 1, R. J. Skowronski 1, K. A. Wesnes 2, S. Alvarez-Horine 1, B. A. Benson 1, J. Black 1
1 Jazz Pharmaceuticals, Inc., 2 Bracket

Purpose
To evaluate potential drug-drug interactions of sodium oxybate (SXB) and ibuprofen with regard to PK, PD, and safety. SXB is the sodium salt of gamma-hydroxybutyrate, a substrate for the monocarboxylate transporter that may be inhibited by nonsteroidal anti-inflammatory drugs.

Methods
Healthy volunteers were randomized to SXB+ibuprofen placebo, SXB+ibuprofen, or SXB placebo+ibuprofen in a three-period, double-blind, crossover design with a 2-day washout between periods. Ibuprofen/placebo (4x200mg capsules) was given qid every 4h on days 1 and 2, and 1h before and 3h after the first SXB dose on day 3; SXB/placebo was given as two 3g doses 4h apart on day 3. Blood and urine were taken at predefined times for noncompartmental PK analysis. PD testing, performed during each treatment period, included the Karolinska Sleepiness Scale, and a selection of automated tests from CDR System (bracketglobal.com) including the Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Tracking, and Numeric Working Memory tasks. Safety was assessed at specified time points, and throughout the study.

Results
21 subjects enrolled and completed the study (95% male; 57% white; mean age 34.4±8.4 years). Mean plasma SXB concentrations were approximately 5% lower with ibuprofen co-administration (Figure 1). While this difference was statistically significant, the 90% CIs for SXB PK parameters with and without ibuprofen were within the 80-125% equivalence range (Table 1). Urinary excretion of SXB increased ~2-fold with ibuprofen (renal clearance=874.2 mL/h for SXB+ibuprofen and 463.6 mL/h for SXB+ibuprofen placebo; P<0.0001), and exceeded the 125% value (Table 1). Cognitive function impairments and increased sleepiness were observed with SXB with and without ibuprofen, but no PD interactions were observed. The most common adverse events (AEs) (≥2 subjects) are listed in Table 2.

Conclusion
Although renal excretion of SXB increased, likely as a result of monocarboxylate transporter inhibition by ibuprofen, plasma PK ratios were within the equivalence range, suggesting the interaction was not clinically significant. No PD interactions were observed, and AEs with SXB+ibuprofen reflect a combined effect of both drugs.