Sodium Oxybate in Treatment-Resistant REM Sleep Behavior Disorder (RBD): A Randomized Placebo-Controlled Trial

Statistical Analysis Plan

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Statistical analysis (using SAS 9.4, Cary, NC) was by intention-to-treat for the primary efficacy analysis, comparison of baseline characteristics, safety and tolerance and per-protocol (PP) for secondary/exploratory analyses. PP analysis included all participants who completed titration and the 4-week treatment period. Sample size calculation was based on a prior randomized controlled study by Brunetti et al.25 To detect an effect size of 50% reduction in the number of RBD episodes per month ([placebo - active] / placebo) with a power of 80% and alpha of 5%, the number of participants needed to be 10 per arm. Anticipating a dropout rate of 20%, 24 participants required to be enrolled.

We tested the primary hypothesis that SXB is superior to placebo in reducing the number of RBD episodes from baseline, as observed in the last month of treatment using linear mixed effects models with random intercepts. Models were parameterized in two ways to estimate separate group trajectories and between-group differences in change over time. Cohen's d was calculated as a measure of treatment effect size. Similar hypotheses were tested on secondary and exploratory outcomes. Within- and between-group differences were assessed with paired- and unpaired t-tests, or with the Wilcoxon Signed Rank and Mann-Whitney U tests for nonnormal data. Bootstrapped percentile-based 95% confidence intervals were calculated based on 10,000 randomly resampled datasets. Participants scoring below 4 on the CGI-I and CGI-E were classified as "responders"; chi-square tests were performed to compare the proportion of responders between groups. All statistical tests were conducted using a 2-sided alpha level of 0.05. For secondary/exploratory analyses, bootstrapped percentile-based 95% confidence intervals were calculated based on 10,000 randomly resampled datasets. Descriptive statistics on safety data are provided for all randomized participants (intention-to-treat), by treatment group and study phase.