Document Title:	Statistical Analysis Plan
Protocol Title:	Treating Insomnia and Improving Metabolic Health in Midlife Women With Insomnia
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Statistical Analysis Plan

Data integrity, safety monitoring, and statistical analysis implementation plan: All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the BWH Research Pharmacist who generates the randomization code will be unblinded to treatment assignment.

Confidentiality will be maintained by storing data with a subject identification number only. No identifying information will be entered in the electronic database. Only the PIs, co-investigators, and study staff will have access to the database and the study binders. Data will be entered into a secure, HIPAA-compliant Research Electronic Data Capture (REDCap) database hosted by MassGeneralBrigham and analyzed using SAS (Cary, NC) and/or STATA (College Station, TX). The final database will not be unblinded until all study data are complete and entered and the Independent Safety Monitor has completed a medical and scientific review, consistent with procedures we use in our previous clinical trials.

Overview of analytic plan and study endpoints

The primary hypothesis for this trial is that suvorexant is superior to placebo in treating insomnia symptoms. The primary endpoint is the ISI score at week 4 of each Treatment Block. Additional analyses will: (1) examine the effect of suvorexant compared to placebo on: (i) the secondary endpoint of proportion of participants with improvement in one or more cardiometabolic risk factors [HDL,LDL, total cholesterol, triglycerides, blood glucose, hypertension] , and (ii)mean levels of individual cardiometabolic risk factors; (2) explore the correlation between the change (Week 1 to Week 4) in cardiometabolic risk factors with the change in ISI and WASO. All endpoint measures are continuous variables. For data collected daily during the trial (i.e., sleep diary, actigraphy, meal diary), averages across the week of data collection at the pre- and post-Block intervals will be used as point estimates.

Primary analysis

The primary analysis will test the effect of suvorexant compared to placebo using a mixed-effects model with terms for baseline value, treatment, sequence, period, and time (as a categorical variable), consistent with the analysis approach of previous randomized crossover trial of suvorexant.[47] Secondary multivariate regression analyses will be conducted using age, BMI, and hot flash frequency as pre-specified covariates.

Diagnostic methods will be used for all models to assess their distributional assumptions, model adequacy, potential outlying or influential data points, and possible carryover effects. This analytical method will similarly be used to assess secondary and exploratory outcomes. An additional exploratory ISI responder analysis will be conducted using random effects logistic regression to determine whether there is a group difference in the proportion of participants that had at least an 8-point reduction in the ISI score from baseline.[3826] Proportion of participants with improvement in one or more cardiometabolic risk factors will be compared between suvorexant and placebo using Fisher's exact. Associations of the change in cardiometabolic endpoints with changes in ISI and WASO will be assessed using generalized linear mixed models accounting for the correlated nature of the change data within individuals from each Treatment Block and the strength of the association will be estimated using simple Pearson or Spearman correlations. Correlational analyses will be

conducted for the entire study population followed by stratified analyses for each treatment condition separately.

Power and sample size

To initiate treatment in 43 women, we will enroll up to 61 midlife women. This estimate is based on the screen-failure rate from our prior suvorexant trial in midlife women and the proportion of women we expect will fail our pre-diabetes screening based on the estimated prevalence of pre-diabetes in this age-group.

The planned sample size of 34 completed participants provides at least 80% power for detecting an effect size of 0.50 or larger in a two-tailed, matched-samples contrast of group-level means, consistent with our primary analysis plan to assess the difference between suvorexant and placebo on the primary endpoint of ISI scores with repeated measures. We based our estimates on our recently completed MISP-sponsored suvorexant trial in which we found an effect size of 0.5 in the reduction of ISI scores from baseline to the end of the 4-week treatment interval between suvorexant and placebo treatment arms.

For one of the secondary endpoint of fasting plasma glucose, an open-label study of suvorexant reported a reduction in fasting glucose compared to baseline with 4 weeks of treatment in a non-prediabetic population with an effect size of 0.5.[38]