

Requirements for Submitting a Full Proposal	
Section #1 - MISP Protocol Identification	
Study Title:	A Phase IV 3-Way Double-blind, Randomized, Crossover Study to Compare the Awakening Threshold Effects (responsivity) of Belsomra 10 mg and 20 mg to Placebo in non-elderly Insomniacs
Request Date:	Revised – August 23, 2017
Institution Name	Henry Ford Hospital Sleep Disorders and Research Center
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Section #2- Core Protocol

2.1 Objectives & Hypotheses

Primary

To determine the absolute and relative effects at Tmax of Belsomra 10 mg; 20 mg; and placebo on responsiveness in nonelderly insomniacs (< 65 yrs).

We hypothesize that:

- 1) Belsomra 20 mg will have a similar awakening/arousal threshold compared to placebo
- 2) Belsomra 10 mg will have a similar awakening/arousal threshold compared to placebo
- 3) Belsomra 20 mg will have a similar awakening/arousal threshold to Belsomra 10 mg

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data

Insomnia is characterized by difficulty falling asleep, waking frequently during the night, waking too early in the morning and not being able to get back to sleep, and waking feeling unrefreshed. Insomnia can be transient (lasting for several days), intermittent (when transient insomnia recurs), or chronic (lasting for more than a month and has been reported in all age groups. An estimated 30%-50% of the adult population is affected by insomnia and prevalence tends to increase with age.

Hypnotic medications are utilized to improve sleep initiation and/or maintenance. The most commonly used hypnotics, Benzodiazepine Receptor Agonists (BzRAs), bind at the benzodiazepine receptor at the GABA-A complex and demonstrate broad CNS depressant effects which been shown to reduce responsiveness to the environment, particularly at peak plasma concentrations (Frey, et al., 2011; Zammit et al., 2008). The ability to respond following a nocturnal stimuli is critical to safety (e.g., responding to fire alarms, infants, burglary, or other emergencies) (Johnson et al., 1983). Recently, the hypnotic suvorexant (dual orexin antagonist) has been shown to have no effects on the ability to wake to a novel auditory stimuli and thus may have a comparative benefit to BzRA hypnotics in terms of auditory awakening threshold (Tannenbaum et al., 2014; 2016). However, the previous study was not done in humans. The present study is designed to test arousal response (responsivity) at peak plasma levels following administration of Belsomra (10 and 20 mg) compared to placebo. Specifically, responsiveness will be assessed using standardized measures as in a previous study of auditory awakening threshold (Drake et al., 2017). The doses proposed are Belsomra 10 mg and 20 mg as these represent the clinically recommended and utilized doses.

The Primary objective is to determine the absolute and relative effects of Belsomra 10 mg and 20 mg on responsiveness during sleep in patients with insomnia at estimated Tmax versus placebo (~2.5 hrs post-dosing).

	<p>Our Sleep Research Center has considerable experience in the design and execution of responsivity studies. In a recent trial published in 2017 we compared the effects of a 10 mg dose of zolpidem to placebo in men to determine the level of responsivity and balance/Ataxia effects at T-max (~2.5 hrs.). Results of this trial showed a significantly higher auditory awakening threshold for zolpidem compared to placebo ($p < .001$). In addition, the effects of zolpidem on middle of the night balance were also significantly greater than placebo ($p < .005$). We expect a similar effect size in the present study as compared to what was found for placebo in our previous trial.</p>
<p>2.3 Study Design</p>	<p>The proposal is for an interventional single site study using a double blind, randomized 3-way crossover design with Belsomra 10 mg and 20 mg compared to a placebo. The total number of enrolled patients proposed is 12 providing reasonable power (>70%) to detect differences of 15 db vs. placebo for Belsomra if present (although no differences are expected). Patients will be crossed over to experience all treatment conditions in a controlled order (Belsomra 10 mg, 20 mg and placebo). Both men and women with insomnia will be utilized as the study population to improve the generalizability of outcome data. However, we will enroll equal numbers of men and women in order to allow comparative analyses within both men and women, albeit with reduced power. In the overall analyses sex will be utilized as a covariate. Subjects with other sleep disorders or unstable medical/psychiatric disorders will be excluded from the trial. Inclusion criteria will be men and women >18 and < 65 years of age.</p> <p>An initial standardized screening PSG will be used to rule out the presence of sleep disordered breathing and/or periodic limb movements during sleep (mean AHI/PLMAI <10/hr for both). The 3 study treatments include Belsomra 10 mg and 20 mg with a middle-of-the-night awakening at ~2.5 hours (BEL10; BEL20), and placebo with a middle-of-the-night awakening at 2.5 hours (PBO). Study drug will be administered under fasted conditions (at least 3 hours) as a single dose at bedtime (approximately 2300 hours), and each subject will receive one dose of each active drug, and one dose of placebo during the treatment period for a total of 3 overnight testing sessions and 1 overnight PSG screening.</p> <p>Subjects will be randomly assigned to treatment sequences using a Latin square design. After a subject has qualified for the study, the next sequentially available randomization number will be assigned. The subject will be administered study drug corresponding with this assigned number.</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Meets DSM-5 diagnostic criteria for insomnia disorder • ISI > 10 • Age >18 and < 65 • Negative audiological screening exam <p>Exclusion Criteria:</p>

- BMI >35 kg/m²
- Have symptoms consistent with the diagnosis of any sleep disorder other than insomnia (e.g., sleep apnea, narcolepsy, periodic leg movements, or restless leg syndrome).
- Have a known or suspected diagnosis of Acquired Immune Deficiency Syndrome (AIDS), or have tested seropositive for human immunodeficiency virus (HIV) antibody or antigen previously.
- Have any clinically significant abnormal finding in physical examination, neurological assessment, vital signs, elevated body temperature, or clinical laboratory tests, as determined by the Investigator.
- Have a known or exaggerated pharmacological sensitivity, hypersensitivity, or intolerance to Belsomra.
- Currently taking CYP3A inhibitors.
- Positive breathalyzer test for alcohol at Screening, PSG Screening or any Treatment night, or a positive urine drug screen (for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, or cannabinoids) at Screening;
- History of hearing difficulty (e.g., use of a hearing aid).
- Intends to use any medication including over-the-counter (OTC) medications that would interfere with normal sleep architecture (such as systemic steroids, beta-adrenergic blockers, amphetamines, modafinil, etc.);
- Self-reports use of products containing nicotine of greater than 15 cigarettes daily, or cannot avoid products containing nicotine during the normal sleep periods;
- Self-report consumption of more than five alcoholic beverages on any one day or > 14 alcoholic beverages weekly over the past week;
- Have a history of epilepsy or serious head injury
- Average TIB < 6.5 hrs.
- Have used prescribed or OTC medications within 7 days of screening (Day 0) or intend to use any prescription or OTC medication during the study that may interfere with the evaluation of the study drug. This restriction includes taking medications that affect the CNS. Any chronic maintenance therapy should have been maintained at a stable dosing regimen for at least 30 days before screening and subjects must continue this regimen throughout the study.
- Have used an investigational drug within 30 days or five half-lives (whichever is longer) before screening, or plans to use an investigational drug during the study or have used BEL/ZOL.

A study timeline is included below:

Evaluation Timing	Screening Period Days -14 to -1	Crossover Treatment Period			
		TX 1	TX 2	TX 3	Final Study Day
Informed Consent	X				
Inclusion/Exclusion	X				
Breathalyzer Test	X	X	X	X	
Urine Drug Screen	X				
Medical History	X				
Sleep Heart Health Survey	X				
Epworth Sleepiness Scale	X				
Restless Leg Questionnaire	X				
Stop Bang Questionnaire	X				
Laboratory (Routine)	X				
Vital Signs	X	X	X	X	X
Physical Examination	X				X
Randomization	X				
Height, Weight, BMI	X				
Prior & Concomitant Medications	X	X	X	X	X
Study Drug Administration		X	X	X	
AAT		X	X	X	
PSG	X	X	X	X	
Adverse Events		X	X	X	X

<p>2.5 Study Procedures</p>	<p>Subjects will be screened by clinical interview and full physical evaluation to establish health, and rule out medical disorders and sleep disorders other than insomnia. In addition, participants will complete medical history and be asked to complete a Sleep Health Survey and sleep disorders questionnaires to rule out restless leg syndrome and sleep disordered breathing (RLS screening questionnaire and STOP-BANG questionnaire). Participants will be screened using standard urine and blood chemistry laboratory tests (LabCorps) and be administered a breathalyzer to screen for alcohol and urine drug screen. AAT protocol will be reviewed and demonstrated with each participant on the morning of the screening PSG.</p> <p>During the night of each respective PSG assessment night, subjects will be awoken at the approximate T-max of the active drug (2.5 hrs), with a matching placebo condition at the same time point using an identical responsivity protocol for each condition. The rationale for this is that t-max represents the time of greatest potential risk for a hypnotic in terms of balance, responsivity, and memory. Responsivity will be assessed using the Auditory Awakening Threshold test (AAT) and will be measured at 2.5 hours post dose for the Belsomra 10 and 20 mg (BEL), and placebo (PBO) conditions. Responsivity will be assessed at the approximate time above immediately after 5 minutes of consolidated (without arousals) NREM stage 2 sleep has occurred.</p> <p>Responsivity Protocol: Responsivity will be measured in response to a series (20-sec intervals) of increasing 1.5-sec. tones at 520 Hz (fire alarm) with a range from 40 db to 110 db. The outcome measure will be the mean decibel level (db) at awakening (mean of 2 awakenings at ~T-max for each subject for each condition).</p> <p>Subjects will be discharged from the sleep center once all assessments have been completed. A 6-12 day drug-free interval will separate each Treatment Period. A final study visit will be performed for subjects either after they have completed all three Treatment Periods or they have prematurely discontinued the study.</p>
<p>2.6 Study Duration</p>	<p>The expected duration of study participation for a patient is ~30 days, including up to 14 days for medical screening, and 3 one-night treatments. All assessments will be separated by a 6-12 day drug free interval. A maximum of 3-4 patients will be enrolled in the study at a given time. Thus, the expected duration for study completion will be ~9 months.</p>
<p>2.7 Statistical Analysis and Sample Size Justification</p>	<p>The Sleep Disorders Center will be responsible for analyzing the study data (Investigator and expert statistical staff). The blind will be maintained during the study and the data will be unblinded at the completion of the trial. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, protocol violations have</p>

been identified and data has been declared complete in conjunction with the study Sponsor.

Data analysis will compare the change from placebo in each active drug condition. The primary analysis will be based on the evaluable population, defined as subjects who have data from each of the three Treatment Periods with no major protocol violations. Safety analyses will be presented descriptively for the safety population; defined as all subjects who were randomized and received at least one dose of study medication.

The primary endpoint will be the mean Auditory Arousal Threshold in decibels (AAT).

All statistical analyses will be conducted using IBM SPSS Statistics for Windows – Version 23 (Armonk, NY). The primary outcome of the study include within-person differences between active medications and respective placebo on the AAT. Univariate within-group comparisons for these continuous endpoints will be accomplished via paired samples t-tests. Repeated-measures analysis of covariance (ANCOVA) analyses will be used for estimating more complex models involving multiple factors or covariates (e.g., age. Given the extensive array of variables, covariates will be selected for inclusion in omnibus models per recommendations outlined by Mickey and Greenland (1989). Specifically, only those variables are related to the dependent variable in univariate analyses at a significance level of $P < 0.20$ will be retained in the final model. Similar analyses will be used to examine all potential secondary/exploratory endpoints.

Power analyses: Based on a previous study using zolpidem 10 mg in younger men, we estimate the power for this project to be 70% or greater for detecting a mean difference of ~15 db between belsomra and placebo given a sample of 12 individuals. This assumes a variance of 15 db. In our previous study the variance was ~15 db indicating an effect size of $d=1.0$. We do not expect insomnia status to impact the arousal threshold effect size as shown in previous studies (Johnson et al., 1978).

Safety and tolerability will be assessed by statistical and clinical review of the data on adverse clinical events, such as complex sleep-related behaviors, predefined limits of change for selected laboratory and vital sign values, as well as next-day residual effects. The primary approach for all safety analyses will be the All Patients as Treated (APaT) approach. All randomized patients who receive at least one dose of study medication will be included in the safety analyses.

The results will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

	<p>Demographics will be tabulated and summarized. Medical history data at Screening will be listed, as will Physical Examination data including height and weight. Vital signs (resting heart rate, systolic/diastolic blood pressure, respiratory rate and temperature) will be tabulated and summarized.</p> <p>Treatment-emergent adverse events will be listed and summarized. Adverse events reported in this study will be coded using MedDRA (Medical Dictionary for Regulatory Activities).</p> <p>Clinical laboratory data will be summarized with descriptive statistics. Abnormal laboratory test results will be flagged in the subject data listings.</p>
<p>2.8 Specific Drug Supply Requirements</p>	<p>Suvorexant will be supplied by Merck. Due to the limited nature of study drug needed the HFHS pharmacy will not require bulk supplies (if necessary study drug can be purchased by HFHS pharmacy and over encapsulated for the study procedures in house). Study drug will be unknown to the patient and therefore will be labeled only with study night number.</p>
<p>2.9 Adverse Experience Reporting</p>	<p>Model Study Agreement will be used and all safety/adverse event reporting will occur in strict accordance with those guidelines.</p>
<p>2.10 Itemized Study Budget</p>	<p>Study budget for 12 completed participants = \$299,435 (see attached detailed budget). In order to facilitate the MISP evaluation of the proposed study and budget we have chosen the most efficient study design, sample population, study duration, and subject numbers. However, we recognize that the present study parameters may have limitations. With this in mind we have provided an initial cost estimate, but adjustments to the proposed design could be effectively made to minimize such limitations (i.e., increase/decrease the number participants, add additional comparison doses, or additional study populations/measures).</p>
<p>2.11 References</p>	<p>Drake, C.L., Durrance, H., Chang, P., Roth, T., Pillai, V., Peterson, E. Singh, M., Tran, K.M. (2017). Arousability and fall-risk during forced awakenings from nocturnal sleep following administration of zolpidem 10 mg and doxepin 6 mg in healthy men: A randomized, placebo-controlled, four-arm crossover trial. <i>Sleep</i>, In Press.</p> <p>Frey, D. J., Ortega, J. D., Wiseman, C., Farley, C. T., & Wright, K. P. (2011). Influence of Zolpidem and Sleep Inertia on Balance and Cognition During Nighttime Awakening: A Randomized Placebo-Controlled Trial. <i>Journal of the American Geriatrics Society</i>, 59(1), 73-81.</p>

	<p>Johnson, Laverne C., and Cheryl L. Spinweber. <i>Benzodiazepine Effects on Arousal Threshold during Sleep</i>. No. NAVHLTHRSCHC-83-17. NAVAL HEALTH RESEARCH CENTER SAN DIEGO CA, 1983.</p> <p>Johnson, L. C., Church, M. W., Seales, D. M., & Rossiter, V. S. (1978). Auditory arousal thresholds of good sleepers and poor sleepers with and without flurazepam. <i>Sleep</i>, 1(3), 259-270.</p> <p>Tannenbaum, P. L., Stevens, J., Binns, J., Savitz, A. T., Garson, S. L., Fox, S. V & Tye, S. J. (2014). Orexin receptor antagonist-induced sleep does not impair the ability to wake in response to emotionally salient acoustic stimuli in dogs. <i>Front Behav Neurosci</i>, 8, 182.</p> <p>Tannenbaum, P.L., Tye, S.J., Stevens, J., Gotter, A.L., Fox, S.V., Savitz, A.T., Coleman, P.J., Uslander, J.M., Kuduk, S.D., Hargreaves, R. and Winrow, C.J., 2016. Inhibition of orexin signaling promotes sleep yet preserves salient arousability in monkeys. <i>Sleep</i>, 39(3), p.603.</p>
<p>2.12 Publication Plan</p>	<ul style="list-style-type: none"> • We anticipate 1-3 manuscripts generated from the present study, 1 from primary objectives and 1-2 additional from exploratory analyses. However, total number will be dependent upon study outcomes. • The projected target date for manuscript submission will be August 2018 submitted to Journal of Clinical Sleep Medicine. • We anticipate 3-4 abstracts generated from this protocol. • Results will be present by the PI and Co-Investigators at the National Sleep Meeting and the American Psychiatric Association National Conference.
<p>2.13 Curriculum Vitae</p>	<p>Dr. Drake’s CV is attached including previous trials/grants.</p>
<p>2.13 Protocol Submission for Investigator-Initiated Studies</p>	<p>U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckisp.com</p> <p>Non U.S. protocols should be submitted to the MSD office by the investigators.</p>