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Merck's BELSOMRA C-IV meets primary efficacy endpoint in Ph3 trial

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First Randomized Controlled Polysomnography Trial of Insomnia Medication in Alzheimer's Disease Dementia Population

Merck known as MSD outside the United States and Canada, has announced the presentation of results of a Phase 3 trial evaluating the efficacy and safety of BELSOMRA (suvorexant) C-IV for the treatment of insomnia in people with mild-to-moderate Alzheimer's disease dementia.

This is the first dedicated Phase 3 polysomnography study of an insomnia medication in people with mild-to-moderate Alzheimer's disease dementia, and in the trial, BELSOMRA met its primary and secondary efficacy endpoints. For the primary endpoint, 4-weeks of treatment with BELSOMRA improved mean total sleep time (TST) by 28.2 minutes versus placebo (n=135 vs. n=139, respectively; [95% CI:11.1,45.2], p<0.005). This corresponded to a mean increase from baseline of 73.4 minutes with BELSOMRA [95% CI: 61.3, 85.5] and a mean increase from baseline of 45.2 minutes with placebo [95% CI: 33.3, 57.2]. Adverse events were reported in 22.5% of patients receiving BELSOMRA compared to 16.1% of those receiving placebo. The results are being presented at the 2019 American Academy of Neurology Annual Meeting, held May 4-10 in Philadelphia, PA.

"Insomnia and other sleep disturbances are more common in people with Alzheimer's disease dementia, but evidence for the efficacy and safety of sleep medications in this population remains limited," said Dr. W. Joseph Herring, associate vice president, Global Clinical Research, Neuroscience, Merck Research Laboratories. "We are encouraged by the efficacy and

safety results of BELSOMRA in those living with Alzheimer's disease dementia. Merck plans to file these data with the U.S. Food and Drug Administration for potential inclusion into the BELSOMRA prescribing information."

BELSOMRA (suvorexant) C-IV 5 mg, 10 mg, 15 mg and 20 mg tablets are currently approved in the United States for treatment of insomnia characterized by difficulties with sleep onset and sleep maintenance.

Study Design

he Phase 3 randomized, double-blind, clinical trial evaluated the efficacy and safety of BELSOMRA (suvorexant) 10 mg, which could be increased to a 20 mg dose based on clinical response (77% of patients treated with BELSOMRA increased their dose from 10 mg to 20 mg after the second week of study) or matching placebo in participants with mild-to-moderate Alzheimer's disease dementia (a score of 12-26 on the Mini Mental State Examination) and insomnia (mean total sleep time less than 6 hours). Sleep was measured by overnight polysomnography in a sleep laboratory. The trial consisted of a 3-week screening period with a 2-week single blind placebo run in followed by a 4-week double blind randomized treatment period. Overnight polysomnography in a sleep laboratory was performed during a visit 14 days prior to randomization, at a baseline visit 7 days prior to randomization and following the 4-week double-blind treatment period. The primary endpoint of the study was change-from-baseline in polysomnography-measured mean TST in minutes (higher score indicating improved sleep) at Week 4. The secondary efficacy endpoint was mean wake after persistent sleep onset (WASO) measured in minutes and defined as the total wake time over the PSG recording period after the first period of continuous sleep lasting at least 10 minutes (lower score corresponds to better sleep). Additional exploratory measures included physician-assessed Clinician Global Impression of Severity (CGI-S) of insomnia and a caregiver-reported participant subjective Sleep Quality Rating (sSQR).

Study Results

Of those participants completing the trial (BELSOMRA n=136; placebo n=141), mean (SD) baseline TST was 278 (77) minutes for those receiving BELSOMRA and 274 (84) minutes for placebo. Measurement at Week 4 showed an increase in TST in the BELSOMRA group compared with placebo (model-based least squares mean change-from-baseline in TST: BELSOMRA 73.4 minutes, placebo 45.2 minutes; difference = 28.2 minutes [95% CI:11,45]; $p<0.01$).

The secondary efficacy endpoint measurement at Week 4 showed an improvement in WASO in the BELSOMRA group compared with placebo (model-based least squares mean change-from-baseline in WASO: BELSOMRA -41.8 minutes, placebo -32.5 minutes; difference = 15.7 minutes [95% CI:-28.1,-3.3]; p=0.01).

Safety was assessed by adverse event reports, laboratory analyses, electrocardiograms and physical examinations performed as stated in the protocol. Adverse events were recorded in 22.5% (n=32/142) of patients in the BELSOMRA group and 16.1% (n=23/143) in the placebo group. One patient in each group discontinued treatment due to an adverse event. The most common recorded adverse event was somnolence (drowsiness), which was reported in 4.2% (n=6) of patients in the BELSOMRA-treated group and 1.4% (n=2) of placebo-treated patients. Somnolence was recorded as mild-to-moderate severity. Other adverse events included: headache (n=5 on BELSOMRA vs. n=6 on placebo), dry mouth (n=3 vs. n=1) and falls (n=3 vs. n=0).

Insomnia and Alzheimer's Disease

Findings indicate that insomnia affects up to 45% of people living with Alzheimer's disease.

Many factors contribute to insomnia, which evidence suggests includes when wake-promoting signaling overrides sleep-promoting signaling in the brain. There are many neurotransmitters in the brain that regulate wakefulness, including the orexin signaling system. Elevated orexin levels in cerebral spinal fluid are found in those living with Alzheimer's disease.

Changes occurring in the brain tissue of people with Alzheimer's disease are associated with the loss of mental abilities and are also believed to cause disruptions in the sleep/wake cycle resulting in sleep problems. Many people with Alzheimer's disease wake up more often and stay awake longer than those without the disease, which may lead to significant shifts in sleep/wake patterns.

BELSOMRA (suvorexant) is a first-in-class oral, highly selective antagonist for orexin receptors. Orexin is a neurotransmitter found in a specific part of the brain that can help keep a person awake. The mechanism by which BELSOMRA exerts its therapeutic effect is presumed to be through antagonism of orexin receptors.