



NEWS RELEASE

Merck's BELSOMRA® (suvorexant) C-IV Meets Primary Efficacy Endpoint in Phase 3 Trial for the Treatment of Insomnia in People with Mild-to-Moderate Alzheimer's Disease Dementia

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

Data to be Filed with FDA for Potential Inclusion in BELSOMRA Prescribing Information

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today 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

The 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.

About BELSOMRA (suvorexant)

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.

Indication for BELSOMRA (suvorexant)

BELSOMRA is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Select Safety Information about BELSOMRA

BELSOMRA is contraindicated in patients with narcolepsy.

BELSOMRA contains suvorexant, a Schedule IV controlled substance.

BELSOMRA can impair daytime wakefulness. Central nervous system (CNS) depressant effects can last for up to several days after discontinuation.

BELSOMRA can impair driving skills and may increase the risk of falling asleep while driving. Caution patients taking BELSOMRA 20 mg against next-day driving and other activities requiring full mental alertness.

Coadministration with other CNS depressants increases the risk of CNS depression. Patients should be advised not to consume alcohol in combination with BELSOMRA due to additive effects. Dosage adjustments of BELSOMRA and of other concomitant CNS depressants may be necessary when administered together because of potentially additive effects. The use of BELSOMRA (suvorexant) with other drugs to treat insomnia is not recommended.

The risk of next-day impairment, including impaired driving, is increased if BELSOMRA is taken with less than a full night of sleep remaining, if a higher than recommended dose is taken, if co-administered with other CNS depressants, or if co-administered with other drugs that increase blood levels of BELSOMRA. Patients should be cautioned against driving and other activities requiring complete mental alertness if taken in these circumstances.

Reevaluate patients for comorbid conditions if insomnia persists after 7 to 10 days of treatment.

A variety of cognitive and behavioral changes (e.g., amnesia, anxiety, hallucinations, and other neuropsychiatric symptoms) have been reported with the use of hypnotics such as BELSOMRA. Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after taking a hypnotic) and other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex), with amnesia for the event, have been reported in association with the use of hypnotics. Discontinuation of BELSOMRA should be strongly considered for these patients. The use of alcohol and other CNS depressants may increase the risk of such behaviors. These events can occur in hypnotic-naïve as well as hypnotic-experienced persons. Discontinuation of BELSOMRA should be strongly considered for patients who report any complex sleep behavior.

In clinical studies, a dose-dependent increase in suicidal ideation was observed in patients taking BELSOMRA, as assessed by questionnaire. Immediately evaluate patients with suicidal ideation or any new onset behavioral changes. Suicidal tendencies may be present and intentional overdose is more common in this group of patients. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

The effect of BELSOMRA on respiratory function should be considered.

Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms can occur. The risk of cataplexy-like symptoms increases with the dose of BELSOMRA.

BELSOMRA is not recommended for patients with severe hepatic impairment or those taking a strong CYP3A inhibitor.

In clinical studies, the most common adverse reaction (reported in 5% or more of patients treated with 15 mg or 20 mg of BELSOMRA and at least twice the placebo rate) was somnolence (BELSOMRA 7%, placebo 3%).

The recommended dose of BELSOMRA is 5 mg in patients receiving moderate CYP3A inhibitors.

Digoxin levels should be monitored, as slight increases were seen with coadministration of BELSOMRA (suvorexant).

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general

economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2018 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see Prescribing Information for BELSOMRA (suvorexant) at
https://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_pi.pdf

Please see the Medication Guide for BELSOMRA (suvorexant) at
https://www.merck.com/product/usa/pi_circulars/b/belsomra/belsomra_mg.pdf

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