Late Breaking

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OVEPOREXTON (TAK-861) FOR THE TREATMENT OF NARCOLEPSY TYPE 1: EFFICACY AND SAFETY RESULTS FROM TWO PIVOTAL PHASE 3 TRIALS

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PURPOSE: Narcolepsy type 1 (NT1) is a chronic neurological disorder of hypersomnolence resulting from the loss of orexin-producing neurons, leading to markedly reduced levels of orexin neuropeptides in the brain and cerebrospinal fluid (CSF). Orexin deficiency manifests with excessive daytime sleepiness (EDS), cataplexy, fragmented nocturnal sleep, sleep paralysis, hallucinations, and cognitive symptoms. Existing therapeutic options for NT1 do not address the pathophysiology of NT1. Oveporexton (TAK-861), an investigational oral orexin receptor 2 (OX2R) agonist, is designed to restore orexin signaling. Oveporexton improved NT1 symptoms and was well tolerated in a phase 2b trial. Here, we present results from two phase 3 trials evaluating efficacy, safety, and tolerability of oveporexton in individuals with NT1.

METHODS: The phase 3 trials, namely First Light (NCT06470828) and Radiant Light (NCT06505031), were global, multicenter, randomized, double-blind, placebo-controlled studies. In First Light, participants were randomized 2:3:3 to placebo or 1 of 2 dose levels of oral oveporexton twice daily (BID) ≥3 hours apart for 12 weeks. In Radiant Light, participants were randomized 1:2 to placebo or oral oveporexton BID ≥3 hours apart for 12 weeks. A washout of all prior narcolepsy treatments was required before randomization. Upon completion of treatment, participants entered either a long-term extension phase or a 4-week follow-up period. Key inclusion criteria included individuals aged 16–70 years with a diagnosis of NT1 based on the *International Classification of Sleep Disorders, Third Edition* (ICSD-3), or ICSD-3 text revision, supported by polysomnography/Multiple Sleep Latency Test; positivity for HLA genotype HLA-DQB1*06:02 or CSF orexin levels ≤110 pg/mL; an Epworth Sleepiness Scale (ESS) score ≥11; and ≥4 partial or complete cataplexy episodes per week. Individuals with a medical disorder associated with EDS, other than narcolepsy with cataplexy, were excluded. In both trials, the primary endpoint was change from baseline (CFB) to week 12 in mean sleep latency on the Maintenance of Wakefulness Test. The key secondary endpoints were CFB to week 12 in ESS total score, weekly cataplexy rate at week 12, and the occurrence of ≥1 treatment-emergent adverse event (AE) during the study.

RESULTS: Participants from 19 countries were enrolled: 168 in the First Light trial and 105 in the Radiant Light trial. Both trials demonstrated statistically significant improvements with oveporexton compared with placebo ($P<0.001$) across all primary and key secondary endpoints at week 12, regardless of dose. Improvements in all assessed symptoms, including EDS and cataplexy, were statistically significant and clinically meaningful, with outcomes approaching normative ranges upon completion of the 12-week treatment period. Oveporexton was generally well tolerated, with a safety profile consistent with previous studies. The most reported AEs were insomnia, urinary urgency, and urinary frequency. No serious treatment-related AEs were observed.

CONCLUSIONS: Findings from the phase 3 trials provide further evidence regarding the efficacy and safety of oveporexton as a potentially transformative therapeutic option for NT1.

CLINICAL IMPLICATIONS: Oveporexton demonstrated significant efficacy and was well tolerated, supporting its potential as a treatment for NT1 by addressing underlying orexin deficiency.

DISCLOSURES:

No relevant relationships by Alice Cai

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