Abstract citation ID: zsaf090.0830

0830

EFFECTS OF THE OREXIN 2 RECEPTOR AGONIST ALKS 2680 ON QEEG IN PATIENTS WITH NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA

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Introduction: ALKS 2680 is a highly potent, orally bioavailable, and selective orexin 2 receptor agonist being developed as a once-daily treatment for narcolepsy and idiopathic hypersomnia (IH). Quantitative electroencephalography (qEEG) was conducted as an exploratory measure in a phase 1b study to evaluate the central pharmacodynamic effects of ALKS 2680 in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and IH.

Methods: In a randomized, double-blind, placebo-controlled study, single doses of ALKS 2680 (1, 3 and 8 mg for NT1; 5, 12 and 25 mg for NT2 or IH) and placebo were evaluated in a four-way crossover design following two-week washout from prior medications. At baseline and on dosing days, the Maintenance of Wakefulness Test (MWT) and Karolinska Sleepiness Scale (KSS) were administered at five post-dose timepoints. During each MWT assessment, three EEG epochs were extracted for oscillatory and fractal spectral qEEG analysis corresponding to test initiation, sleep onset, and test termination. Effects on baseline-corrected qEEG spectra were analyzed using a mixed-models repeated measures approach.

Results: In the combined cohort of patients with NT1 (N=10), NT2 (N=9), or IH (N=8), ALKS 2680 decreased amplitude in bands associated with sleepiness at the central midline region: oscillatory delta (least squares mean difference (LSMD), high dose vs placebo: −0.05μV/Hz; standard error [SE], 0.01; p< 0.001) and oscillatory theta (LSMD high dose vs placebo: −0.09μV/Hz; SE 0.02; p< 0.001). ALKS 2680 also increased amplitude in bands associated with wakefulness/vigilance: oscillatory beta3 (LMSD high dose vs placebo: 0.05μV/Hz; SE, 0.01; p< 0.001) and fractal gamma (LMSD high dose vs placebo: 0.03μV/Hz; SE, 0.01; p=0.001). The effects of ALKS 2680 on spectral parameters were maintained for up to 10 hours at the high dose. Decreased low frequency amplitude and increased high frequency amplitude was associated with higher sleep latency on MWT (eg. central midline delta×MWT: r=−0.359, p=0.001) and lower scores on the KSS (eg. frontal right beta3×KSS: r=−0.366, p< 0.001).

Conclusion: ALKS 2680 demonstrated statistically significant wake-promoting effects on qEEG spectral parameters in patients with NT1, NT2, and IH. These effects were correlated with objective and subjective improvements in wakefulness/alertness by ALKS 2680 (ie, MWT and KSS).

Support (if any): Alkermes