Abstract citation ID: zsaf090.0830

0830

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

Meera Modi[1], Brendon Yee[2], Julia Chapman[3], Angela D'Rozario[2], Roman Rosipal[4], Leonardo Trejo[4], Ge Ruigt[4], Ronald Grunstein[5], Bhaskar Rege[1], Daniel Smith[1]

[1] Alkermes, Inc., [2] The Woolcock Institute of Medical Research, [3] CIRUS, Centre for Sleep and Chronobiology, Woolcock Institute of Medical Research, Macquarie University, [4] Pacific Development and Technology, LLC, [5] Woolcock Institute of Medical Research, Macquarie University CPC-RPAH Clinic, Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia

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

Effects of the Orexin 2 Receptor Agonist ALKS 2680 on qEEG in Patients With Narcolepsy and Idiopathic Hypersomnia

Meera Modi,[1] Brendon Yee,[2] Julia L. Chapman,[2] Angela D'Rozario,[2] Roman Rosipal,[3] Leonardo Jose Trejo,[3] Gé S.F. Ruigt,[3] Ron Grunstein,[2] Bhaskar Rege,[1] Daniel G. Smith[1]

[1]Alkermes, Inc., Waltham, MA, USA; [2]Woolcock Institute of Medical Research, Sydney, Australia; [3]Pacific Development and Technology, LLC, Capitola, CA, USA

Poster No: 392

INTRODUCTION

- ALKS 2680 is a highly potent, oral, and selective orexin 2 receptor agonist being developed as a once-daily treatment for narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH)
- Quantitative electroencephalography (qEEG) provides an objective measure of brain activity that reflects states of alertness
- Narcolepsy and IH are characterized by a sleepy qEEG profile during wakefulness (ie, increased amplitude in low frequency bands; **Table 1**)[1,2]
- Wake-promoting effects of orexin 2 receptor agonists are hypothesized to shift the qEEG profile toward an alert state (ie, increased amplitude in high frequency bands; **Table 1**)
- In a preclinical study, ALKS 2680 dose-dependently increased high frequency power and decreased low frequency power correlating with cortical activation in rats during period of high sleep pressure (see Poster 410)[3]
- In a phase 1b study, ALKS 2680 was generally well tolerated and led to statistically significant, clinically meaningful, dose-dependent improvements in mean sleep latency on the Maintenance of Wakefulness Test (MWT) across patients with NT1, NT2, or IH. ALKS 2680 also showed clinically meaningful, dose-dependent improvements in self-reported alertness on the Karolinska Sleepiness Scale (KSS) (see Poster 400)[4]
- In non-sleep deprived healthy volunteers, ALKS 2680 dose-dependently increased beta power over placebo in eyes-open qEEG[5]
  - Beta power increase was correlated with improvements in the KSS[5]

TABLE 1: Frequency Bands of Interest and Their Corresponding Ranges

	Frequency Band	Ranges[6]	Wake State
Low Frequency	Delta	2-4 Hz	Drowsiness/ reduced alertness[7]
	Theta	4-8 Hz	
High Frequency	Beta	12-15 Hz 15-18 Hz 18-25 Hz	Alert, active, attentive mind; concentration[8]
	Gamma	30-50 Hz	

OBJECTIVE

- To use qEEG as an exploratory measure in the phase 1b study to evaluate the central pharmacodynamic effects of ALKS 2680 in patients with NT1, NT2, or IH

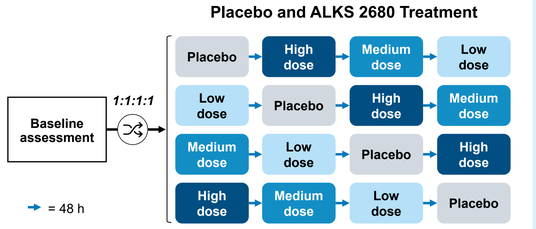
METHODS

- The phase 1b study was a single-dose crossover study with a baseline assessment followed by 4 treatment days with 48 hours of washout in between treatment days for patients with NT1 (N = 10), NT2 (N = 9), and IH (N = 8) (**Figure 1**)[4]

qEEG SPECTRAL ANALYSIS OF WAKE EEG EPOCHS DERIVED FROM MWT SESSIONS

- EEG was recorded during MWT assessments, which were conducted according to the American Academy of Sleep Medicine guidance[9] (**Figure 2**)
- For each of the 5 MWTs, EEG was extracted from a 2-minute "wake" period immediately preceding test termination (**Figure 2**)
- EEG was decomposed into oscillatory and aperiodic components using irregular-resampling auto-spectral analysis (IRASA)
- To increase signal-to-noise ratio, the 10-20 electrode array was collapsed into 13 spatial locations
- Consistent and dose-dependent changes were observed across all cohorts (see **Figure 3** for example in delta frequency range)
- Based on consistent effects in NT1, NT2, and IH across subjective, objective, and physiological endpoints, subsequent analyses were based on a combined cohort
- Effects on baseline-corrected qEEG spectra were analyzed using a mixed-models repeated measures approach
- Linear regression models were used to assess the relationship between qEEG endpoints and KSS or sleep latency

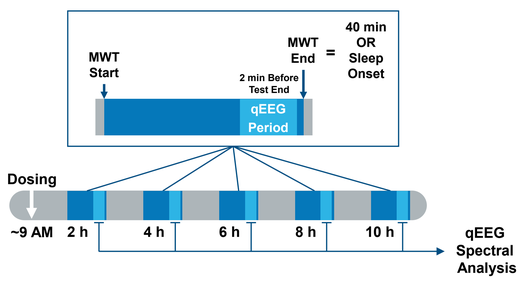
FIGURE 1: Phase 1b Study Design, Single-Dose Crossover



ALKS 2680 Dose	Low	Medium	High
NT1 (N = 10)	1 mg	3 mg	8 mg
NT2 (N = 9)	5 mg	12 mg	25 mg
IH (N = 8)	5 mg	12 mg	25 mg

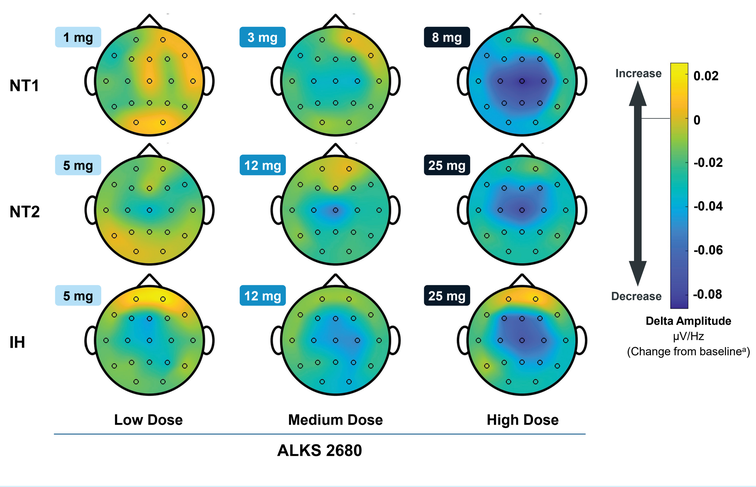
IH = idiopathic hypersomnia; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

FIGURE 2: Maintenance of Wakefulness Test



MWT = Maintenance of Wakefulness Test; qEEG = quantitative electroencephalography.

FIGURE 3: Topographic Maps of Spectral Amplitude Across NT1, NT2, and IH Patients With ALKS 2680

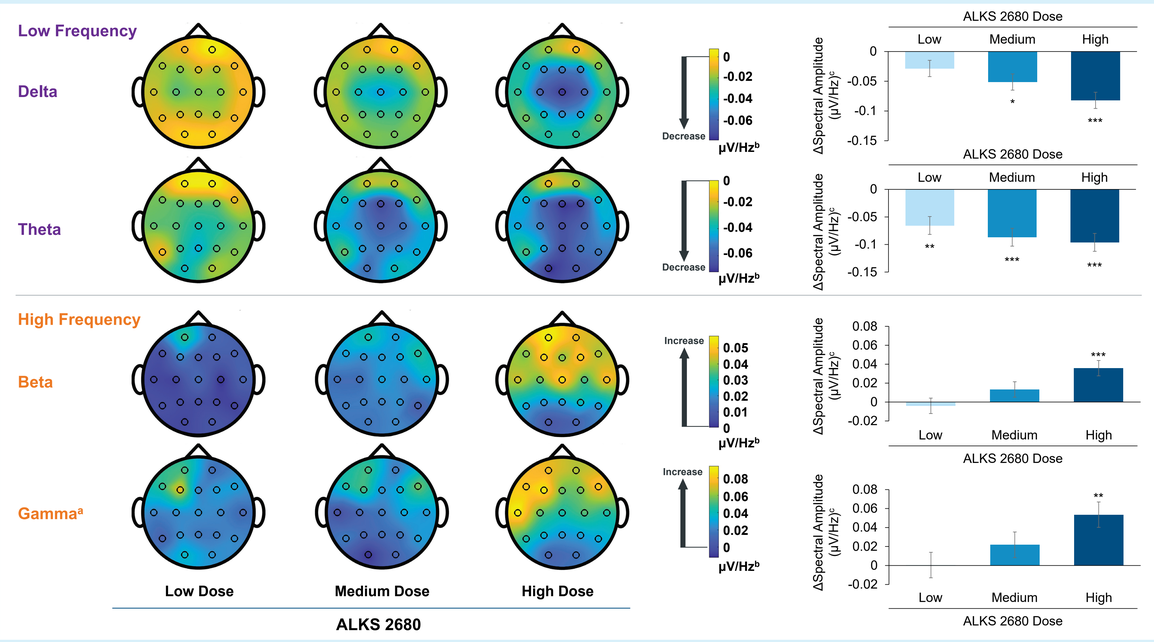


[a]Time-matched baseline-corrected spectral amplitudes were averaged across the 5 MWT sessions.
IH = idiopathic hypersomnia; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

RESULTS

- In the combined cohort analysis, ALKS 2680 demonstrated:
  - Dose-dependent decreases in amplitude of sleepiness-associated low frequency bands (delta and theta) (**Figure 4**)
  - Dose-dependent increases in amplitude of alertness-associated high frequency bands (beta and gamma) (**Figure 4**)
- Low frequency band amplitudes are significantly associated with subjective and objective endpoints (**Figure 5A**)
  - Positively correlated with reported sleepiness on the KSS
  - Inversely correlated with sleep latency on the MWT
- High frequency band amplitudes are significantly associated with subjective and objective endpoints (**Figure 5B**)
  - Inversely correlated with reported sleepiness on the KSS
  - Positively correlated with sleep latency on the MWT

FIGURE 4: Spectral Amplitude Across Combined Cohort of NT1, NT2, and IH Patients With ALKS 2680



[a]Aperiodic. [b]Time-matched baseline-corrected spectral amplitudes were averaged across the 5 MWT sessions. [c]Baseline-corrected least squares mean change from placebo in spectral amplitude in the central midline region (delta and theta) and frontal right region (beta and gamma).
Error bars represent standard error. *$P < 0.01$, **$P < 0.001$, ***$P < 0.0001$; P values based on mixed-models repeated measures analysis vs placebo.
IH = idiopathic hypersomnia; MWT = Maintenance of Wakefulness; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

FIGURE 5: A. Low Frequency Band Amplitudes and B. High Frequency Band Amplitudes Are Correlated With Subjective and Objective Endpoints

A. Low Frequency

		KSS ↓ with ALKS 2680 (↓ = more alert)			MWT ↑ with ALKS 2680 (↑ = more awake)		
	Region[a]	Left	Center	Right	Left	Center	Right
Delta ↓ with ALKS 2680	Frontal						
	Temporal						
	Central						
	Parietal						
	Occipital						
Theta ↓ with ALKS 2680	Frontal						
	Temporal						
	Central						
	Parietal						
	Occipital						

B. High Frequency

		KSS ↓ with ALKS 2680 (↓ = more alert)			MWT ↑ with ALKS 2680 (↑ = more awake)		
	Region[a]	Left	Center	Right	Left	Center	Right
Beta ↑ with ALKS 2680	Frontal						
	Temporal						
	Central						
	Parietal						
	Occipital						
Gamma ↑ with ALKS 2680	Frontal						
	Temporal						
	Central						
	Parietal						
	Occipital						

Positive Correlations
- **Dark green:** Statistically significant correlations ($P < 0.05$)
- **Light green:** Non-significant relationships

Inverse Correlations
- **Dark blue:** Statistically significant correlations ($P < 0.05$)
- **Light blue:** Non-significant relationships

- White cells indicate no electrode or no correlation analysis conducted

[a]Left frontal (Fp1, F7, F3); right frontal (Fp2, F4, F8); left temporal (T3, T5); right temporal (T4, T6). The remaining regions (left/right central, left/right parietal, left/right occipital, frontal/central/parietal midline) had 1 electrode each.
Linear regression models were used to generate correlation coefficients and P values.
KSS = Karolinska Sleepiness Scale; MWT = Maintenance of Wakefulness Test.

CONCLUSIONS

In the phase 1b study:

- ALKS 2680 increased wakefulness on the MWT and alertness on the KSS in patients with NT1, NT2, and IH (see Poster 400)[4]
- ALKS 2680 resulted in dose-dependent effects on spectral amplitude in the combined cohort analysis
  - Decrease in drowsiness-associated low frequency band amplitudes
  - Increase in alertness-associated high frequency band amplitudes
- Spectral changes were generally correlated with changes on the patient-reported KSS and objectively measured MWT
- Phase 2 studies are further evaluating effects of once-daily ALKS 2680 on qEEG spectra in patients with NT1, NT2, and IH

qEEG Spectral Profiles During Wake

qEEG Bands	Narcolepsy / IH Sleepy	ALKS 2680
Low Frequency Drowsiness/ reduced alertness	↑	↓
High Frequency Alert, active, attentive mind; concentration	↓	↑

References

1. Alloway CE, et al. *Sleep*.1999;22(2):191-203. **2.** Saletu MT, et al. *Eur Arch Psychiatry Clin Neurosci*. 2005;255(1):20-32. **3.** Brooks J, et al. Poster presented at SLEEP 2025; June 8-11, 2025; Seattle, WA, USA. **4.** Grunstein RR, et al. Poster presented at SLEEP 2025; June 8-11, 2025; Seattle, WA, USA. **5.** Yee B, et al. Oral presentation at 17th World Sleep Congress; October 20-25, 2023; Rio de Janeiro, Brazil. **6.** Abhang PA, et al. Chapter 2 - Introduction to EEG- and Speech-Based Emotion Recognition In: *Introduction to EEG- and Speech-Based Emotion Recognition*, Academic Press, 2016. **7.** Plunkett G, et al. *J Sleep Res*. 2024:e14428. **8.** Curley TM, et al. *Top Cogn Sci*. 2024;16(1):113-128. **9.** Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498.

Acknowledgments

The study was supported by Alkermes, Inc. Medical writing support was provided by Rebecca Jarvis, PhD, at Envision Pharma Group, and was funded by Alkermes, Inc. This poster was developed in accordance with Good Publication Practice (GPP4) guidelines. Authors had full control of the content and made the final decision on all aspects of this poster.

Disclosures

MM, **BR**, and **DGS** are employees and shareholders of Alkermes. **BY** has received funding from Alkermes, Eli Lilly & Company, GlaxoSmithKline, SomnoMed, Takeda, Teva Pharmaceuticals, and Vanda Pharmaceuticals. **JC** and **AD** have nothing to disclose. **RR** and **LJT** are employees of Pacific Development and Technology, LLC, which received funding from Alkermes, Inc. to design and perform the analysis of the qEEG data. **GSFR** is a subcontractor consultant to Pacific Development and Technology, LLC. **RG** has received funding from Apnimed, Eli Lilly & Company, SomnoMed, and his department has received funding from Alkermes, Eisai, Takeda, and Vanda Pharmaceuticals.

Scan QR code to download poster