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, 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

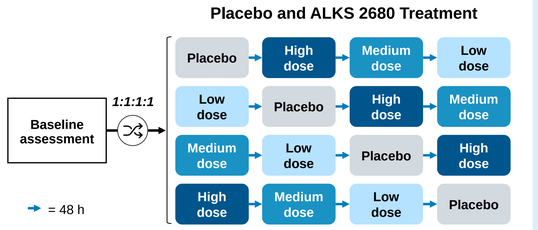
METHODS

- 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**)

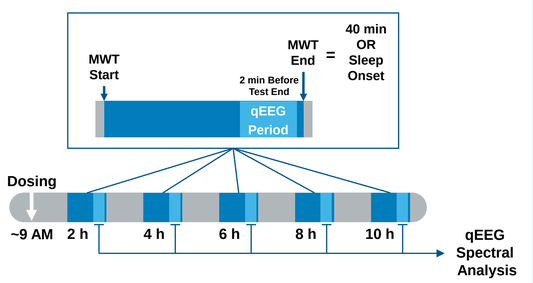
FIGURE 1: Phase 1b Study Design, Single-Dose Crossover



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.

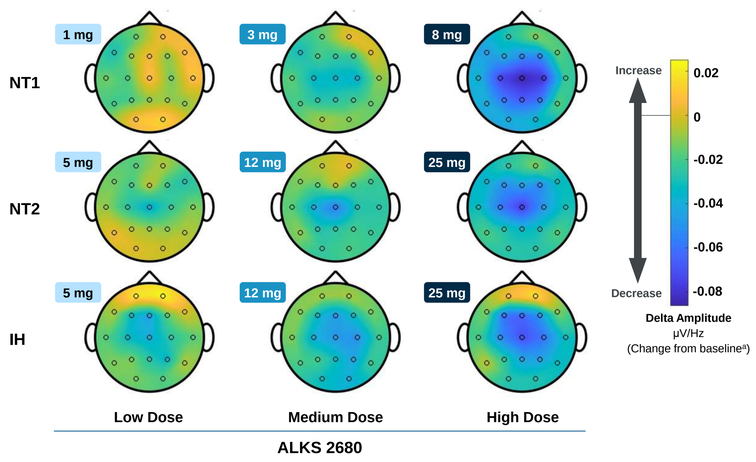
FIGURE 2: Maintenance of Wakefulness Test



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

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

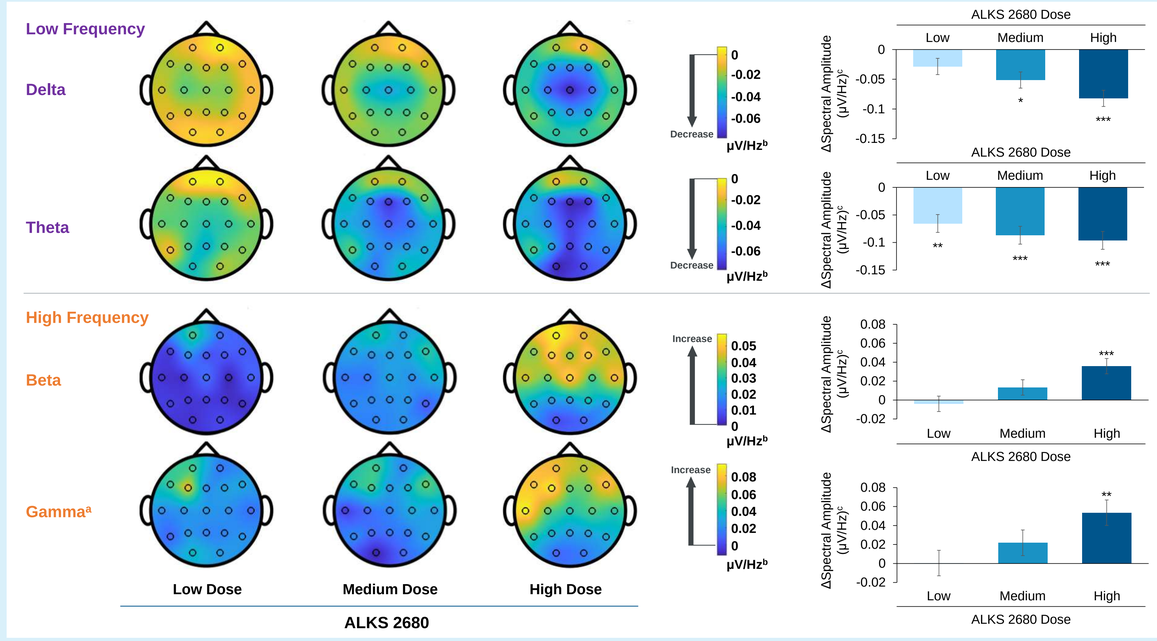


[a]Time-matched baseline-corrected spectral amplitudes were averaged across the 5 MWT sessions.
IH = idiopathic hypersomnia; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

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

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