# 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<br>15-18 Hz<br>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

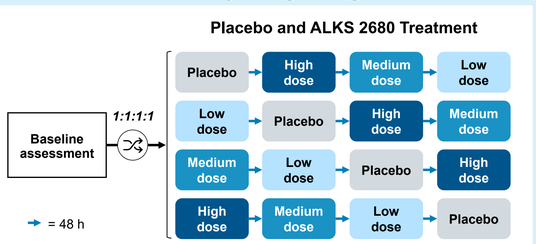
## METHODS

- 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**

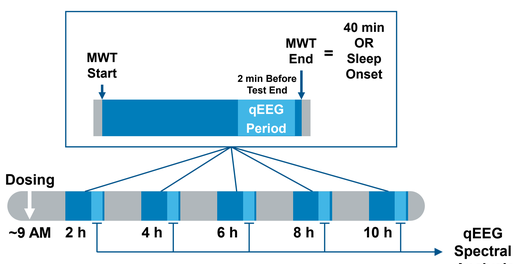



ALKS 2680 Dose

| | 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.

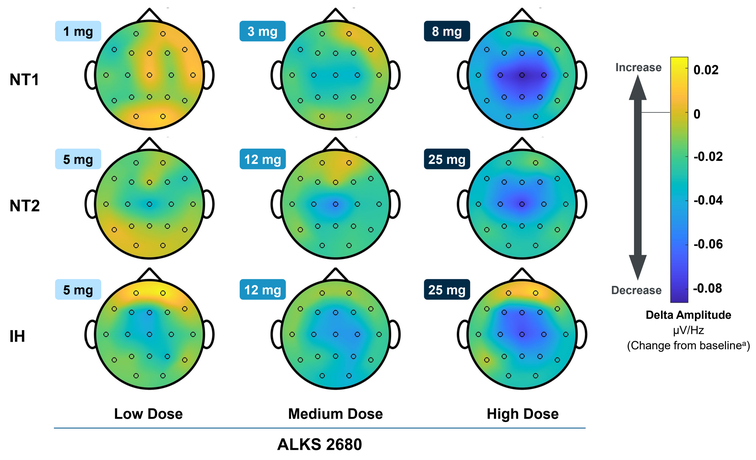
**FIGURE 2: Maintenance of Wakefulness Test**




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**

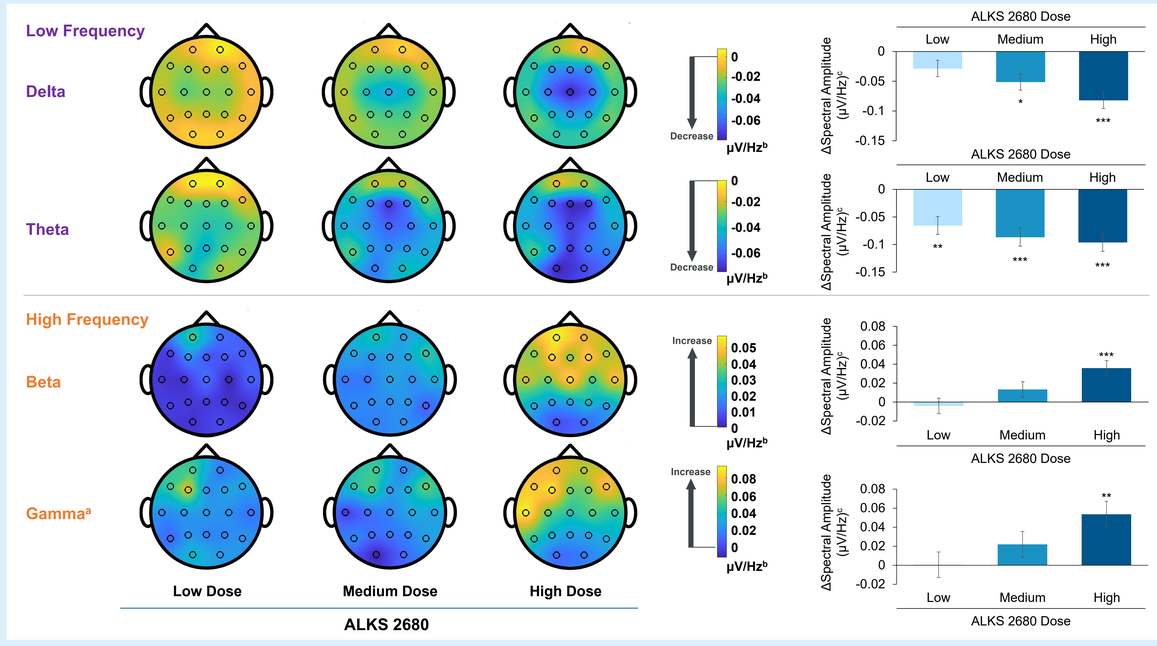



[a]Time-matched baseline-corrected spectral amplitudes were averaged across the 5 MWT sessions.
IH = idiopathic hypersomnia; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

## 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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