

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 qEEG⁵
 - Beta power increase was correlated with improvements in the KSS⁵

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

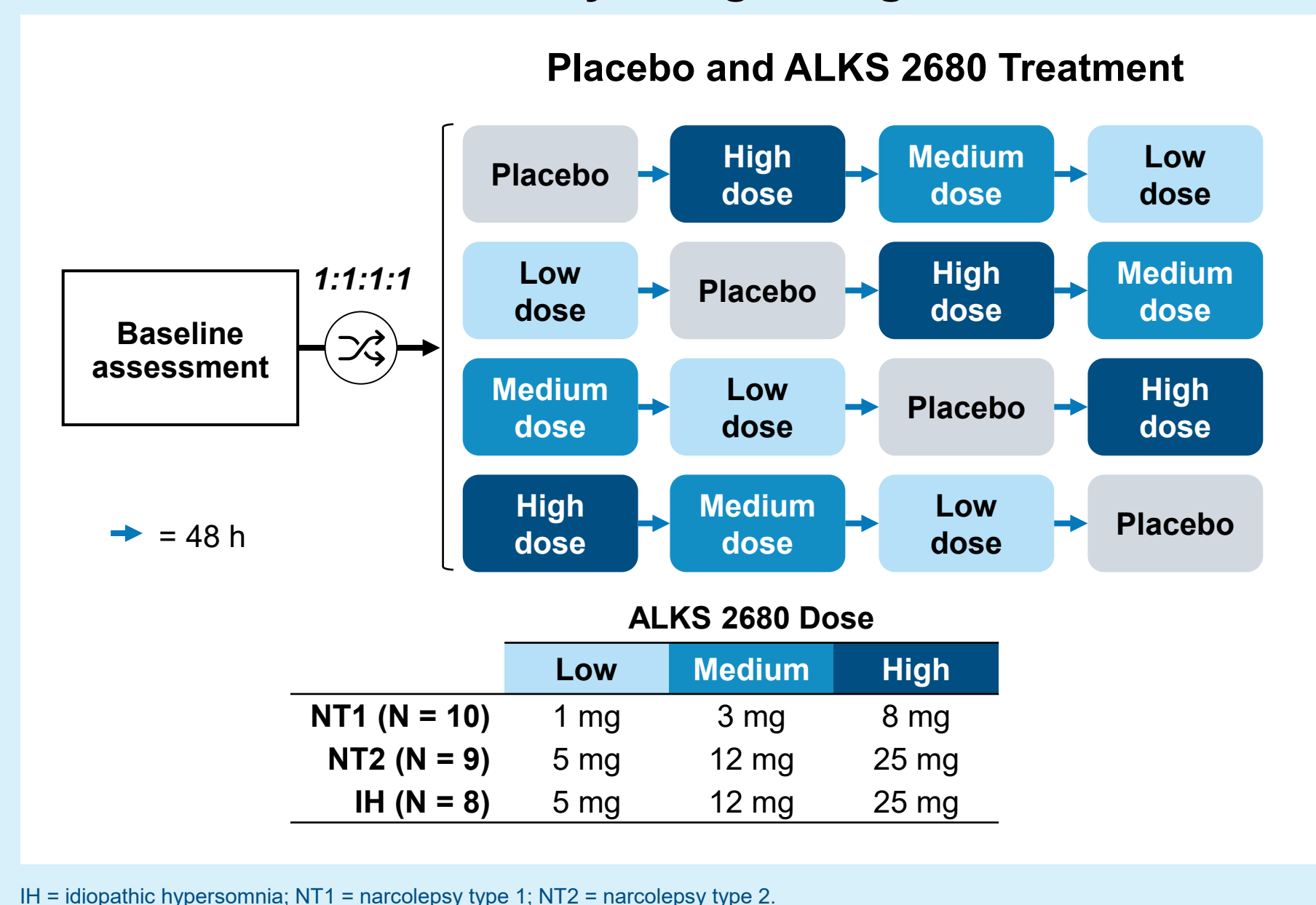
METHODS

- 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 guidance⁹ (**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



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

FIGURE 2: Maintenance of Wakefulness Test

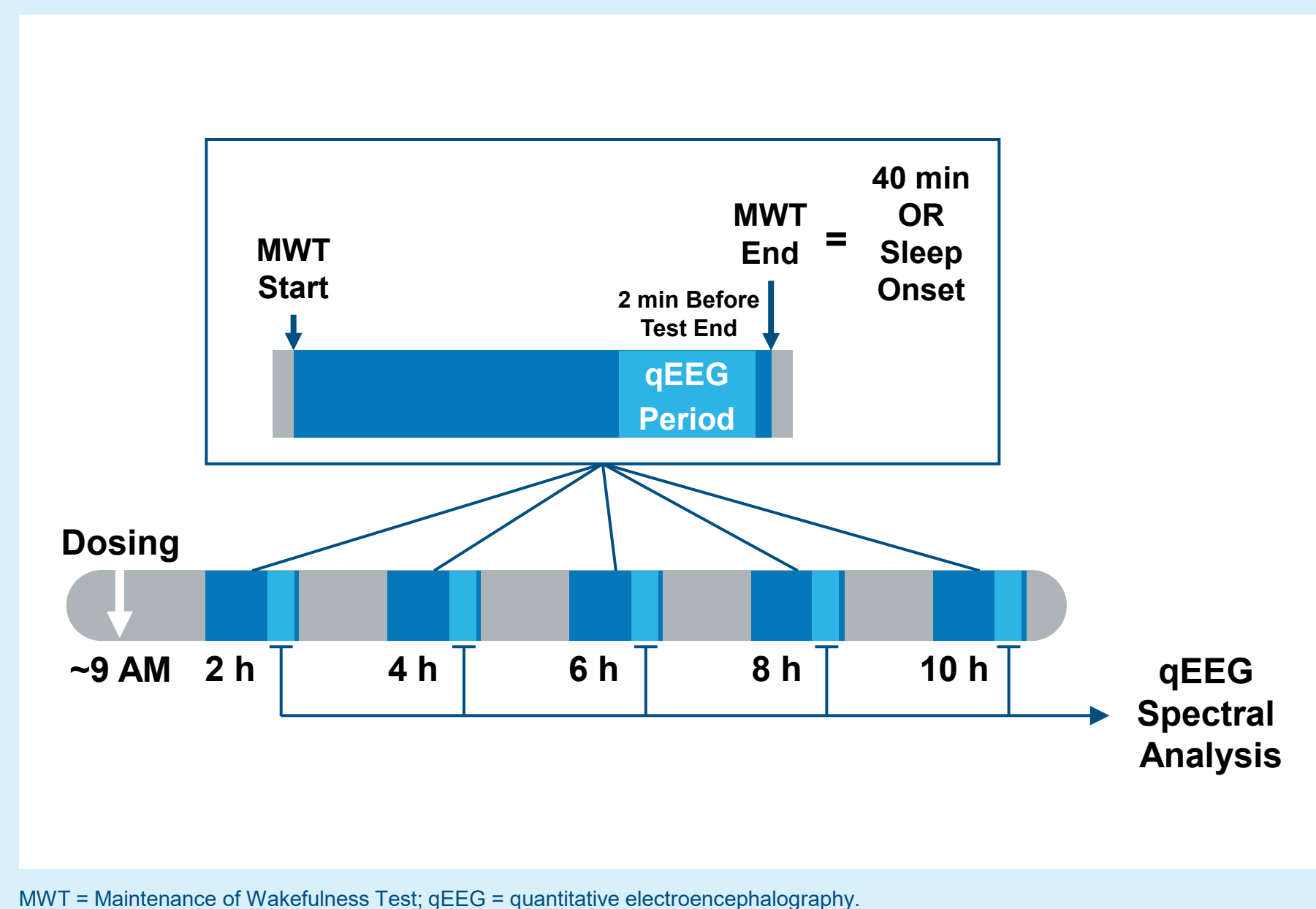
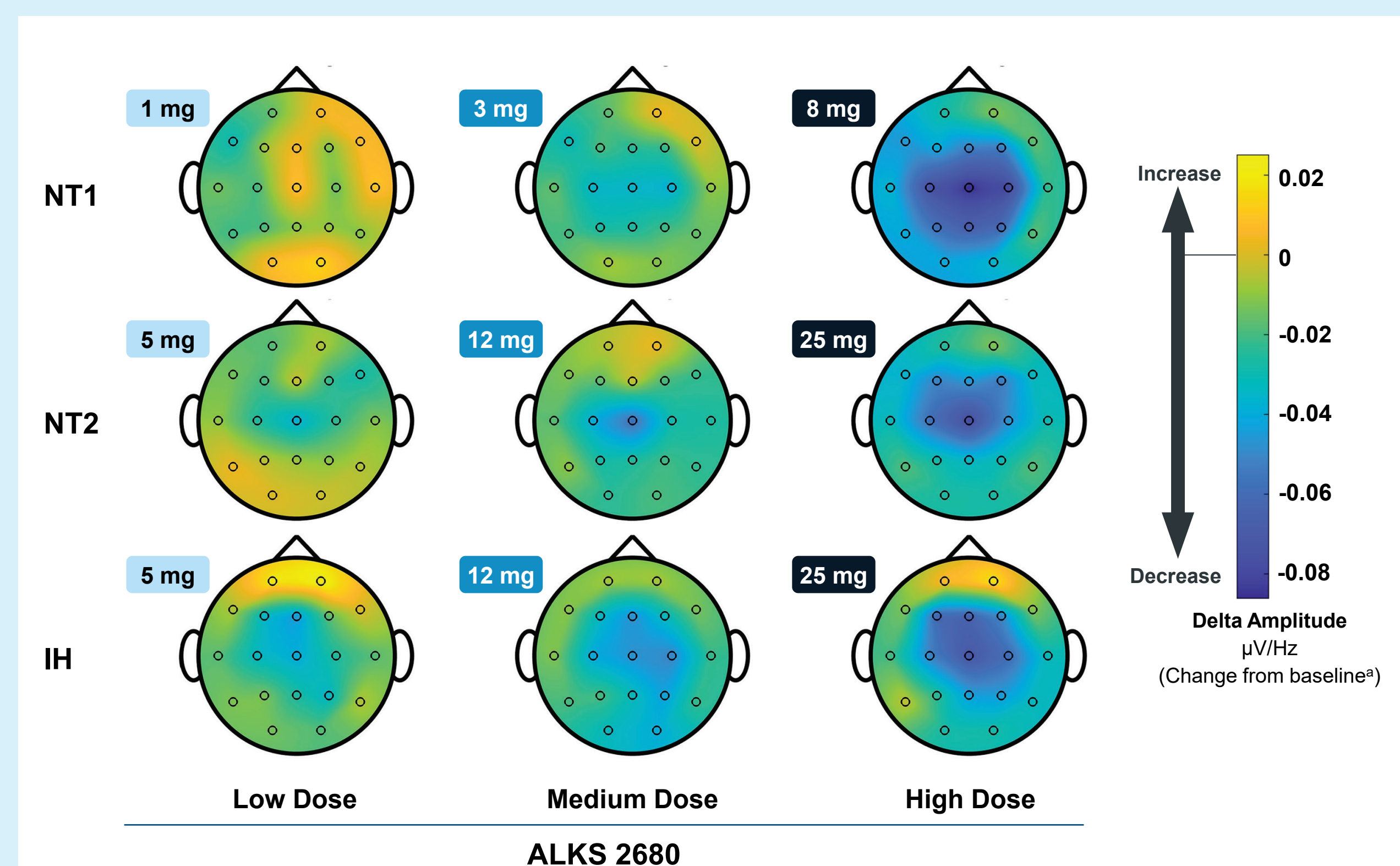


FIGURE 3: Topographic Maps of Spectral Amplitude Across NT1, NT2, and IH Patients With ALKS 2680

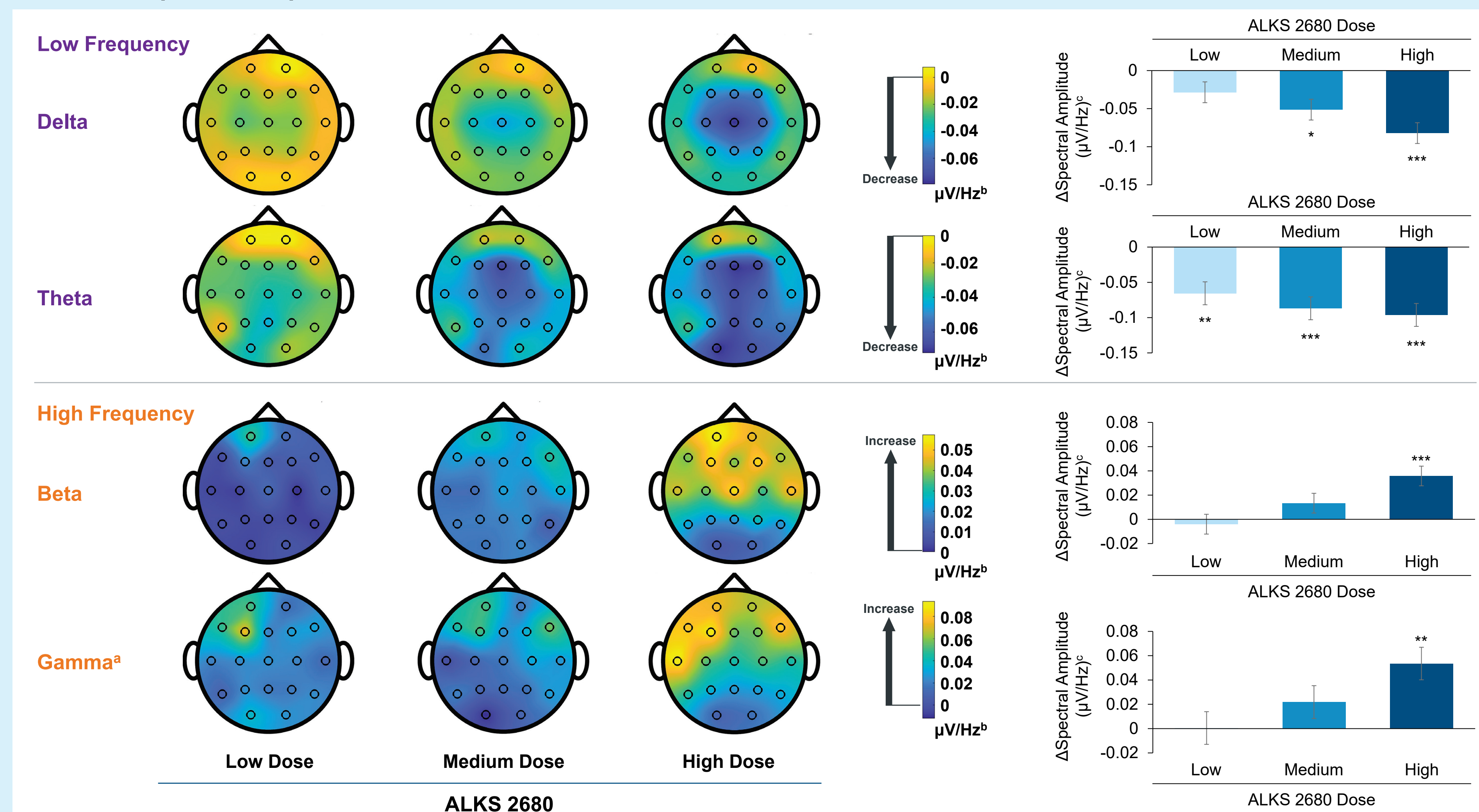


*Time-matched baseline-corrected spectral amplitudes were averaged across the 5 MWT sessions. IH = idiopathic hypersomnia; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

RESULTS

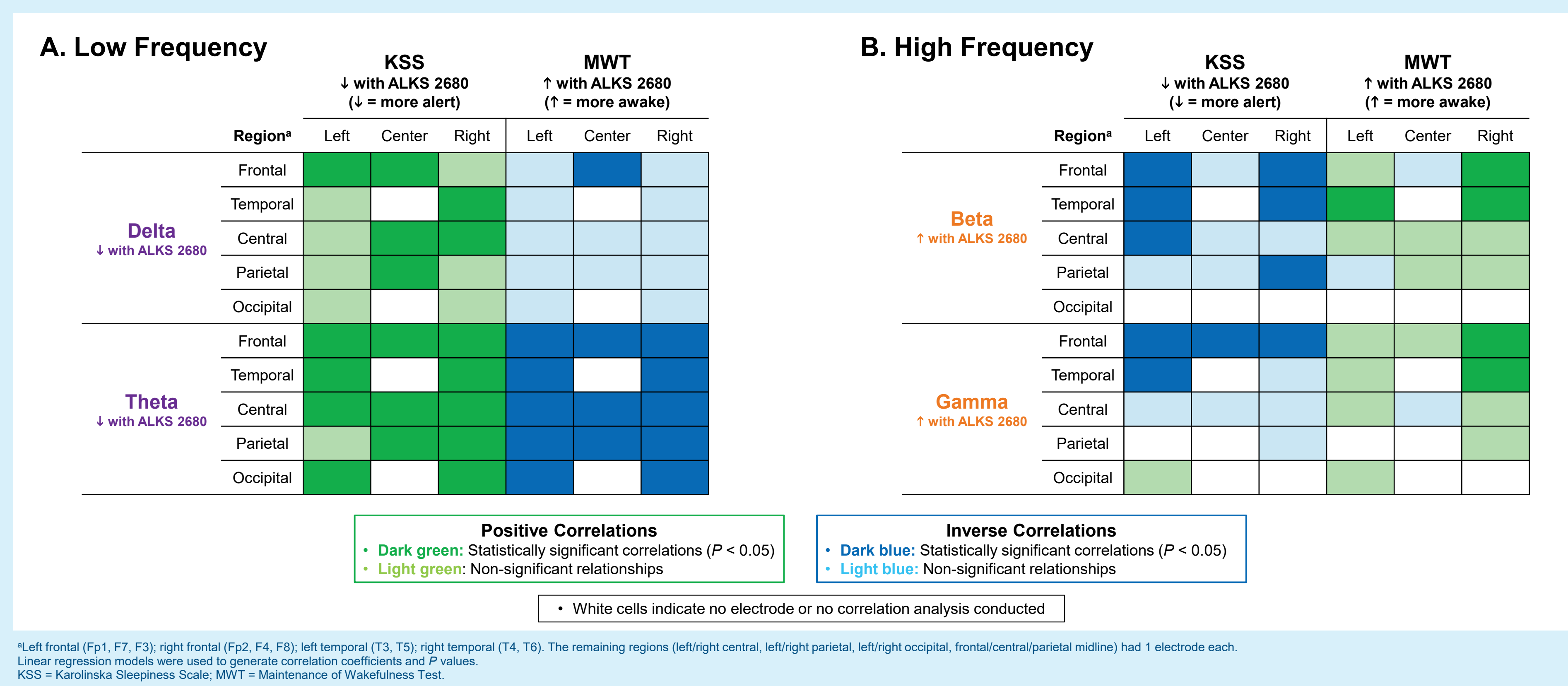
- In the combined cohort analysis, ALKS 2680 demonstrated:
 - Dose-dependent decreases in amplitude of sleepiness-associated low frequency bands (delta and theta) (**Figure 4**)
 - Dose-dependent increases in amplitude of alertness-associated high frequency bands (beta and gamma) (**Figure 4**)
- Low 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



*Aperiodic. *Time-matched baseline-corrected spectral amplitudes were averaged across the 5 MWT sessions. *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



*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	↓	↑

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