Pharmacodynamic Profile of GRX-917 Using Quantitative EEG in a Phase 1 Study

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Introduction

- Current pharmacological treatments of anxiety are limited by important shortcomings: inadequate efficacy, slow onset, sedation, memory deficits, risk of falling, dependence and abuse.
- GRX-917 is a novel, deuterated form of etifoxine hydrochloride (Stresam®) for treating anxiety.
- GRX-917 is a ligand at the mitochondrial translocator protein 18k Da (TSPO), stimulating the endogenous neurosteroids production in the brain, including allopregnanolone[1]. Neurosteroids act as modulators of GABA-A receptors.
- Pharmaco-EEG can assess the effects of drugs on the human brain by measuring the magnitude (power) of cortical oscillations at specific frequency band.
- Neuroactive steroids, like allopregnanolone, increase EEG beta power (13-30Hz)[2], whereas benzodiazepines increase beta and suppress alpha power (8-12Hz), indicating anxiolytic and sedative effects, respectively[3].

Aims & Hypotheses

- The study aim was to assess safety, tolerability and PK/PD of GRX-917. We assessed spontaneous Alpha and Beta oscillations as biomarkers of GABAergic neurotransmission in healthy human volunteers.
- GRX-917 is hypothesized to increase beta band power in line with effects of both benzodiazepines and neurosteroids, indicating potential for anxiolytic activity. In addition, GRX-917 is hypothesized to not decrease alpha power which is associated with sedative side effects.

Methods

- In this Phase I, randomized, double-blind, placebo-controlled study, healthy volunteers receive single and multiple ascending doses (SAD/MAD) of GRX-917. Dosing regimen in MAD followed a q12h dosing pattern for 7 days.
- EEG signal is recorded using 20 channels Stat X24 wireless EEG system (ABM).
- A sensitivity analysis of high doses in fed conditions, combining 200mg and 300mg has been performed using the cluster-based permutation approach.
- Pearson's correlation analysis is used to investigate PK/PD relationships.

References :
1. Nuss. P. *et al.*, (2019), *Neuropsychiatric Disease and Treatment*, 15, 1781-1795;
2. Broekhoven F.V. , et al., (2007) *Psychoneuroendocrinology* 32(5):555-64
3. Barbanoj M.J., *et al.*, (2007), *Neuropsychobiology*, 55(3-4):203-12;

Study Design

Condition	Dosage	Cohort	*n*	Age	Sex M	Sex F
MAD (Fed)	Placebo		15	30.3 (±7.1)	9	6
	100mg	6	9	30.8 (±9.1)	6	3
	150mg	8	9	28.4 (±9.8)	8	1
	200mg	7	7	28.6 (±6.1)	5	2
	200mg	9	9	26.3 (±5.5)	8	1
	300mg	10	9	29.6 (±7.1)	8	1

Table 1. Demographic Characteristics: Dose cohorts included in the MAD study, including number (n) of participants, age and sex (M=male, F=female).

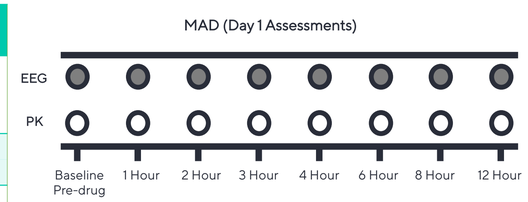

Fig 1. Timeline of Assessments: Resting state EEG and PK samples were collected from Baseline (pre-drug) up to hour 12 for both SAD and MAD (Day 1) studies

- Because of methodological requirements for minimal sample size, the main statistical analysis is limited to the 200mg dose group (n =16) vs placebo (n=14). A sensitivity analysis was done combining 200+300mg groups (n=25).
- One subject's data (on placebo) was excluded due to poor quality EEG recordings.

Results: EEG Difference Wave Calculation

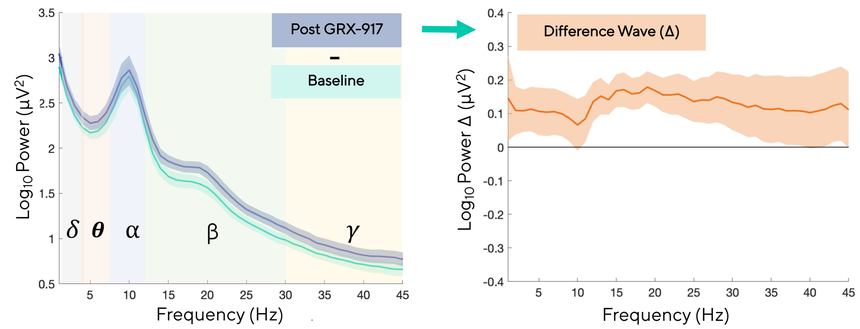

Fig 2. Calculation of Difference Wave (Δ): For each participant and each condition (GRX-917 and Placebo), Baseline EEG power spectra were subtracted from each post-drug EEG. Difference Waves (Δ = post *minus* pre) were compared between GRX-917 and Placebo at each hour and frequency of interest.

Results: GRX-917 EEG Profile

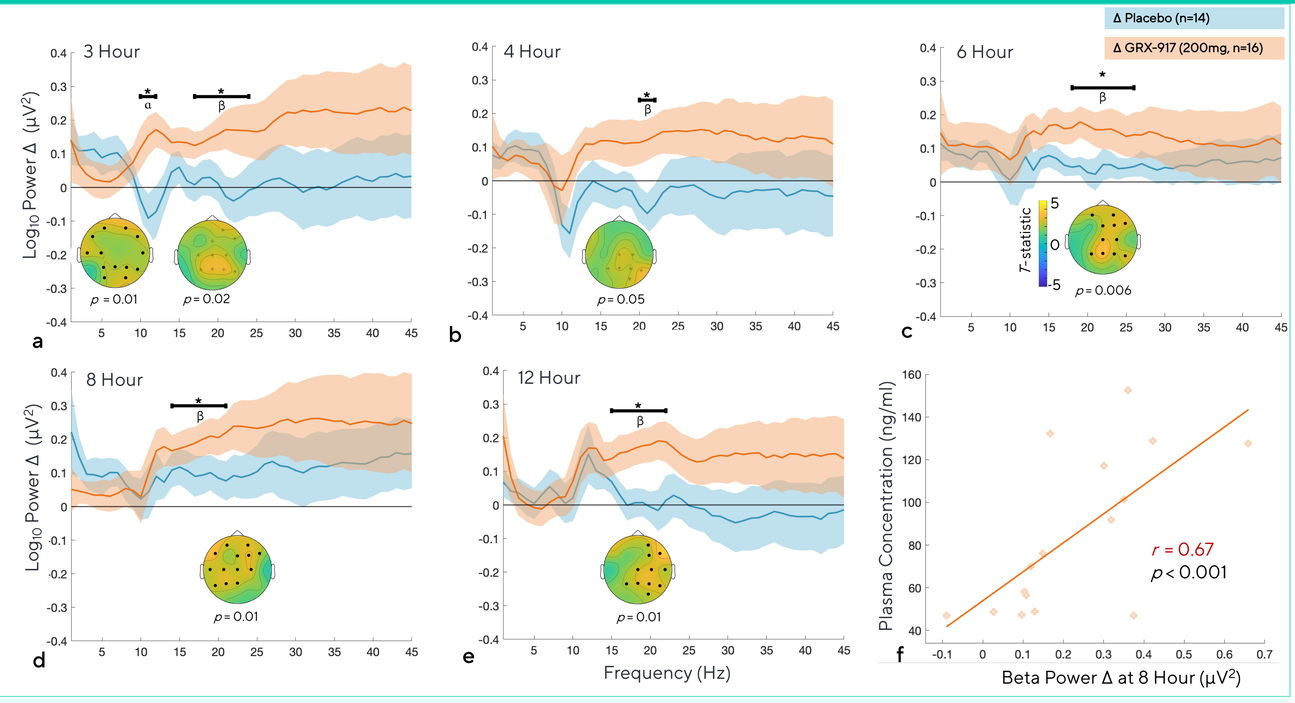

Figure 3. Statistical Analysis: Comparison between GRX-917 200mg (Δ) and Placebo (Δ) for each FOIs. GRX-917 shows significant beta power increase at: (a) hour 3 (p=0.02), (b) 4 (p=0.05), (c) 6 (p=0.006), (d) 8 (p=0.01) and (e) 12 (p=0.01). (a) Alpha power is increased at hour 3 (p=0.01), whereas other FOIs were not significant. (f) Significant correlation between GRX-917 plasma concentration at hour 8 and Δ Beta power at hour 8, r=0.67, p<0.001.

- A sensitivity analysis, combining the 200mg and 300mg cohorts compared to placebo, showed the same sustained and statistically significant increase in Beta power across all timepoints, from 3-12 hours (**Figure 4**). The significant increase in Alpha power at 3 hours (p=0.03) remained and Alpha power was also significantly increased at 8 hours (p=0.045).

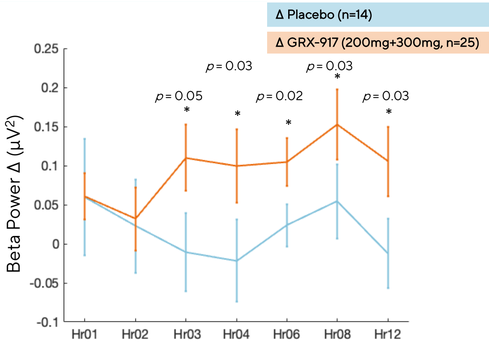

Figure 4. Sensitivity Analysis: Line plot showing Beta power Δ (mean±SEM) at each hour for placebo and GRX-917 (combined 200mg and 300mg cohorts).

Conclusions

- GRX-917 (200mg, fed-state) increase of Beta power is in line with pharmacodynamic efficacy of exogenous neurosteroids and benzodiazepines and may indicate anxiolytic effects.
- The absence of Alpha reduction with GRX-917 suggests a basis for less sedation than with benzodiazepines.
- GRX-917 was safe and well-tolerated, including sedation in-line with placebo, which is consistent with EEG results.

Disclosures : PK, GM, SMC, GK, KC, RGE, SR & IP are atai Life Sciences employees. AHM, CB are ABM employees. MS is an employee of GABA Therapeutics.

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