Functional central nervous system effects of the novel AMPA positive allosteric modulator (PAM) TAK-653 consistent with increased cortical excitability

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Introduction

- TAK-653 is a novel AMPA PAM in development for Treatment-Resistant Depression (TRD).
- Using transcranial magnetic stimulation (TMS), TAK-653 6 mg but not 0.5 mg demonstrated increased cortical excitability by enhancing peripheral motor evoked potentials (MEP's) in healthy volunteers [1].
- TAK-653's concurrent functional pharmacodynamic (PD) effects on various central nervous system (CNS) domains are reported here.

Methods

- Randomized, double-blind, placebo-controlled, three-way crossover study in 24 healthy male and female volunteers (**Figure 1**).
- Oral doses (0.5 and 6 mg compared to placebo) based on prior preclinical and clinical studies.
- NeuroCart®: a validated pharmacodynamic CNS test battery, consisting of body sway (postural stability), saccadic peak velocity (visuomotor coordination), adaptive tracking (sustained attention and alertness), Visual Analogue Scales Bond and Lader (VAS-BL) (subjective drug effects) performed pre-dose and 2.5 and 4 hours post-dose.
- Data were analysed using a mixed model (ANCOVA) with baseline as covariate.

Results

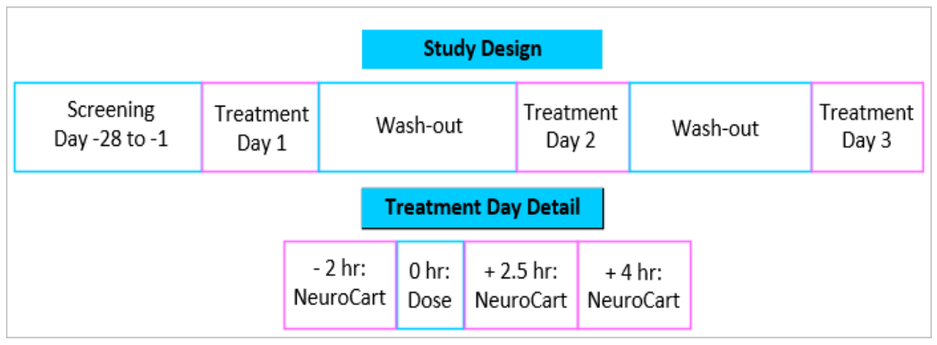
Compared to placebo, TAK-653:

- Did not affect body sway (mm) (-1.3, 90%CI [-13.4; 12.4], p=0.86), (-8.2, 90%CI [-19.4; 4.6] p=0.28) (**Figure 2**) or VAS-BL alertness (mm) (0.65, 90%CI [-0.38; 1.67] p=0.30), (0.77, 90%CI [-0.24; 1.79] p=0.21) (**Figure 3**) at either 0.5 or 6 mg, respectively.
- Increased saccadic peak velocity (degrees/second) at both 0.5 mg (+19.49, 90%CI [5.98, 32.99], p=0.02) and 6 mg (+15.40, 90%CI [1.91, 28.90], p=0.06) (**Figure 4**).
- Improved adaptive tracking (%) at 6 mg (+1.675, 90%CI [0.510, 2,840], p=0.02) but not at 0.5 mg (+0.412, 90%CI [-0.734, 1.557], p=0.55) (**Figure 5**).

Conclusions

- Acute administration of the AMPA PAM TAK-653 demonstrated functional PD effects consistent with CNS stimulation such as increased visuomotor coordination and alertness, and improved sustained attention.
- These findings are consistent with TAK-653's increase of cortical excitability, which support future proof-of-concept studies in psychiatric patient populations that may benefit from CNS stimulatory effects.

Figure 1. General and detailed study design



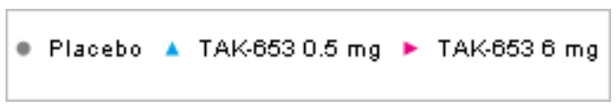


Figure 2. Least squares mean (LSM) change from baseline (CFB) body sway

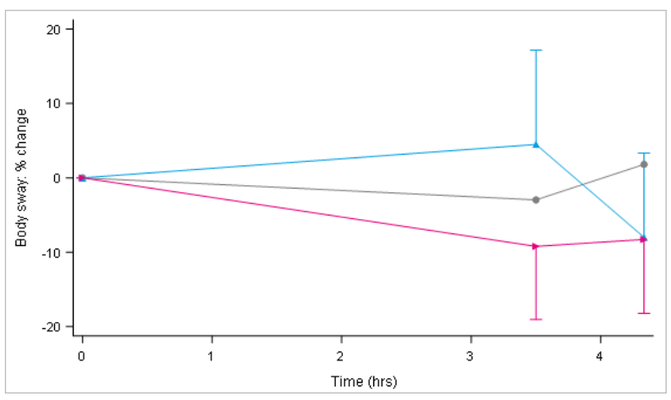


Figure 3. LSM CFB VAS alertness

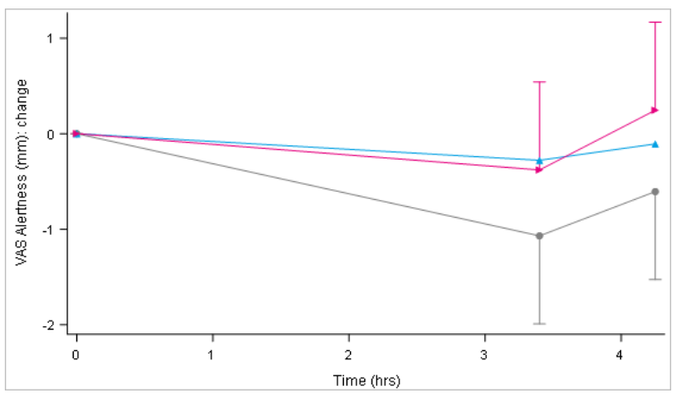


Figure 4. LSM CFB saccadic peak velocity

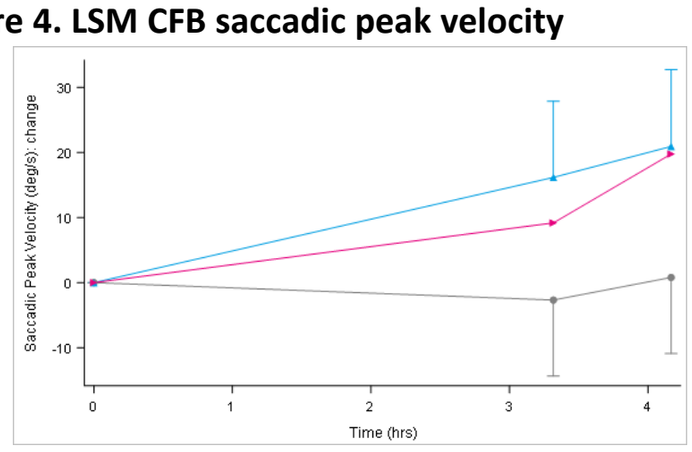
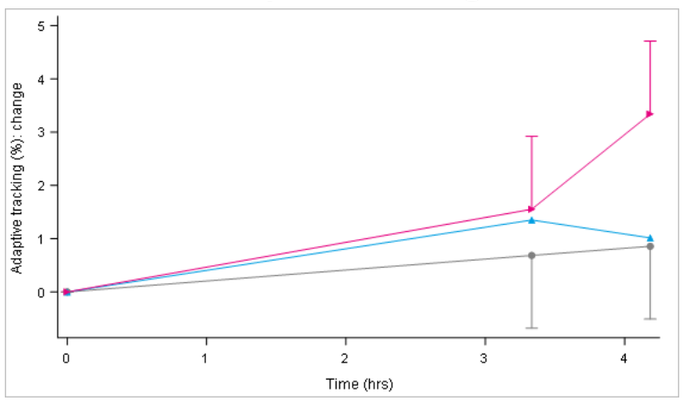


Figure 5. LSM CFB adaptive tracking



Reference:
1. O'Donnell P. (2019, December). *Transcranial Magnetic Stimulation as a Translational Biomarker for Modulation of AMPA Receptor Function*. Poster Session presented at American College of Neuropsychopharmacology. Orlando, Florida

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