Quantitative EEG as a translational measure for the assessment of ATH-1017 neurophysiological changes in mild-to-moderate Alzheimer's disease

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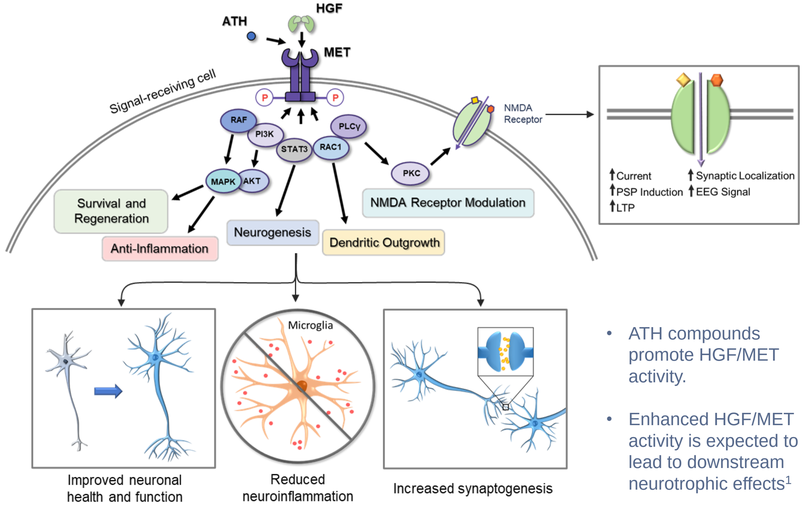
The utility of non-neuroimaging biomarker qEEG as a translational tool for PK/PD modeling, dose-optimization and assessment of ATH-1017 in healthy volunteers and Alzheimer's subjects

INTRODUCTION

Athira Pharma, Inc. is developing a new class of blood-brain barrier (BBB)-penetrant small molecule drugs aimed at activating the neurotrophic system HGF/MET to promote multiple neurorestorative processes, with the potential to ultimately improve brain function. ATH-1017 is the lead clinical candidate for the treatment of Alzheimer's disease (AD). Electroencephalogram (EEG) plays a growing role in facilitating dose exploration of investigational agents like ATH-1017 by demonstrating brain penetration and target engagement, helping to accelerate CNS drug development.



- ATH compounds promote HGF/MET activity.
- Enhanced HGF/MET activity is expected to lead to downstream neurotrophic effects[1]

METHODS

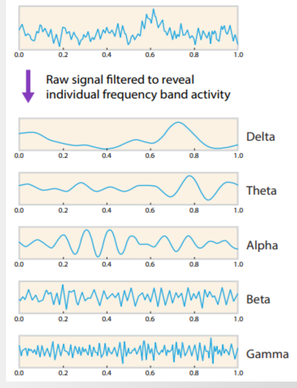
The translational measure quantitative electroencephalogram (qEEG) was assessed in preclinical animal models and in human volunteers, including healthy young, healthy elderly, and AD subjects as part of a randomized, double-blind Phase 1a/b trial assessing the safety and pharmacodynamics of ATH-1017. The Phase 1 clinical study of ATH-1017 including EEG was performed by Biotrial Phase 1 unit and Biotrial Core Lab.

The primary utilization of qEEG was as a translational biomarker related to ATH-1017's mechanism in promoting HGF/MET activity with a downstream effect on potentiation of NMDA receptor currents, synaptic relocation of NMDA receptors, and LTP[2].

QUANTITATIVE EEG (qEEG)

- Translational tool from rodents to humans
- PK/PD modeling for dose selection

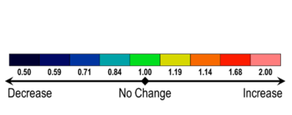
Noninvasive EEG recordings reflect brain activity and function



EEG records brain electrical activity from electrodes placed on the scalp

RESULTS

As measured by qEEG, ATH-1017 induced a fast onset and sustained gamma power induction across a range of active doses in humans and animals based on equivalent PK exposures. Additionally, these exposures directly overlapped with the pharmacodynamic active dose range of behavioral and neuroprotective effects shown in dementia animal models. The translational utility of qEEG across species thus allowed for effective pharmacokinetic/pharmacodynamic (PK/PD) modeling and dose-optimization across healthy volunteers and AD subjects, defining the dose range for late-stage randomized, double-blind studies of ATH-1017 in AD.



A

Fold Change from Baseline

Frequency Band	Placebo (n=12)	Low Dose (n=12)	Mid Dose (n=12)	High Dose (n=11)
Gamma 1 (30 - 40 Hz)				
Gamma 2 (41 - 58 Hz)				

Panel A: ATH-1017: single dose EEG, 1-hour post-dose

Increased gamma power observed after a single SC injection at doses between 20-90 mg in healthy young volunteers

B

Fold Change from Baseline

Frequency Band	Day 1		Day 4			Day 8		
	Hour 1 (n=6)	Hour 3 (n=6)	Pre-dose (n=6)	Hour 1 (n=6)	Hour 3 (n=6)	Pre-dose (n=5)	Hour 1 (n=4)	Hour 3 (n=5)
Gamma 1 (30 - 40 Hz)								
Gamma 2 (41 - 58 Hz)								

Panel B: ATH-1017: multiple dose EEG, 1-hour and 3-hour post-dose, on Day 1, 4 and 8

Increased gamma power observed in healthy elderly treated with ATH-1017 20 mg SC once daily for 8 days; Similar results were observed for the 40 and 60 mg doses

C

Fold Change from Each Day's Pre-dose Baseline

Frequency Band	Day 1		Day 4		Day 8	
	Hour 1 (n=7)	Hour 3 (n=7)	Hour 1 (n=7)	Hour 3 (n=7)	Hour 1 (n=7)	Hour 3 (n=7)
Gamma 1 (30 - 40 Hz)						
Gamma 2 (41 - 58 Hz)						

Panel C: ATH-1017: multiple dose EEG, 1-hour and 3-hour post-dose, on Day 1, 4 and 8

Increased gamma power observed in AD subjects treated with ATH-1017 40 mg SC once daily for 8 days

CONCLUSIONS

The use of qEEG as a translatable tool for PK/PD modeling and dose-optimization supported brain penetration and pharmacodynamic activity of ATH-1017 and is indicative of promoting synaptic NMDA receptor activity and synaptogenesis across species. The non-invasive and replicable nature of qEEG measurements provides a direct, quantitative measure of brain activity in response to pharmacological intervention. qEEG facilitates the evaluation of CNS drug candidates early in the drug development process and increases confidence in translation before cognitive assessments in long-term treatment trials.

- EEG captures electrical activity in the brain and displays these electrical impulses as waves
- qEEG quantifies the prevalence ("power") of certain frequency bands in healthy and disease conditions
- Gamma waves are the faster, higher frequency waves associated with learning, memory and higher cognitive functions
- Gamma power is reduced in AD patients
- **A shift from low to high frequency bands is indicative of improved activity of the salient network, hence network recovery**

REFERENCES

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