Clinical trial design for a Phase 2a study evaluating the safety, tolerability, pharmacokinetics, and CNS activity of CY6463 in participants with Alzheimer's disease with vascular pathology

P-54463

ISTAART

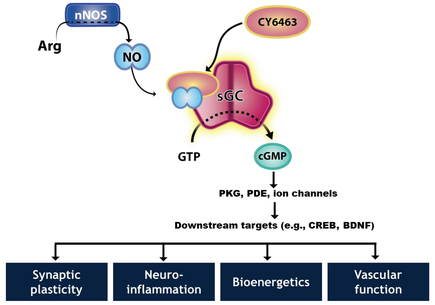
alzheimer's association

Chad Glasser, Jennifer Chickering, Phebe Wilson, Emily Florine, Chris Wright, Chris Winrow
Cyclerion Therapeutics, Cambridge, MA

CY6463 is being evaluated in a signal-seeking, exploratory study to assess changes in biomarkers of AD and vascular function

INTRODUCTION

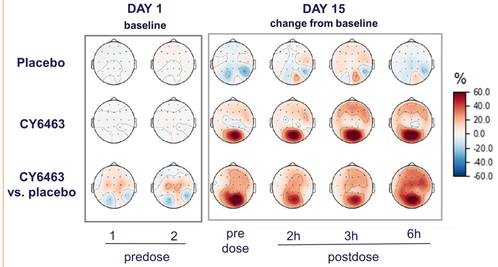
The soluble guanylate cyclase (sGC) stimulator, CY6463, is being developed as a symptomatic and potentially disease-modifying therapy for serious central nervous system (CNS) diseases, including Alzheimer's disease with vascular pathology (ADv). Nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) is a fundamental neurotransmitter pathway critical to neuronal function. Impairment of this pathway plays a role in the pathogenesis of many neurodegenerative diseases. CY6463 is a CNS-penetrant positive allosteric modulator of sGC and amplifies endogenous NO signaling to increase cGMP production. Preclinically, CY6463 improved neuronal function, cerebral blood flow, neuroinflammation, and cellular bioenergetics[1].



BACKGROUND

In two Phase 1 studies* (110 healthy younger adults and 24 healthy elderly >65 years), once-daily CY6463 was well tolerated across dose levels and achieved target CNS concentrations, with predictable, linear, food-independent pharmacokinetics (PK). CY6463 had positive impacts on brain neurophysiology as measured by electroencephalography (EEG) and saccadic eye movements and on neuroinflammatory markers.

Scalp distribution of closed-eye alpha power (8-12 Hz) by visit and treatment in healthy elderly participants



Robust alpha power effects (nominal p-value<0.02)

Posterior alpha power has been linked to attention and cognitive processes and is known to decline with aging and in mild cognitive impairment and neurodegenerative diseases such as AD [2,3].

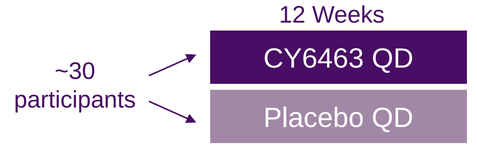
METHODS

The Phase 2a study is a 12-week, randomized, placebo-controlled, parallel study designed to evaluate safety, tolerability, PK, and CNS activity of once-daily CY6463 in approximately 30 participants who have a combination of AD pathology, sub-cortical vascular disease, and cardiovascular risk factors. This defined subset of the larger AD population, referred to as AD with vascular pathology (ADv), is hypothesized to be more likely to respond to CY6463 treatment due to CY6463's expected impact on cerebrovascular and CNS biology. (ClinicalTrials.gov:NCT04798989)

The primary objectives are safety and tolerability, which will be evaluated based on adverse events. Exploratory evaluations assessed variously at baseline and weeks 2, 4, 8, and 12, include:

- plasma and CSF biomarkers of disease; PK, and neuroinflammation
- quantitative EEG and event-related potentials (ERPs) as biomarkers of neurophysiology
- functional magnetic resonance imaging measures of cerebral perfusion and brain connectivity
- cognitive performance tests of attention, executive function, and memory.

METHODS



Objectives

- Safety & tolerability
- Pharmacokinetics
- CNS activity

Key assessments

- Neuroimaging (MRI, fMRI)
- Electrophysiology (EEG, ERP)
- Neuroinflammatory biomarkers
- Cognitive battery

CONCLUSIONS

Results from this study in participants with ADv will inform the design of larger, longer studies evaluating the potential for CY6463 to improve cognition in this patient population.

ACKNOWLEDGEMENTS

This study funded in part by a Translational Research Award from the Alzheimer's Association Part the Cloud-Gates Partnership Program. Phase 1 EEG analyses were conducted with Beacon Biosignals.

REFERENCES

[1] Correia, S.S. et al. The CNS-penetrant soluble guanylate cyclase stimulator CY6463 reveals its therapeutic potential in neurodegenerative diseases. Front Pharmacol. 2021 May; 12:656561.

[2] Babiloni C, et al. INSIGHT-preAD Study Group. Resting-state posterior alpha rhythms are abnormal in subjective memory complaint seniors with preclinical Alzheimer's neuropathology and high education level: the INSIGHT-preAD study. Neurobiol Aging. 2020 Jun;90:43-59.

[3]Ishii R, et al. Healthy and Pathological Brain Aging: From the Perspective of Oscillations, Functional Connectivity, and Signal Complexity. Neuropsychobiology 2017;75:151-161.

CONTACT

Chad Glasser, Cyclerion Therapeutics
cglasser@cyclerion.com
www.cyclerion.com

alzheimer's association AAIC 21 ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®

*ClinicalTrials.gov Identifiers: Ph2 ADv (NCT04798989); Ph1 healthy participants (NCT03856827); Ph1 healthy elderly (NCT04240158)