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Delivering impact in CNS diseases

INVESTOR CALL - OCTOBER 14, 2020

Safe Harbor Statement

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Applicable risks and uncertainties include those listed under the heading “Risk Factors” and elsewhere in our 2019 Form 10-K filed on March 12, 2020, and in Cyclerion’s subsequent SEC filings, including the Form 10-Q filed on May 4, 2020 and the Form 10-Q filed on August 3, 2020. These forward-looking statements speak only as of the date of this presentation, and we undertake no obligation and do not intend to update these forward-looking statements, except as required by law.

INTRODUCTION

Peter Hecht, Chief Executive Officer

Results in healthy elderly subjects

- ✓ *favorable safety and tolerability*
- ✓ *crossed the blood brain barrier (BBB)*
- ✓ *pathway target engagement confirmed*
- ✓ *delivered rapid, robust, and selective neurophysiological changes*

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Independent expert joining us today

Andrew E. Budson, MD
Chief of Cognitive & Behavioral Neurology,
Associate Chief of Staff for Education, and
Director of the Center for Translational Cognitive Neuroscience,
Veterans Affairs (VA) Boston Healthcare System

AFFILIATIONS: Associate Director for Research, Boston University Alzheimer's Disease Center;
Professor of Neurology, Boston University School of Medicine;
Lecturer in Neurology, Harvard Medical School; and
Medical Director, Boston Center for Memory (Newton, MA)

Agenda

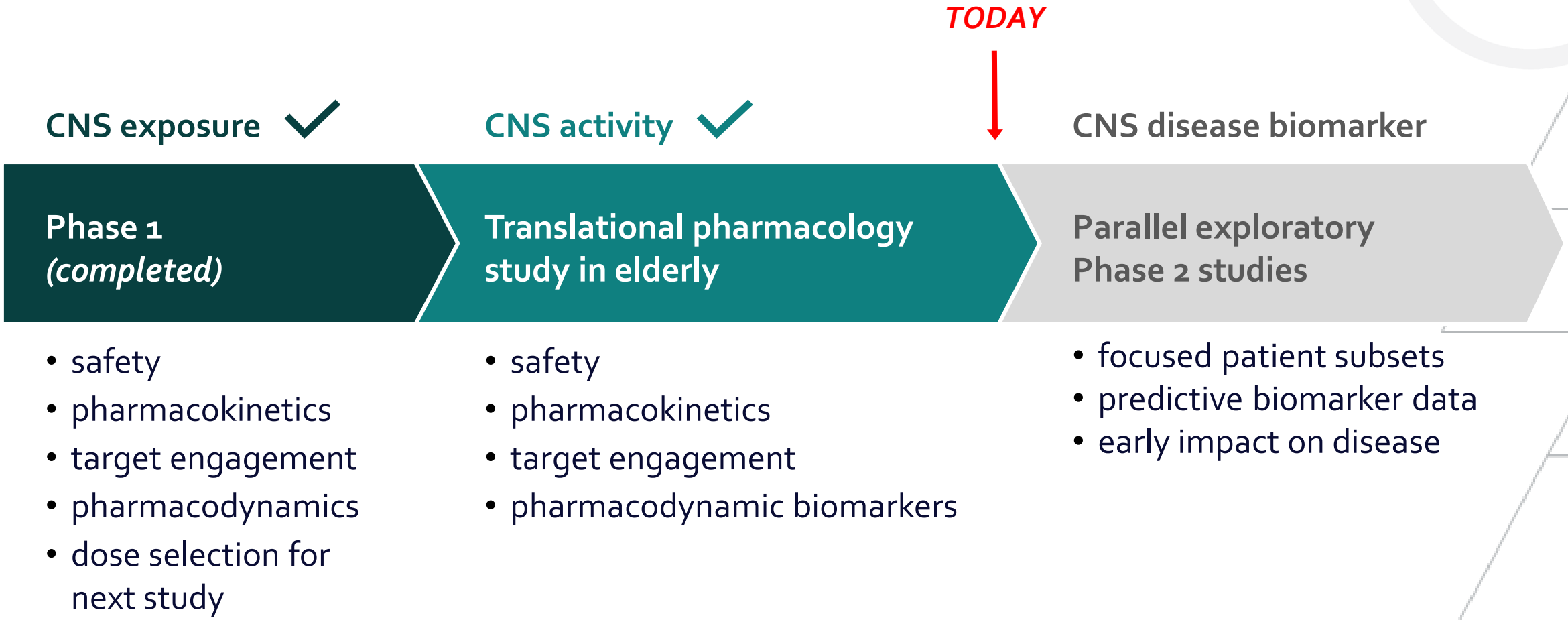
1 Introduction and overview

2 Translational pharmacology results

3 Strategic focus

4 Q&A

Biomarker-driven IW-6463 early clinical development strategy



IW-6463 translational pharmacology study results support advancement

In 24 healthy elderly subjects

- safe and well tolerated
- crosses the blood brain barrier (BBB) at 2-3X concentrations needed for pharmacodynamic effect[1]
- confirmed target engagement: blood pressure, cGMP in CSF
- no effects observed on blood flow or metabolism
- clear improvements--in a short 15-day study---in brain neurophysiology and quantitative performance measures

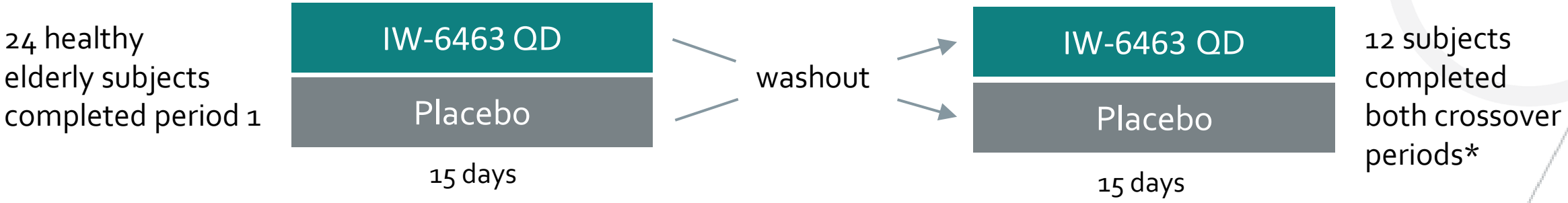
Cyclerion focus on serious CNS diseases

- continue with Phase 2 MELAS* trial activities
- refine and initiate Alzheimer's disease with vascular pathology (ADv) trial in 2021
- focused research and translational science efforts

* Mitochondrial Encephalomyopathy, Lactic acidosis, and Stroke-like episodes

1. Based on pharmacologically active exposures in preclinical studies

C6463-102 study design and objectives



OBJECTIVES TO ASSESS:

✓ *Safety* ✓ *PK* ✓ *Target engagement (cGMP)*

✓ *Activity in the CNS as measured in one or more of the following:*

Neuronal Function
- qEEG, ERP
- cognition and behavior measures

Cerebral Blood Flow
- MRI arterial spin labeling (ASL)

Cellular Bioenergetics
- brain metabolism via magnetic resonance spectroscopy (MRS)

Neuro- inflammation
- cytokines, adhesion molecules

*Period 2 participation was reduced due to Covid-19 related restrictions in the Netherlands

Activity in CNS: neuronal function

Neuronal Function	Encouraging impact on measures associated with aging/cognitive decline • significant increase in alpha power and increase in gamma • improvements in N200 ERP latencies (greater effects at older age) • Significantly shorter saccadic reaction times, trend increase in saccadic velocity
Cerebral Blood Flow	No significant effects observed in this healthy elderly study
Cellular Bioenergetics	No significant effects observed in this healthy elderly study. MELAS study to assess effects of IW-6463 on dysregulated metabolism in mitochondrial disease
Neuro Inflammation	Data analysis ongoing

Positive findings on three relevant CNS biomarkers

- qEEG: Alpha Power
- Event-Related Potential (ERP): N200
- Saccadic eye movement: reaction time and peak velocity

qEEG and basic frequencies

- resting state EEGs: subjects sit facing a featureless wall without moving and are recorded with eyes open and closed for 5 minutes each

EEG-power spectra- analyzing EEG signals in distinct frequency bands

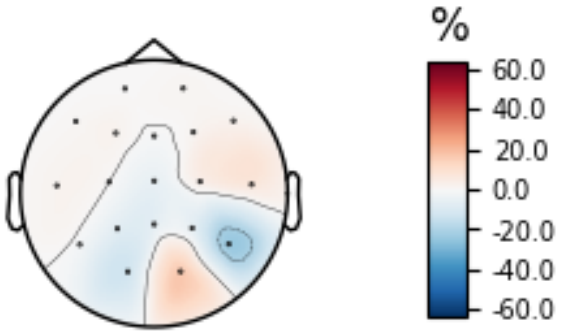
- delta- 0-4 Hz, associated with deep sleep
- theta- 4-8 Hz, waking/falling asleep, some association with cognition
- alpha- 8-14 Hz, passive wakefulness, associated with attention and cognitive processing, declines with aging and in neurodegenerative diseases
- beta- 14-30 Hz, alert, concentration
- gamma- 30-80 Hz, associated with higher cognitive function, declines with aging and in neurodegenerative diseases

BEACON BIOSIGNALS

IW-6463 significantly increases posterior alpha power

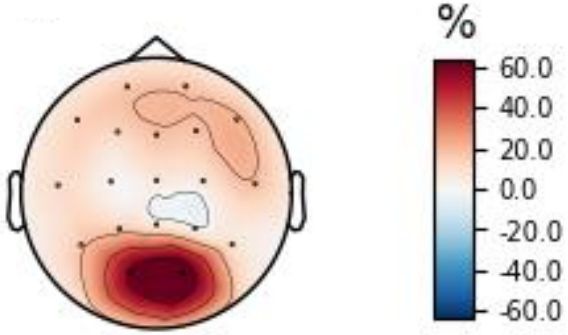
Day 15: % Change From Baseline

Placebo



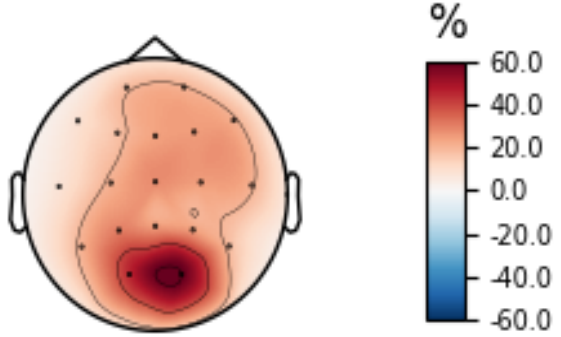
No effect of placebo on EEG alpha power

IW-6463



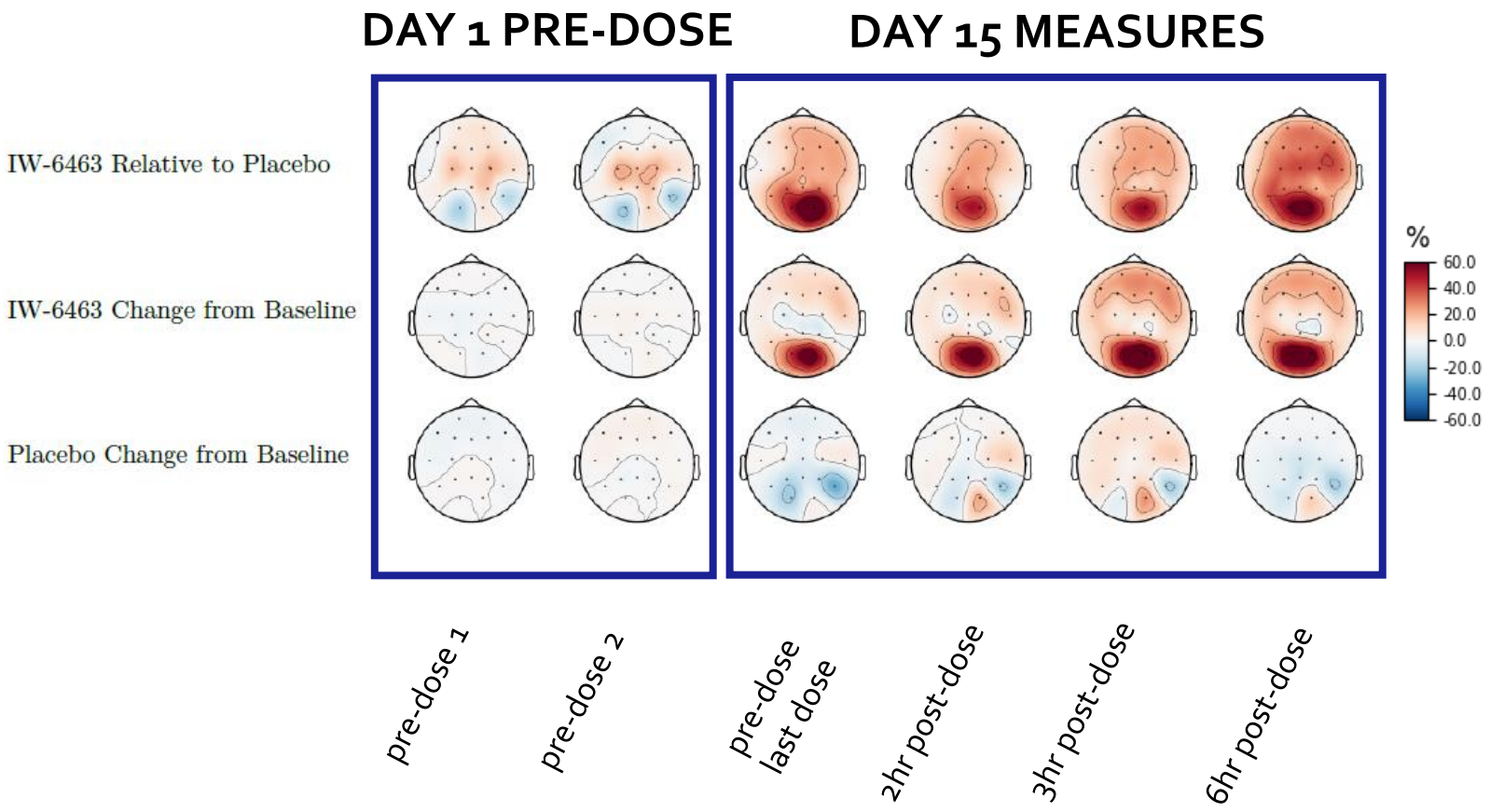
Significant increase in EEG alpha power with IW-6463

IW-6463 vs. Placebo



Significant increase in EEG alpha power with IW-6463 compared to placebo

IW-6463's consistent alpha power effects across repeat sessions indicate a stable and robust signal

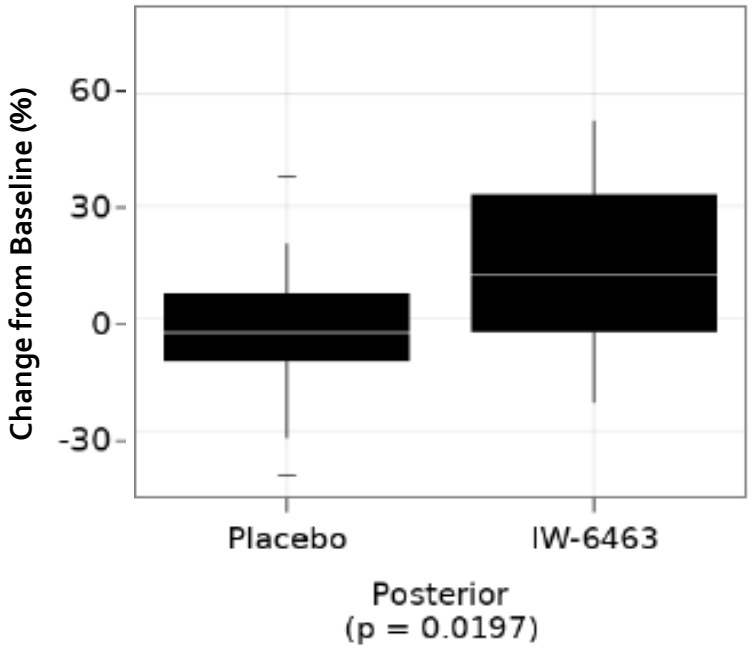


Effect represents up to a 2-year reversal of alpha power aging after 2 weeks of treatment

IW-6463 increases alpha power with consistent treatment responses

Statistically significant alpha power increases

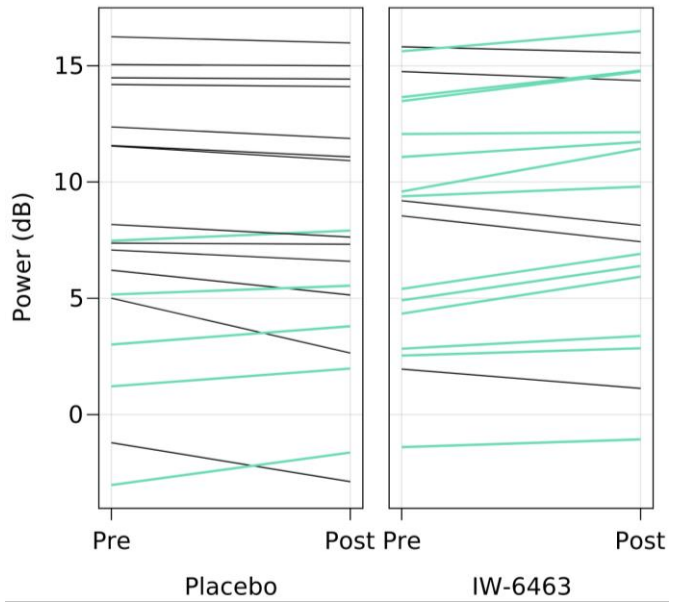
Change in Closed-Eye Alpha (8-12 Hz) Power



- substantial 17% treatment effect
- similar trends in anterior

Persistent, consistent treatment responses

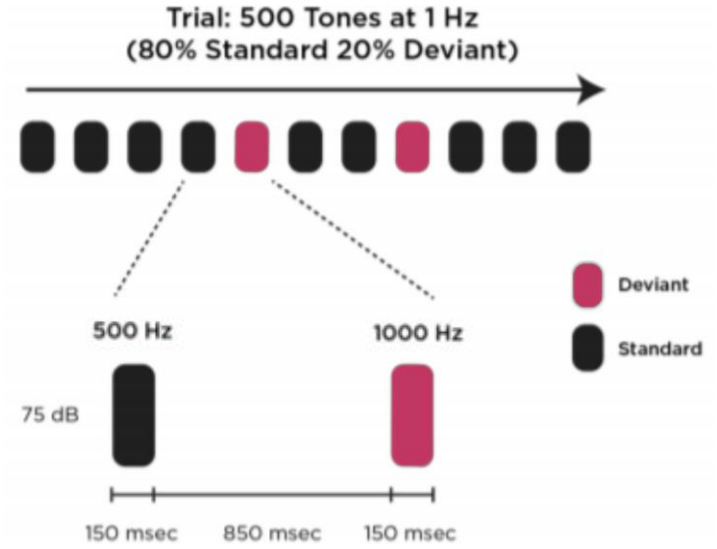
Posterior Closed-Eye Alpha (8-12 Hz) Power

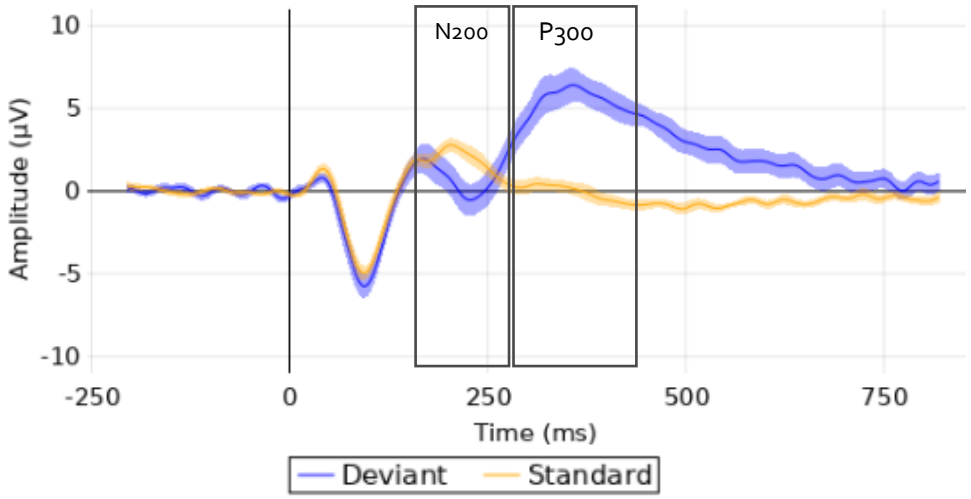


- 13/18 participants exhibit increasing alpha power with IW-6463, vs 5/18 with placebo[1]
- not driven by outliers

1. Includes all subjects. For IW-6463 and pbo each: n=12 for period 1, n=6 for period 2

Event related potential (ERP)

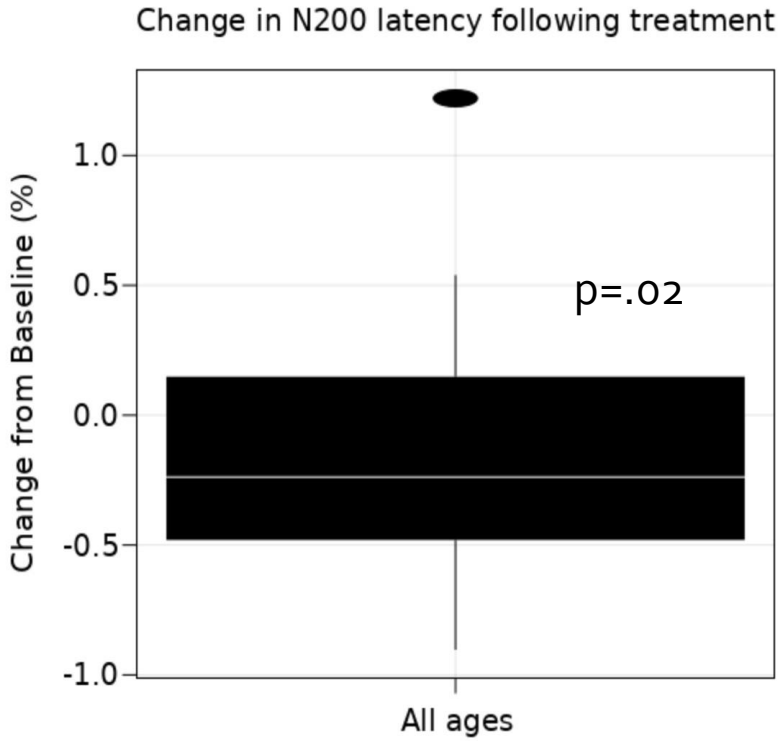


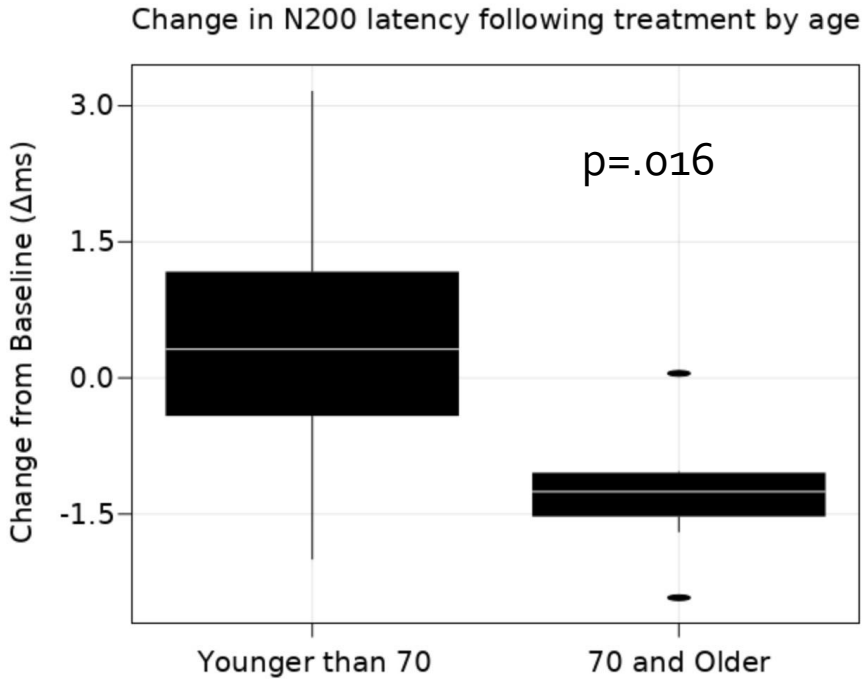


- latency and amplitude of waveforms impacted in aging and neurodegenerative diseases with cognitive impairment (and other CNS diseases)
- participants wear EEG cap and headphones, auditory tones presented with instruction to press a response-button when they hear infrequent/deviant tones
- key ERP waveforms
  - **N200**: associated with stimulus identification and distinction
  - **P300**: associated with cognitive processing capacity
- key parameters
  - **latency**: time after the stimulus to peak signal
  - **amplitude**: size of peak signal

BEACON BIOSIGNALS

IW-6463 improves N200 latency with a greater age-associated effect

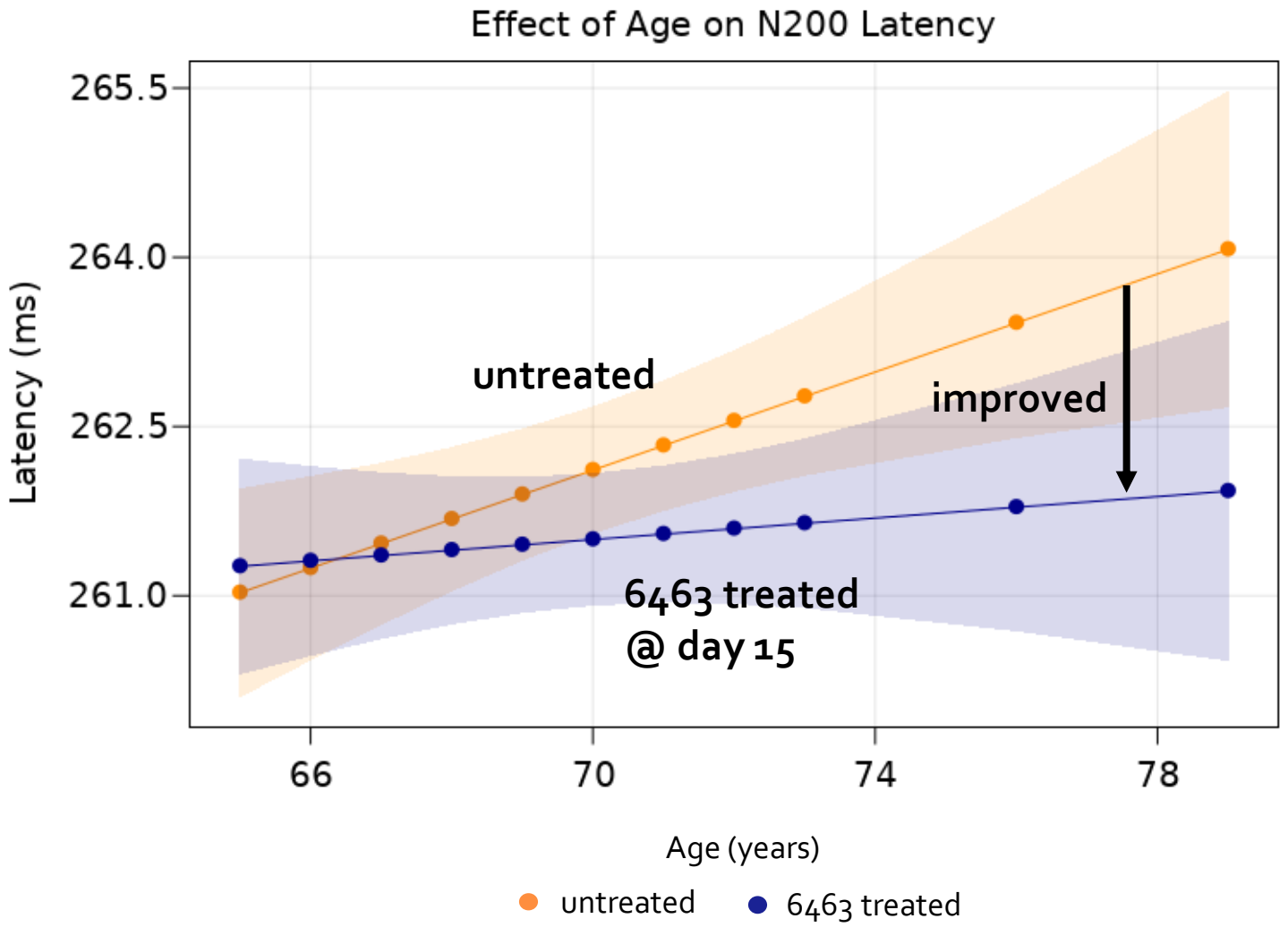




- significant latency reduction of N200 response to IW-6463 in participants treated for 15 days compared to those untreated.

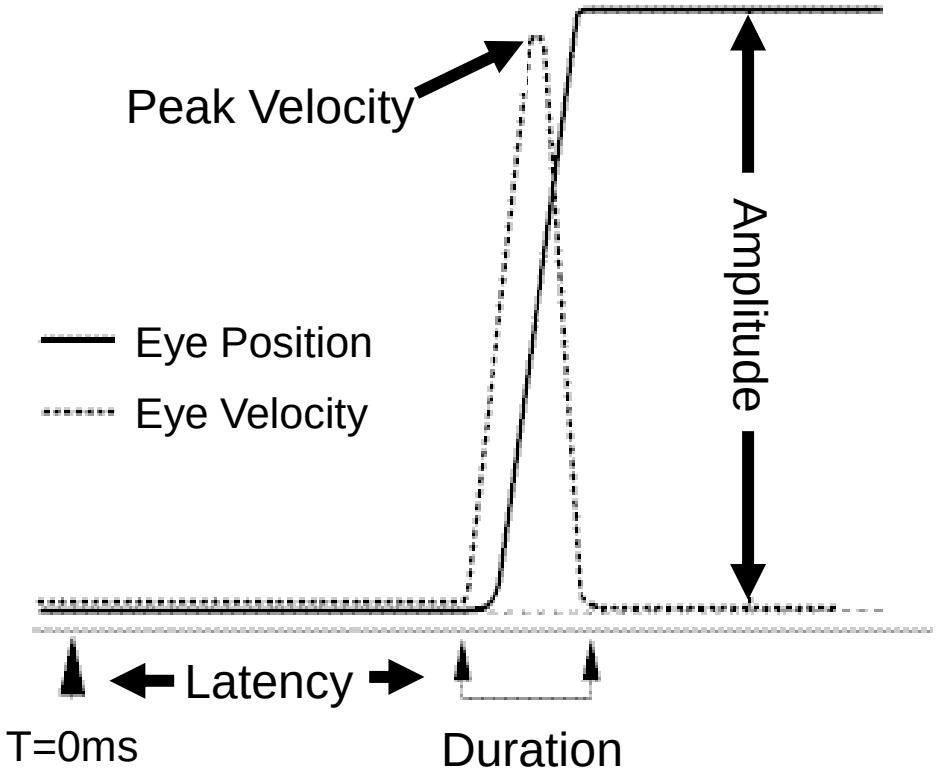
- N200 response to IW-6463 in participants older and younger than 70.
- latency response is significantly stronger with older age.
- narrowing of the variance in 70+ supports a drug effect.

IW-6463 improves N200 latency and effect increases with age



- overall significant decrease in N200 latencies observed on day 15 of IW-6463 treated participants compared to untreated participants ($p<.02$)
- the effects increased with age and were more pronounced in older subjects ($p=.016$)
- at the older ages this represents an approximately 10 years reversal of N200 latency aging after 2 weeks of treatment

Saccadic eye movement, an objective measure of attention

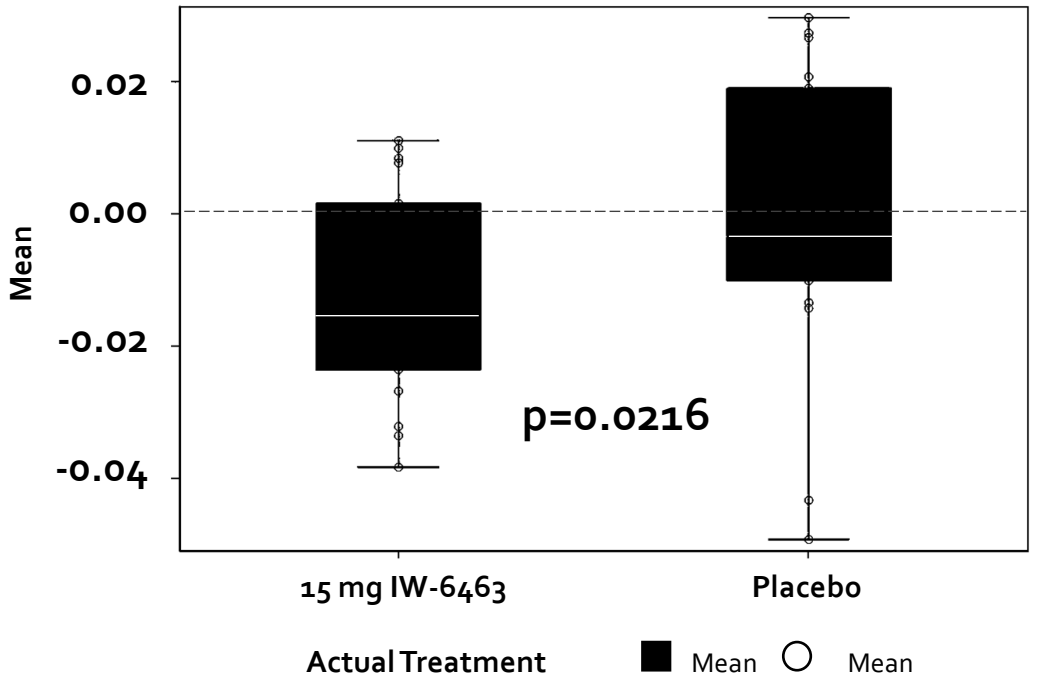


- short, fast, simultaneous tracking of both eyes in the same direction
- related brain areas include the frontal cortex, superior colliculus, substantia nigra, and amygdala
- may be reflective of attention/arousal and influenced by factors such as motivation, time on task, and task difficulty
- sensitive to sedation, fatigue, and CNS depressants/cognitive enhancers and is affected by aging

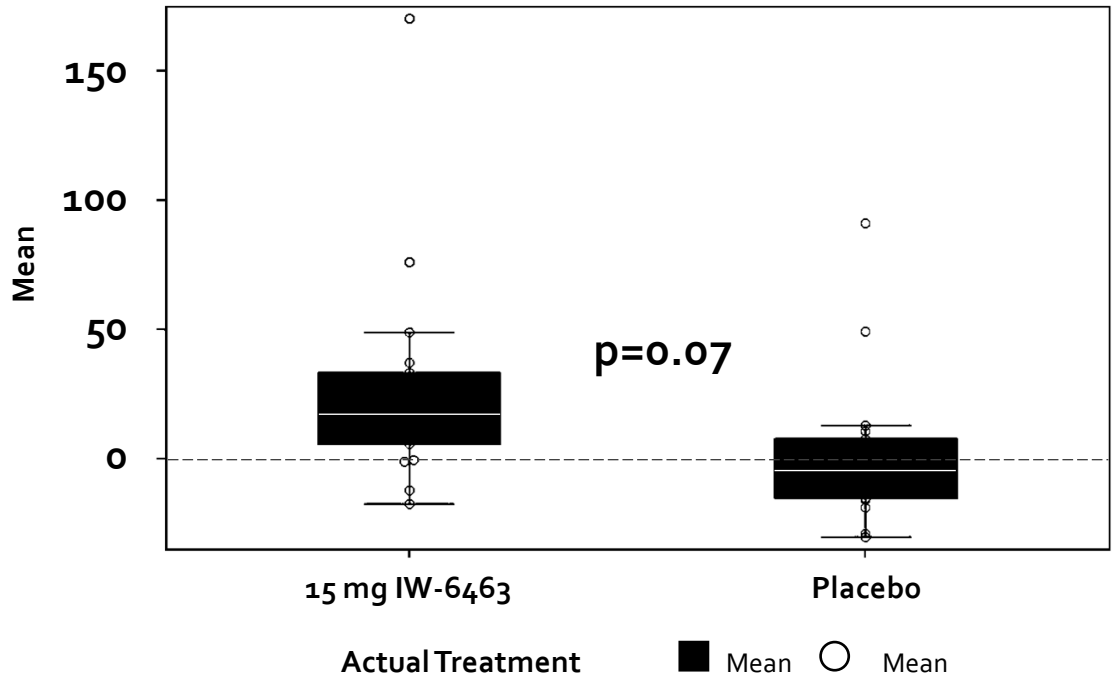
https://www.liverpool.ac.uk/~pcknox/teaching/Eymovs/params.htm

IW-6463 improves eye movement, an objective functional measure

Mean Change From Baseline in Saccadic Reaction Time (sec) on Day 15 Post-Dose (p=0.0216)



Mean Change From Baseline in Saccadic Peak Velocity (deg/sec) on Day 15 Post-Dose (p=0.07)



Saccadic Peak Velocity is the average of the post dose values on Day 15

- shorter saccadic reaction times along with increased saccadic velocities indicates that IW-6463 is also improving CNS functional performance in addition to CNS neurophysiology
- cognitive enhancers (e.g., modafinil) are also known to positively impact measures of saccadic function

Advancing IW-6463 in Phase 2 clinical trials

MELAS
Initiating Q4 2020
TL data mid 2021

Objectives
- evaluate safety, tolerability and pharmacodynamic effects
- assess near-term impact on disease-specific biomarkers
- de-risk and accelerate future development

Treatment (open label)
- once-daily IW-6463
- up to 20 adults (targeting 12 completers)

Enrichment strategy
- genetically confirmed, with MELAS neurological features
- elevated plasma lactate (disease biomarker)

Sites
- centers of excellence for mitochondrial diseases: CHOP, MGH, Children's National Hospital, Columbia, Johns Hopkins

ADv
Initiating 2021*

Objectives
- evaluate safety, tolerability, and pharmacodynamic effects of IW-6463 in a short-term study
- de-risk progression to larger, longer symptomatic and disease modification trials

Treatment
- once-daily IW-6463

Enrichment strategy
- confirmed AD pathology (PET, CSF)
- 3+ cardiovascular risk factors
- mild-moderate subcortical small-vessel disease on MRI
- mini Mental State Exam score (16-26)

Design to be refined based on TP data and ongoing analyses

* Supported partially by a grant from the Alzheimer's Association's Part the Cloud-Gates Partnership Grant Program, which provides Cyclerion with $2 million of funding over the next two years

Our commitment to CNS

Immediate Execution

- deepen understanding of biology and powerful pharmacology
- MELAS study
- ADv study
- strategic partnership

Current

Portfolio Advancement

Mid-term

Portfolio Growth

Long-term

Now

Focused CNS company foundation

- capital allocation to CNS development and pipeline building
- pursuing a risk-reduced development approach
- organization size and capabilities for CNS distinctiveness

Thank you for joining

- ✓ *significant improvements observed in neurophysiological and objective performance measures*
- ✓ *moving forward in MELAS and ADv, informed by these data*
- ✓ *Phase 2 data in 2021*
- ✓ *CNS focus as a company*

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