cyclerion

On a mission to develop treatments that restore cognitive function

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Peter Hecht, Ph.D, CEO
(Nasdaq: CYCN)

Safe Harbor Statement

This document contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended.

Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties, including statements about the anticipated timing of release of topline results of our clinical trials; the progression of our discovery programs into clinical development; and the business and operations of the Company. We may, in some cases use terms such as “predicts,” “believes,” “potential,” “continue,” “anticipates,” “estimates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “likely,” “will,” “should” or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements.

Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to the possibility that any results of operations and financial condition of the Company reported are preliminary and subject to final audit and the risks listed under the heading “Risk Factors” and elsewhere in our 2019 Form 10-K filed on March 12, 2020, and our subsequent SEC filings, including the Form 10-Qs filed on May 4, 2020, August 3, 2020 and November 5, 2020. Investors are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements (except as otherwise noted) speak only as of the date of this report, and the Company undertakes no obligation to update these forward-looking statements, except as required by law.

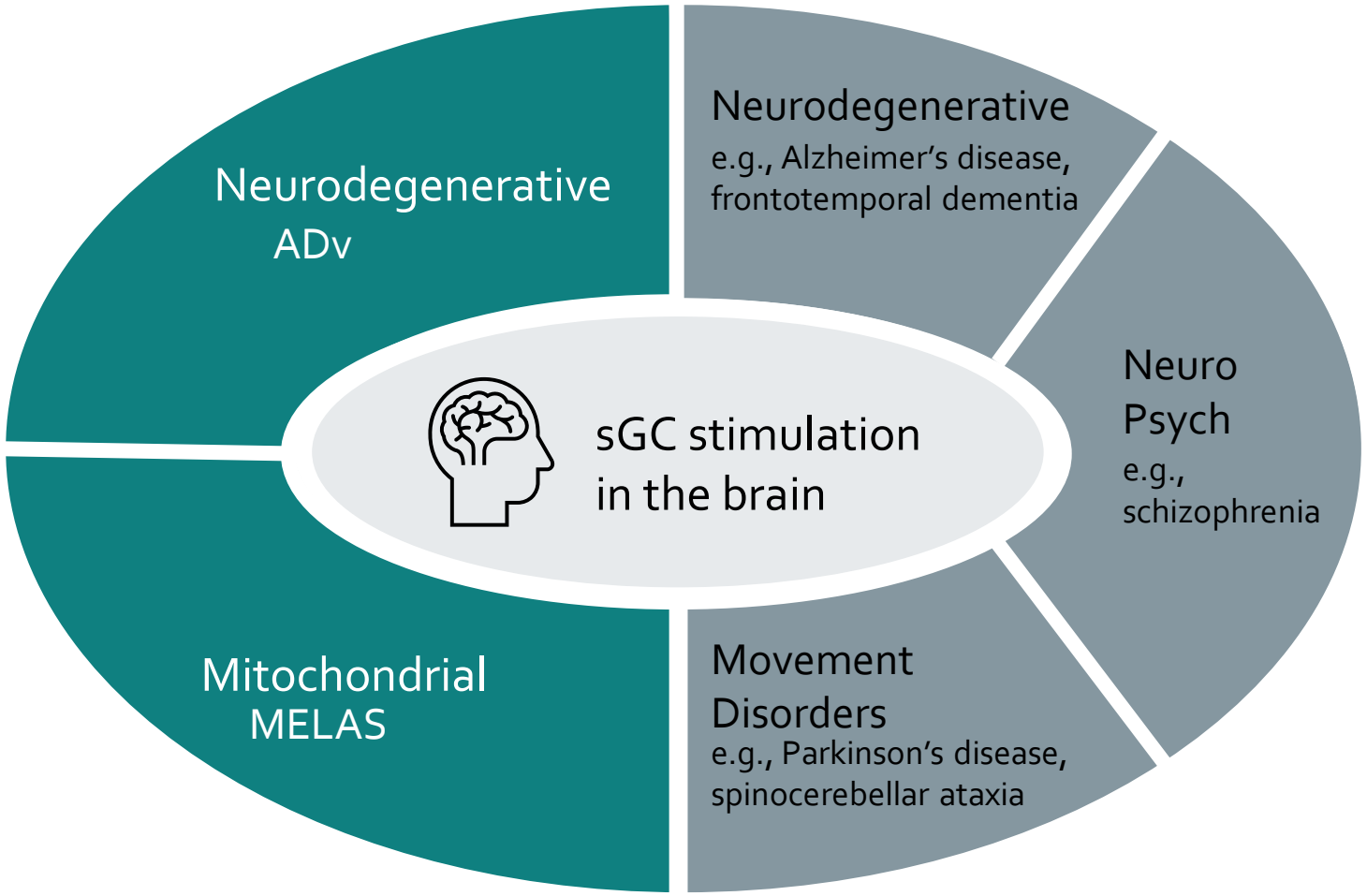
On a mission to develop treatments that restore cognitive function

- **first-in-class:** CY6463 crosses the blood-brain barrier to modulate a key node in a fundamental CNS signaling network
- **broad potential:** multidimensional pharmacology to impact a wide range of CNS diseases
- **promising clinical profile:** rapid improvement in biomarkers associated with cognitive impairment
- **biomarker-guided development strategy:** targeted patient populations ADv and MELAS to start

**previously known as IW-6463*

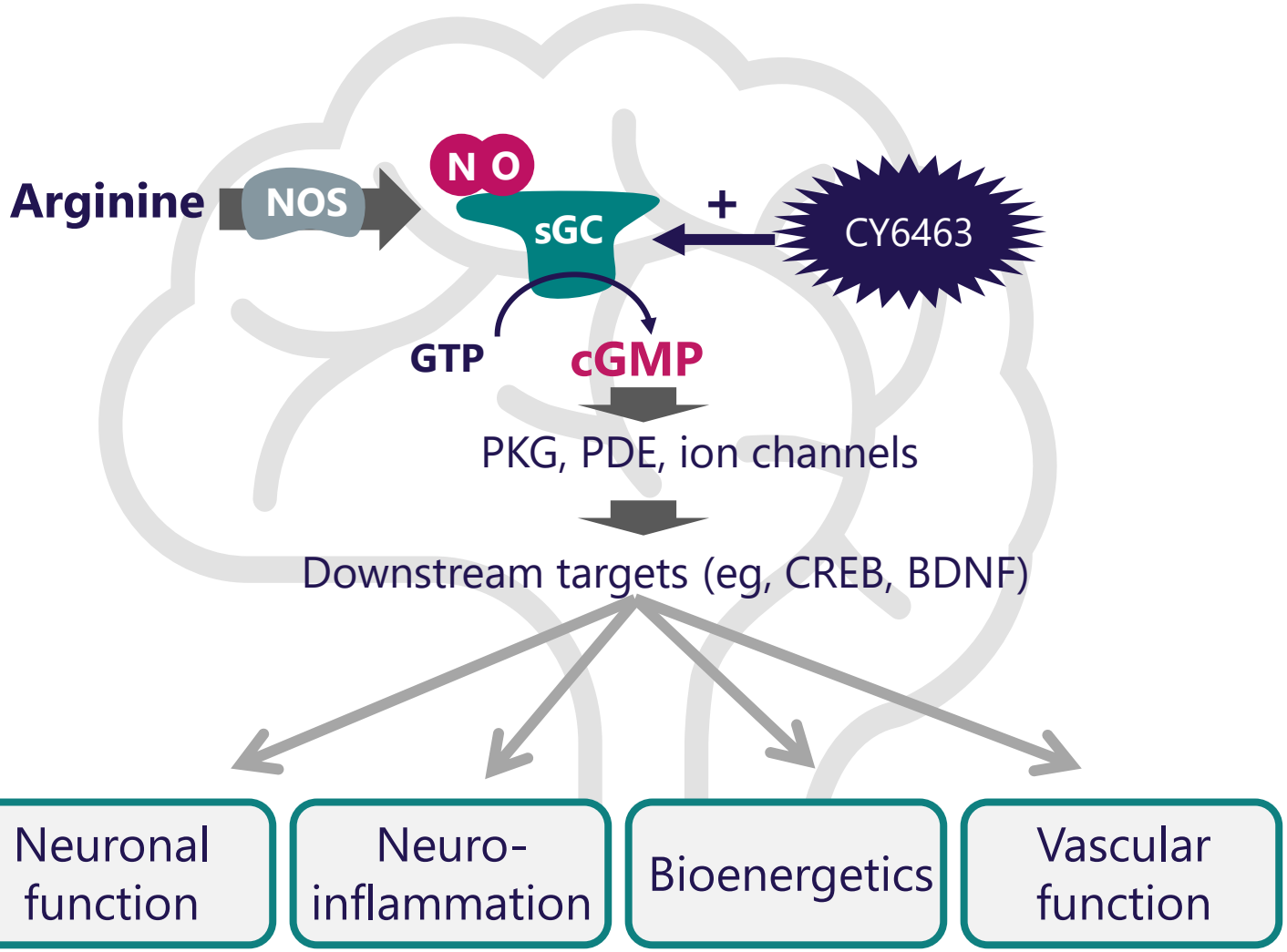
Potential to impact a wide range of CNS diseases

Current Focus



Future Opportunities

CY6463 modulates a key node in a fundamental CNS signaling network



CY6463:

- first in class BBB-permeable, positive allosteric modulator of sGC
- amplifies endogenous NO-sGC-cGMP signaling

Preclinical data and extensive academic work validate the central role of the pathway in brain physiology

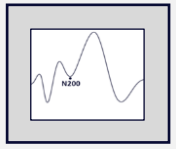
CY6463 biomarker-driven development strategy

Preclinical CNS pharmacology ✓	CNS exposure ✓	CNS activity ✓	CNS disease biomarkers
Pharmacology and disease models	**Phase 1 study in healthy young (<65) (N=110)**	**Translational pharmacology study in healthy elderly (>65) (n=24)**	**Exploratory Phase 2 studies**
ongoing	*completed Jan 2020*	*completed Oct 2020*	*ongoing*
✓ CNS-exposure ✓ drug-like properties ✓ pharmacological profile consistent with known role of pathway in CNS	✓ safety ✓ once-daily ✓ target engagement ✓ dose selection	✓ safety ✓ pharmacodynamic biomarkers ✓ neurodegenerative biomarkers	• focused patient subsets • predictive biomarker data • early impacts on disease

CY6463 showed rapid and persistent improvements in multiple independent biomarkers associated with cognitive impairment

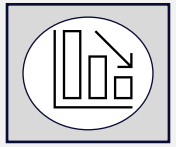
In a 15-day study in 24 healthy elderly subjects CY6463 demonstrated:

increased alpha and gamma power



improved mismatch negativity (MMN) latency

faster saccadic eye movement (SEM) reaction time



reduction in neuroinflammatory biomarkers

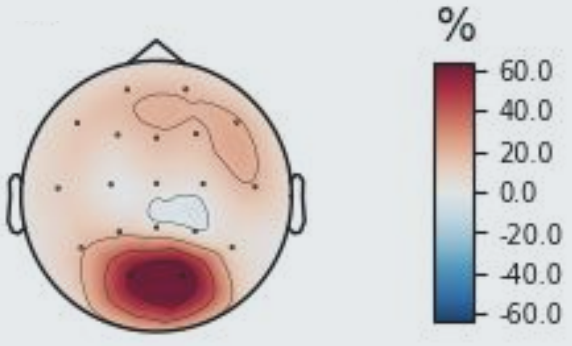
- rapid onset (<15 days)
- effect increased with age
- biomarkers linked to AD and aging

CY6463 improved qEEG measures

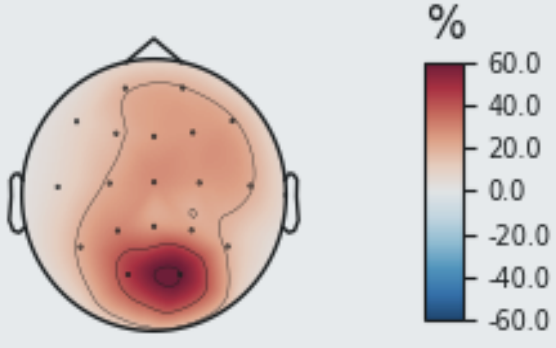
Significant increase in EEG alpha power; trend improvements in gamma power

Significant increase in EEG alpha power

CY6463 vs. baseline

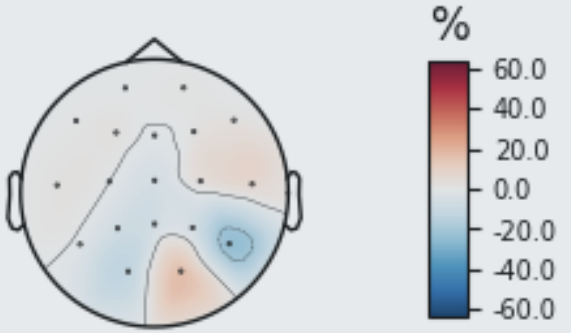


CY6463 vs. placebo



No effect of placebo

Placebo vs. baseline

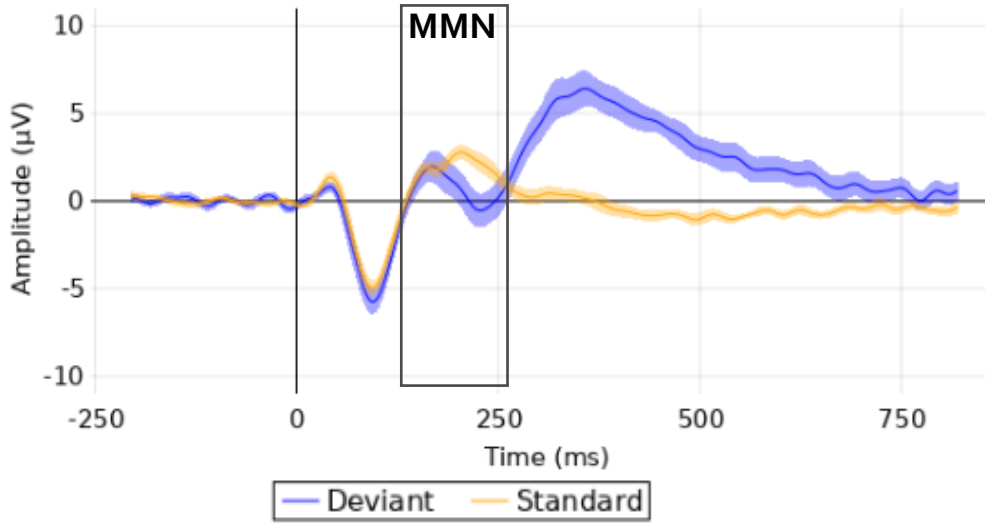


change (%) in alpha power on day 15

qEEG is quantitative electroencephalography, an objective method that measures electrical activity and brain wave patterns

CY6463 improved mismatch negativity (MMN) latency

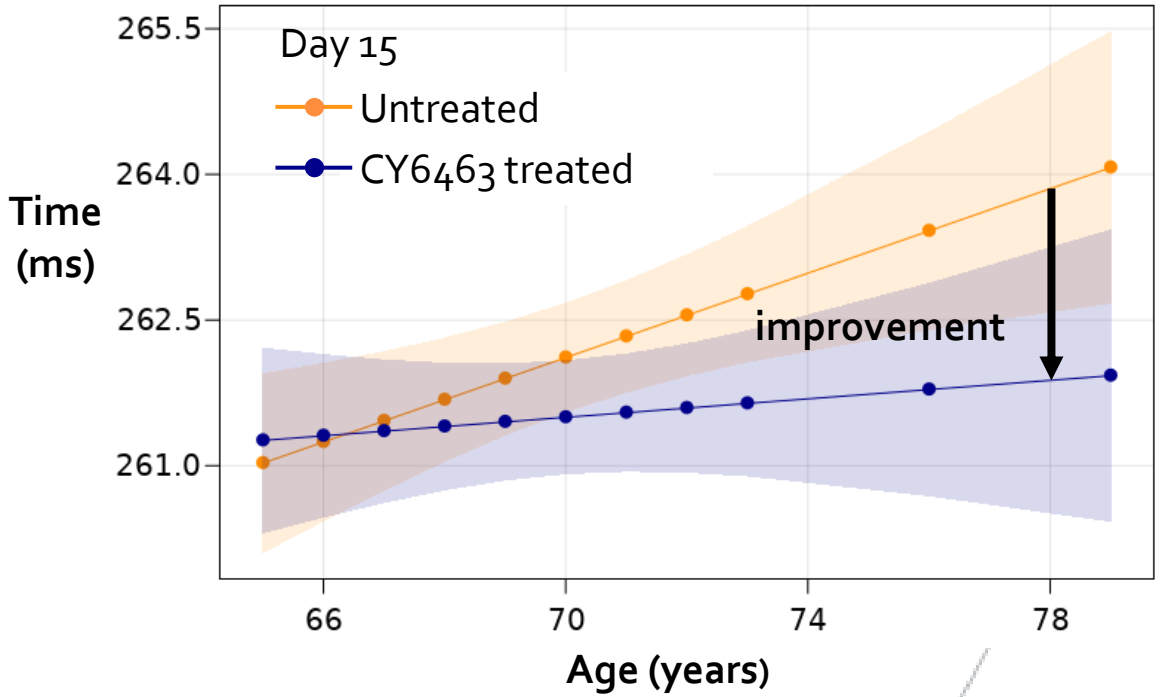
MMN measures reactions between a standard and deviant tone



Latency is affected in aging and neurodegenerative diseases with cognitive impairment

Significant decrease in MMN latencies for CY6463 vs untreated on day 15 ($p<0.02$)

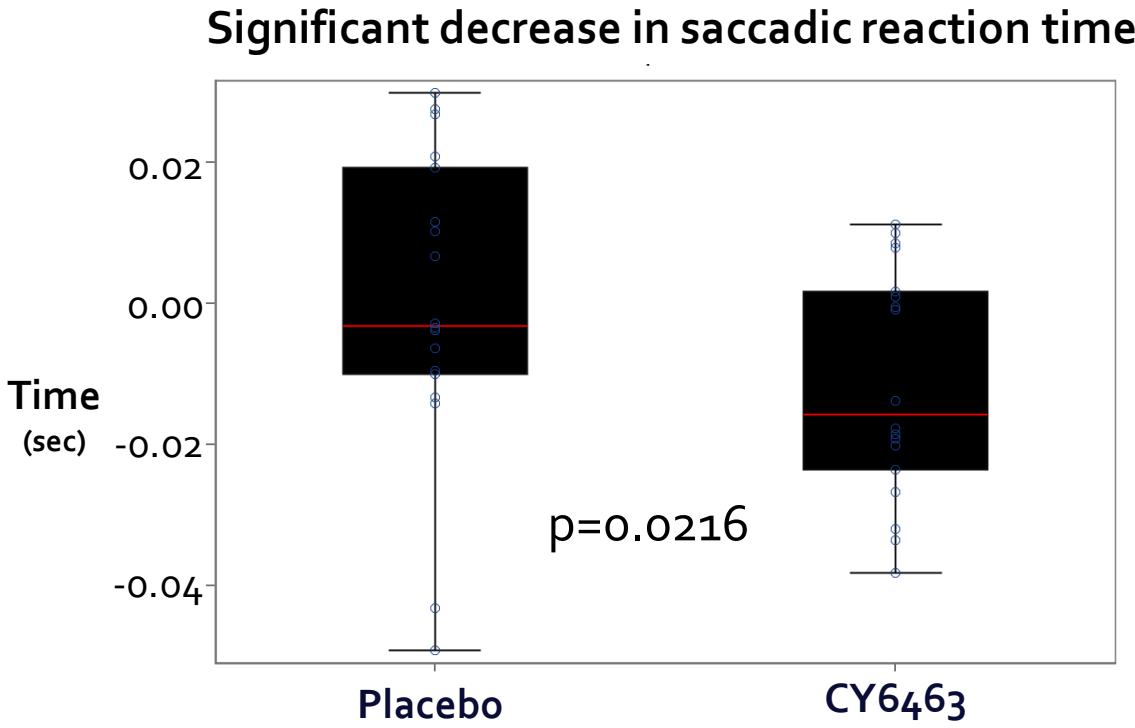
effect more pronounced in older subjects



CY6463 improved saccadic reaction time

Saccadic eye movement is an objective, functional measure associated with cognition

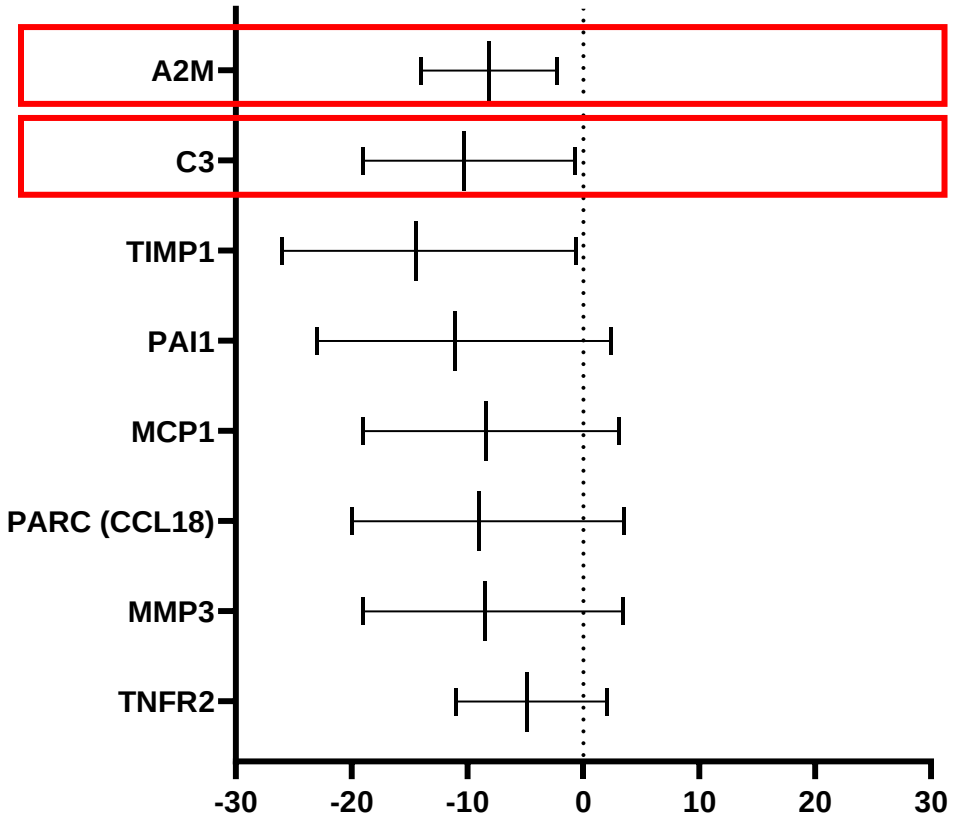
- short, fast, simultaneous tracking of both eyes in the same direction
- reflective of attention/arousal
- aging associated with longer reaction times and slower velocities



Mean change from baseline on day 15

* average of the post dose values on Day 15

CY6463 improved neuroinflammatory biomarkers



LS % Mean Difference from placebo at Day (95% CI)

Alpha-2-macroglobulin (A2M) levels predict cognitive decline and development of AD; may lead to tau hyperphosphorylation

Complement C3 (C3) colocalizes with Aβ plaques and tau tangles; involved in synaptic remodeling and degeneration

A2M and C3 are associated with pathological aging and Alzheimer's Disease

CY6463 biomarker-driven development strategy

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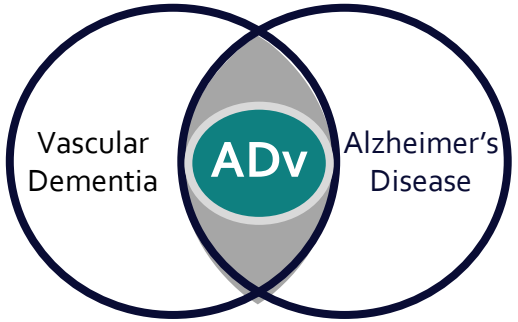
Biomarker-guided development strategy: ADv



growing patient population, devastating impact, limited treatments

Today

Exploratory Phase 2 near-term impact on disease-specific biomarkers and cognition

Tomorrow

Larger, longer symptomatic trials focused on cognition

Initial approval expected on surrogate, symptomatic or functional endpoints

Future

Standard of care for patients with ADv

Potential for disease modification and expansion into broader AD

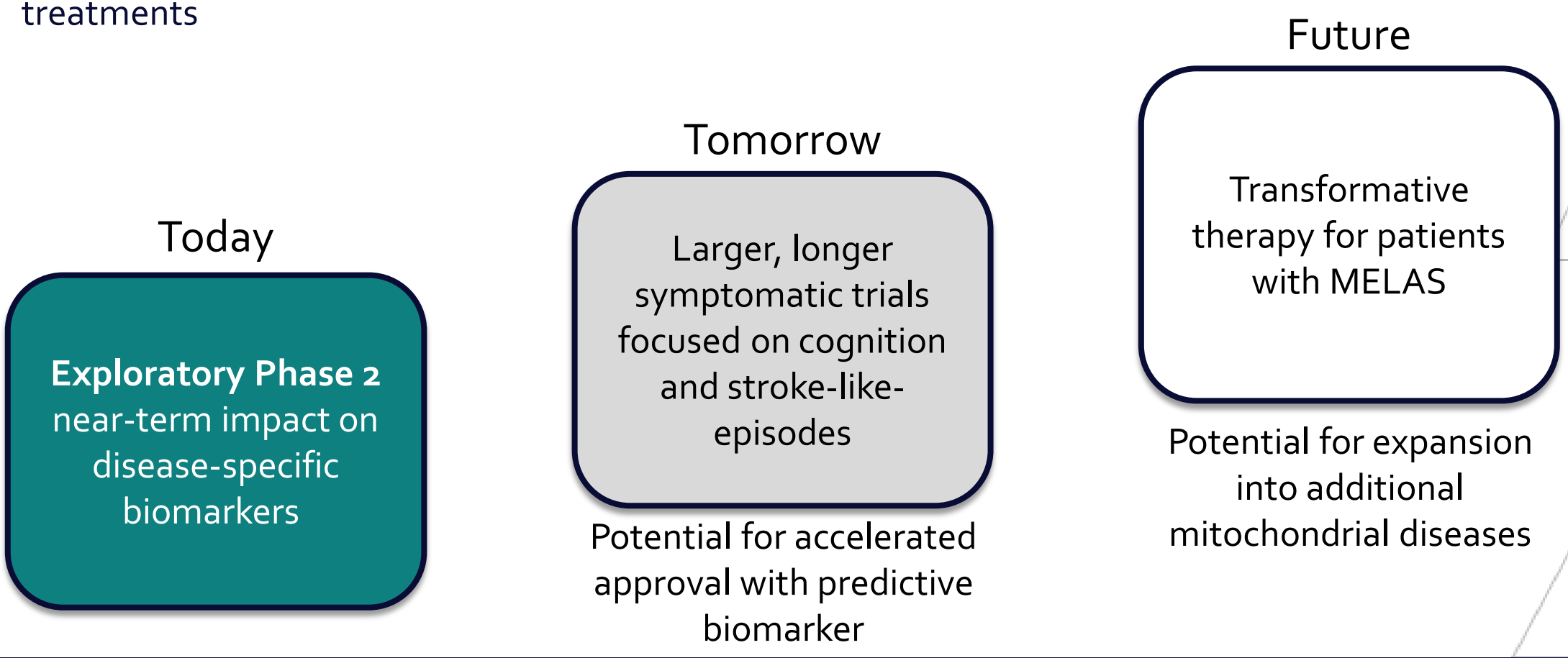
ADv study expected to initiate in mid-2021

Objectives	• evaluate safety, tolerability, and pharmacodynamic effects (EEG, MRI, neuroinflammatory biomarkers, cognition)
Treatment	• once-daily CY6463 vs. placebo • 12 weeks
Enrichment strategy	• confirmed AD pathology (PET, CSF) • 2+ cardiovascular risk factors • mild-moderate subcortical small-vessel disease on MRI • Mini Mental State Exam score (20-26)

With the Alzheimer's Association's Part the Cloud-Gates

Biomarker-guided development strategy: MELAS

MELAS is a serious orphan disease, significant CNS impact, no approved treatments

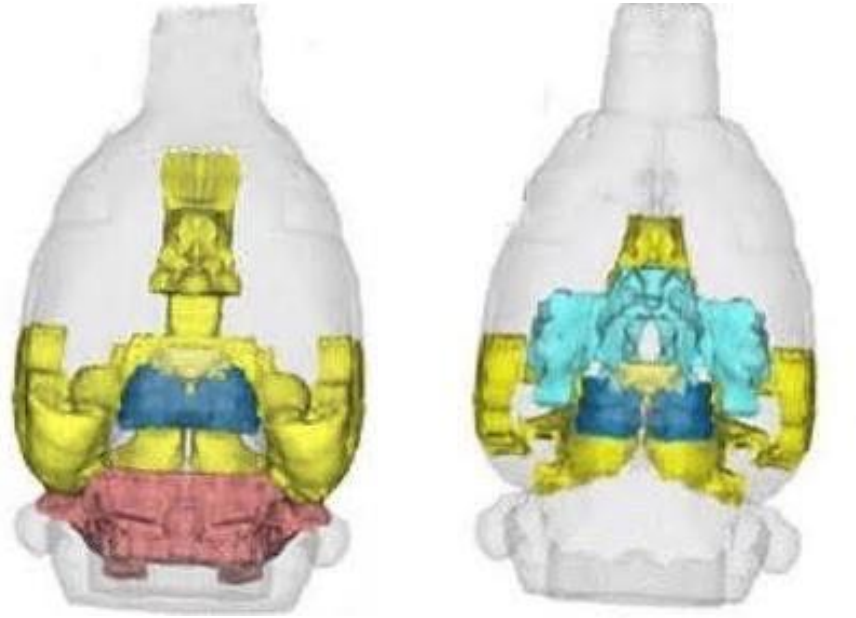


MELAS study underway; topline data expected mid-2021

Objectives	• evaluate safety, tolerability, and pharmacodynamic effects (MRI, EEG, biomarkers)
Treatment	• 29-day open label • once-daily CY6463 • up to 20 adults (targeting 12 completers)
Enrichment strategy	• genetically confirmed mitochondrial disease with neurological features of MELAS • elevated plasma lactate (disease biomarker)
Sites	• centers of excellence for mitochondrial medicine: CHOP, MGH, Children's National Hospital, Columbia, Johns Hopkins

Broadening clinical potential: NextGen sGC program

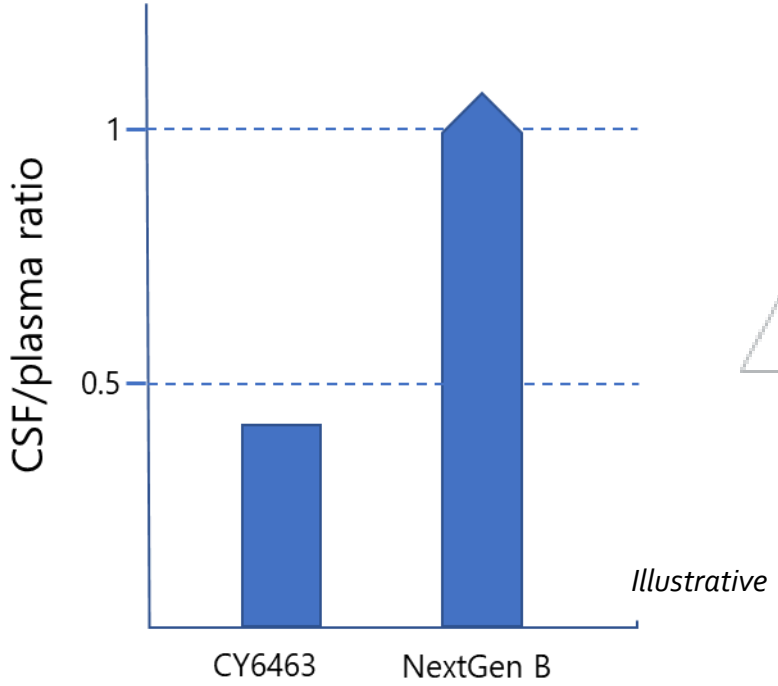
Eliciting different patterns of CNS engagement*



CY6463 NextGen A

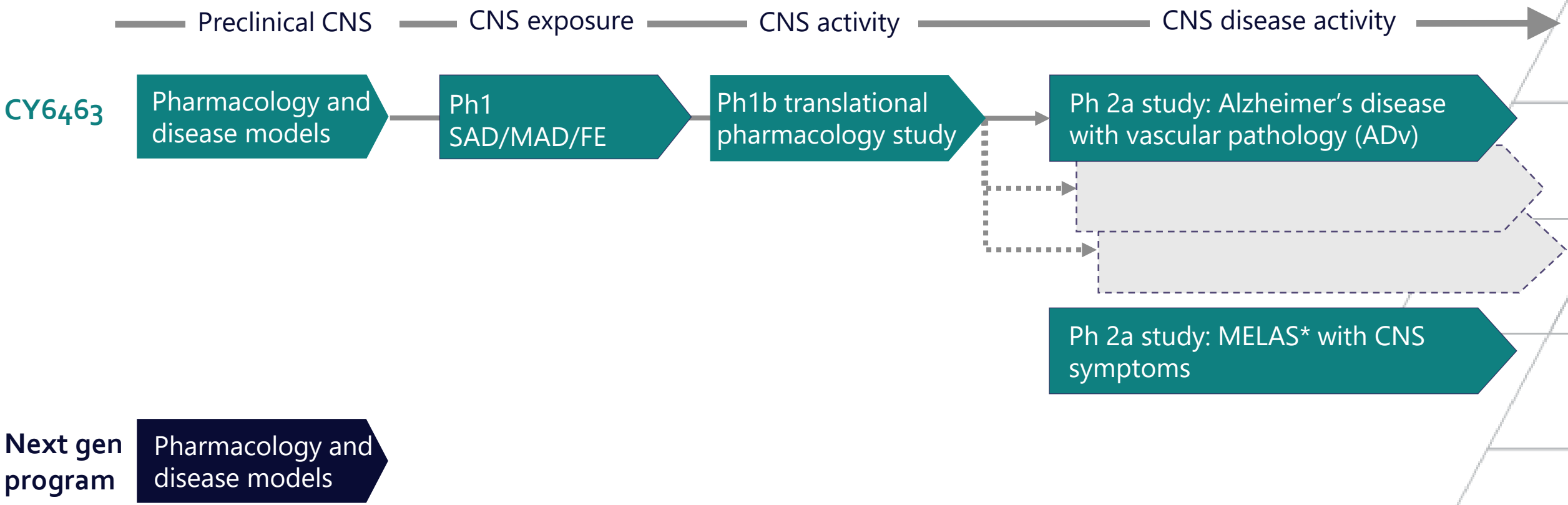
Yellow = hippocampal complex and cortical areas associated with memory
Red = anterior cerebellum
Dark blue = midbrain dopaminergic system
Light blue = amygdala/hypothalamus

Increasing CNS/plasma exposure



*Positive fMRI BOLD activation pattern in healthy rats

Advancing a growing pipeline for targeted patient populations



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

2021: executing on our priorities

Clinical

- ADv Ph2 study start mid-2021
- MELAS Ph2 study topline data mid-2021

Pipeline

- additional indication investigation
- NextGen development candidate

Partnerships, capabilities and capital

- praliciguat out-license; explore CNS partnerships
- grow external CNS network to augment core team
- Q4 2020 ending cash balance of ~$58M* funds current priorities

* Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of December 31, 2020

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Thank you | Questions?