UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): **September 30, 2021**

CYCLERION THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Massachusetts	001-38787	83-1895370
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification Number)

245 First Street, 18th Floor
Cambridge, Massachusetts 02142

(Address of principal executive offices, including Zip Code)
Registrant's telephone number, including area code: **(857) 327-8778**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, no par value	CYCN	The Nasdaq Stock Market LLC (Nasdaq Global Select Market)

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter). Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On September 30, 2021, Cyclerion Therapeutics, Inc. (the "Company") released an updated corporate presentation (the "Corporate Presentation"). The Corporate Presentation includes clinical study progress updates related to the development of CY6463, the Company's first-in-class, CNS-penetrant soluble guanylate cyclase (sGC) stimulator for the treatment of neurological diseases associated with cognitive impairment. The Company announces and the Corporate Presentation states that (1) first patients have been enrolled in a Phase 1b study in Cognitive Impairment Associated with Schizophrenia (CIAS); (2) enrollment remains ongoing in a Phase 2a study in Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS), and that topline clinical results are now expected in H1 2022; and (3) patient screening is underway in a Phase 2a study in Alzheimer's disease with vascular pathology (ADv).

Beginning on September 30, 2021, the Company intends to use the Corporate Presentation, or portions thereof, in one or more meetings with investors. The Corporate Presentation is attached as Exhibit 99.1 to this Current Report on Form 8-K, is incorporated by reference herein and is posted on the Company's website, www.cyclerion.com.

The information set forth in and incorporated by reference into this Item 7.01 is being furnished pursuant to Item 7.01 of Form 8-K and shall not be deemed "filed" for purposes of Section 18 of the Securities and Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, and it shall not be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, whether made before or after the date hereof, except as expressly provided by specific reference in such a filing. By filing this Current Report on Form 8-K and furnishing the information in and incorporated by reference into this Item 7.01, the Company makes no admission as to the materiality of such information. The information contained in the presentations is summary information that is intended to be considered in the context of the Company's filings with the Securities and Exchange Commission (the 'SEC') and other public announcements that the Company makes, by press release or otherwise, from time to time. The Company undertakes no duty or obligation to publicly update or revise the information contained in this report, or incorporated by reference herein, although it may do so from time to time as its management believes is appropriate or as required by applicable law. Any such updating may be made through the filing of other reports or documents with the SEC, through press releases, by updating its website or through other public disclosure.

* * * * *

This report and the Corporate Presentation may contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Exchange Act. 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 the risks listed under the heading "Risk Factors" and elsewhere in our 2020 Form 10-K filed on February 25, 2021, and our subsequent SEC filings including the Form 10-Qs filed on April 30, 2021 and July 29, 2021. Investors are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements (except as otherwise noted) would speak only as of the respective dates of this report and the webcast, and the Company undertakes no obligation to update these forward-looking statements, except as required by law.

Item 9.01 Financial Statements and Exhibits

(d)

Exhibit No.	Description
99.1	Corporate Presentation dated September 30, 2021

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Cyclerion Therapeutics, Inc.

Dated: September 30, 2021

By: /s/ Cheryl Gault

Name: Cheryl Gault
Title: Chief Operating Officer

Exhibit 99.1


cyclerion
ON A MISSION TO DEVELOP TREATMENTS THAT RESTORE COGNITIVE FUNCTION
CORPORATE PRESENTATION

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 2020 Form 10-K filed on February 25, 2021, and our subsequent SEC filings. 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.

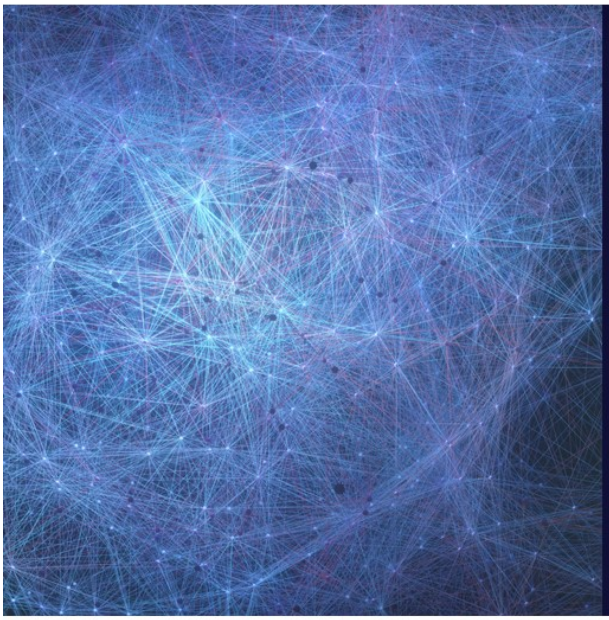
On a mission to develop treatments that restore cognitive function

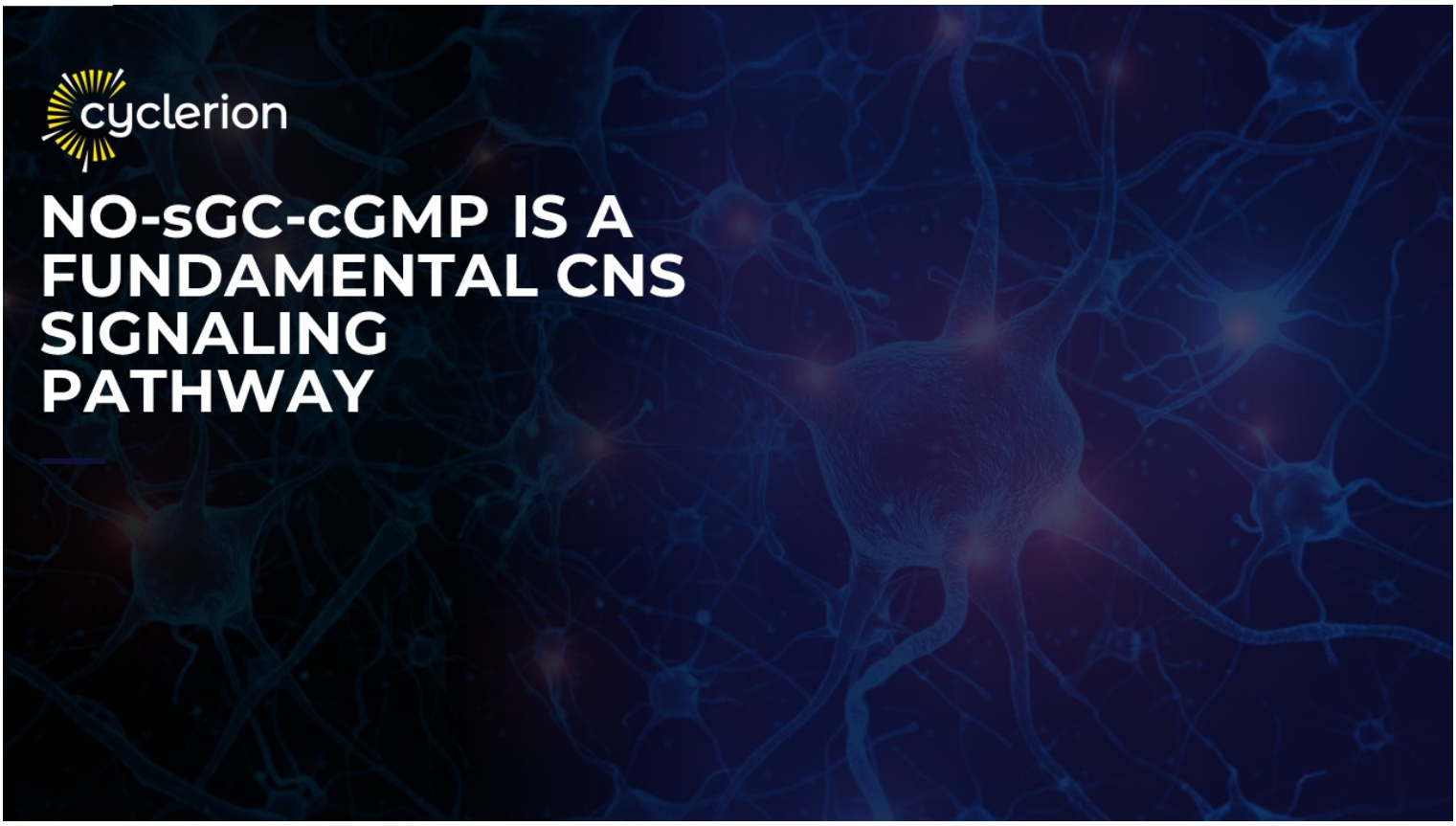
Tapping into a fundamental CNS signaling pathway with CY6463, a first-in-class, CNS-penetrant sGC stimulator

Executing biomarker-guided development strategy in well-defined populations with cognitive impairment

Tackling the enormous burden and breadth of cognitive impairment through an innovative portfolio of indications and molecules

Contents

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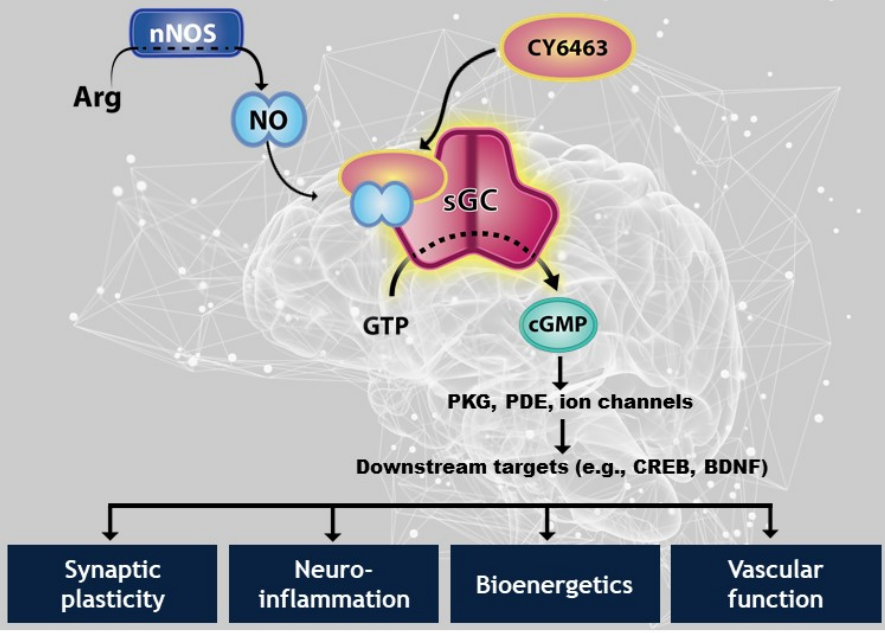
NO-sGC-cGMP IS A FUNDAMENTAL CNS SIGNALING PATHWAY

CY6463 amplifies the fundamental NO-sGC-cGMP signaling pathway



CY6463

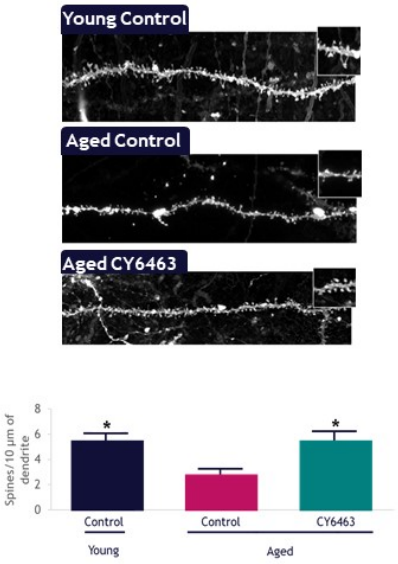
- First-in-class BBB-permeable, positive allosteric modulator of sGC
- Amplifies endogenous NO-sGC-CGMP signaling to address central aspects of disease pathophysiology

Preclinical data and extensive academic work validate the crucial role of the NO-sGC-cGMP pathway in brain physiology

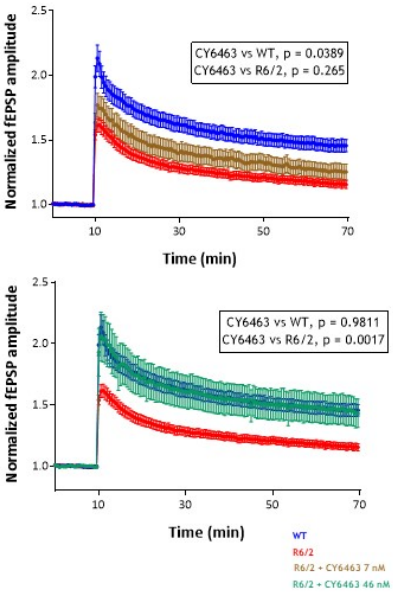
Important role in learning and memory

CY6463 improves endpoints relevant to cognition

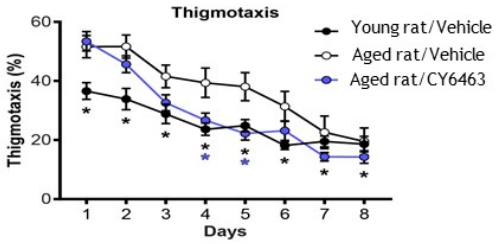
Morphological plasticity

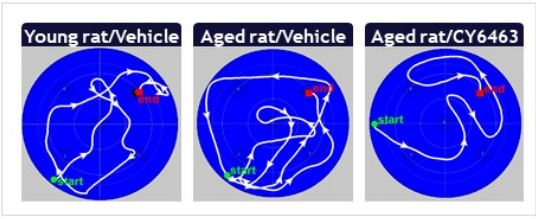


Ex-vivo LTP



In-vivo learning and memory

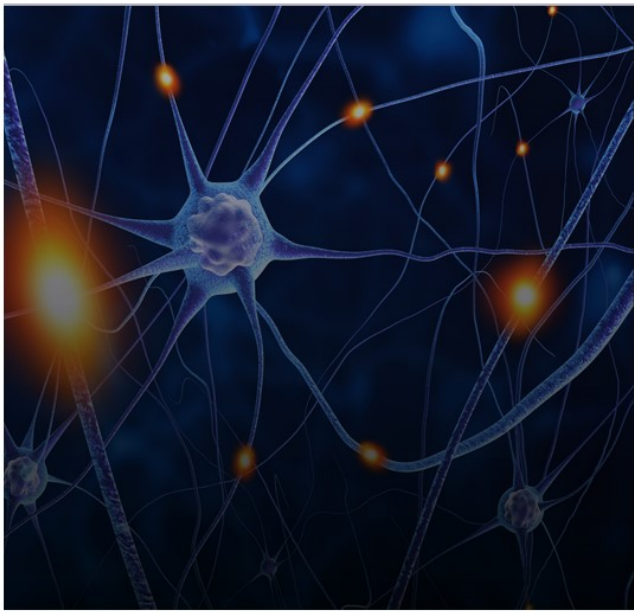




**p<0.05 vs. the aged control group*

CY6463 amplifies a fundamental CNS signaling pathway

- NO-sGC-cGMP pathway plays a critical role in brain function
- sGC stimulation with CY6463 amplifies NO-sGC-cGMP signaling
- Morphological, *ex vivo* and *in vivo* data demonstrate important role of sGC in synaptic plasticity, learning and memory, and 6463's ability to restore deficits in these endpoints

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CY6463
TRANSLATIONAL
PHARMACOLOGY
STUDY RESULTS

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

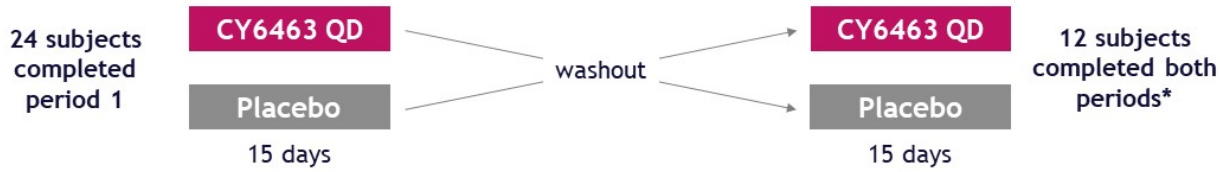
In a 15-day study in 24 healthy elderly subjects CY6463 demonstrated:

- Increased alpha and gamma power
- Improved N200 latency
- Faster saccadic eye movement (SEM) reaction time
- Reduced neuroinflammatory biomarkers

- Rapid onset (<15 days)
- Effect increased with age
- Biomarkers linked to AD and aging

Phase 1b translational pharmacology study designed to evaluate CNS activity

Healthy elderly population (≥65 years)



Objectives

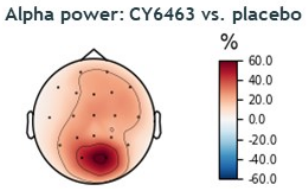
- Safety and tolerability
- Pharmacokinetics
- Target engagement
- CNS activity

*due to COVID restrictions, 12 subjects completed only period 1

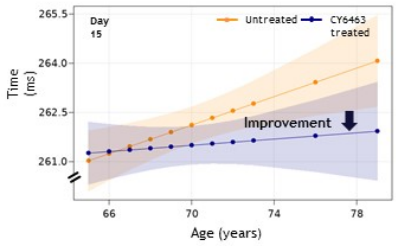
CY6463 showed rapid improvement in biomarkers of cognition

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

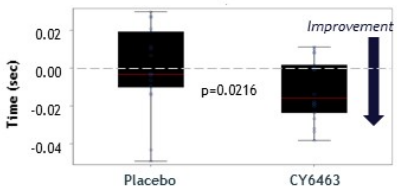
Increased alpha and gamma power



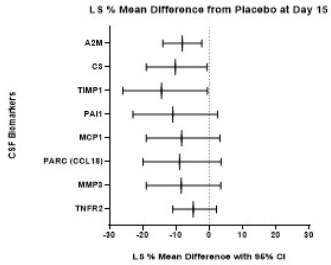
Improved N200 latency



Faster saccadic eye movement reaction time



Reduced neuroinflammatory biomarkers

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PIPELINE CENTERED AROUND IMPROVING COGNITIVE FUNCTION

CY6463 data point to potential in cognition

Preclinical CNS pharmacology

- Neuronal function
- Neuro-inflammation
- Bioenergetics
- Vascular function

+

Clinical CNS pharmacology*

- Increased posterior alpha and gamma power
- Improved N200 latency
- Faster saccadic eye movement (SEM) and reaction time
- Reduced neuroinflammatory biomarkers in CSF

=

Potential to improve cognitive function

*In a 15-day study in 24 healthy elderly subjects

Cognitive impairment is a debilitating facet of many CNS diseases

Neurodegenerative		Neuropsychiatric	
~2M	ADv *ongoing*	~21M	CIAS *ongoing*
~35M	Alzheimer's Disease	~150M	Major Depressive Disorder
~13M	Lewy Body Dementia	~27M	Bipolar Disorder
~5M	Parkinson's Dementia	~10M	Autism

Mitochondrial		Event-related	
Orphan	MELAS *ongoing*	~21M (US)	Traumatic brain injury
Orphan	Leigh Syndrome	~12M	Stroke
Orphan	Kearns-Sayre Syndrome	~5M (US)	Cancer/chemotherapy-induced cognitive impairment

References on file.

Represents approximate prevalence of patients with cognitive impairment associated with other CNS diseases, worldwide in millions, except where noted as US prevalence

Biomarker-guided development strategy in well-defined populations with cognitive impairment

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Improving Cognition

- Parallel studies in distinct populations
- Efficient, signal-seeking studies inform larger and longer studies
- Disease-relevant biomarkers accelerate and guide development
- Translation of insights across programs increases odds of success

ADv — Neurodegenerative

CIAS — Neuropsychiatric

Mitochondrial Disease — MELAS

Significant additional opportunities

ADv | *Alzheimer's Disease with vascular pathology (ADv)*
CIAS | *Cognitive Impairment Associated with Schizophrenia*
MELAS | *Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes*


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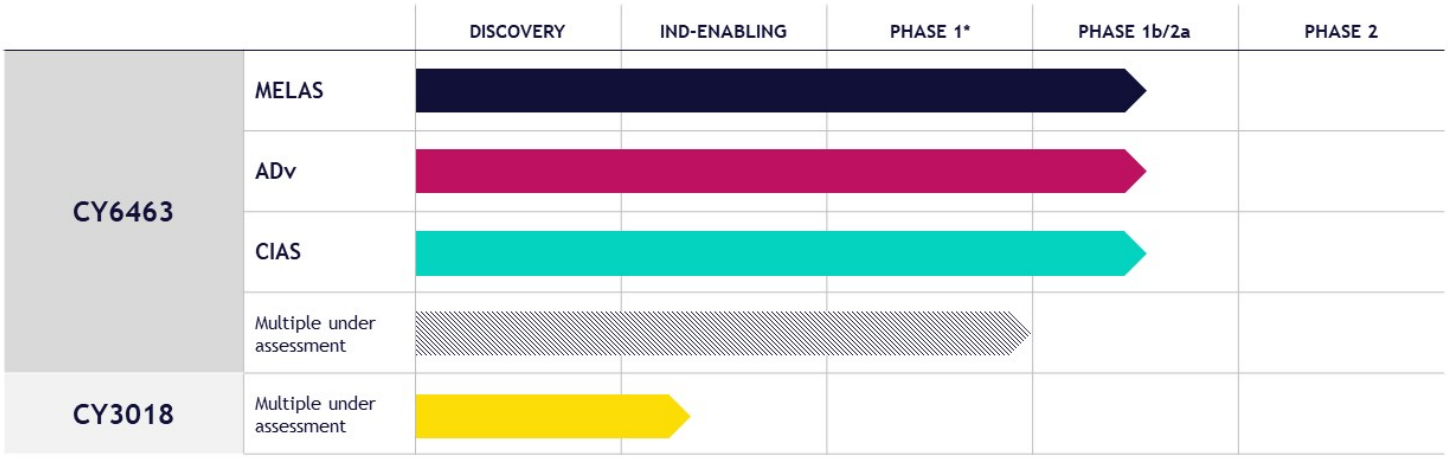
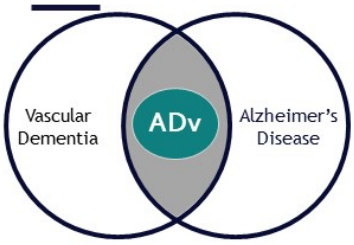
POTENTIAL FOR PATIENT IMPACT: OUR PRIORITY INDICATIONS

Advancing parallel, signal-seeking, exploratory studies in priority patient populations



**Two phase 1 studies were completed in healthy young and old (>65 years of age) volunteers confirming targeted CNS exposure and activity*

Biomarker-guided development strategy: ADv



Growing patient population, devastating impact, limited treatments

Today	Tomorrow	Future
Exploratory Phase 2 Near-term impact on disease-specific biomarkers and cognition	**Larger, longer studies symptomatic trials focused on cognition** Initial approval expected on surrogate, symptomatic or functional endpoints	**Standard of care for patients with ADv** Potential for disease modification and expansion into broader AD

ADv study ongoing

Objectives	Exploratory, signal-seeking study to evaluate safety, tolerability, and pharmacodynamic effects (EEG, MRI, neuroinflammatory biomarkers, cognition)
Study design	• Once-daily CY6463 vs. placebo • 12 weeks • 30 participants
Patient targeting	• Confirmed AD pathology (PET, CSF) • 2+ cardiovascular risk factors • Mild-moderate subcortical small-vessel disease on MRI • Mini mental state exam score (20-26)
Collaborations	• Partially funded by the Alzheimer's Association's Part the Cloud-Gates Partnership • Collaborating with Dr. Andrew Budson at Boston University on a study to examine the relationship between ERP/EEG and cognitive measures in dementias

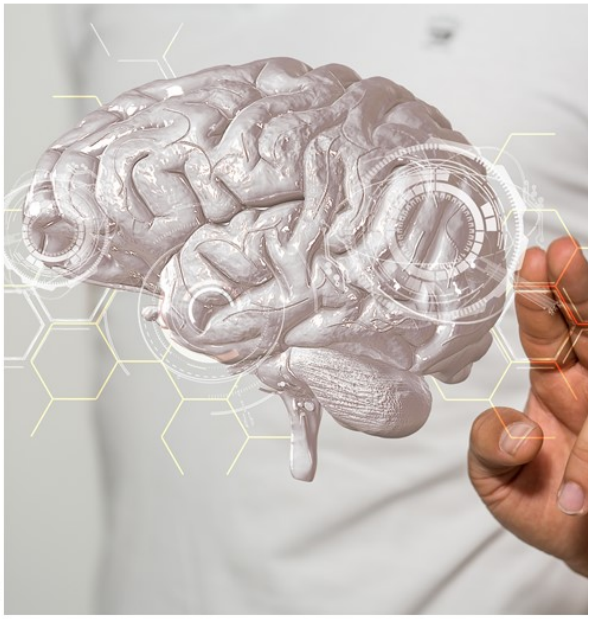
Biomarker-guided development strategy: MELAS

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

Today	Tomorrow	Future
Exploratory Phase 2 Near-term impact on disease-specific biomarkers	**Larger, longer symptomatic trials focused on cognition and stroke-like-episodes** Potential for accelerated approval with predictive biomarker	**Transformative therapy for patients with MELAS** Potential for expansion into additional mitochondrial diseases

MELAS study ongoing; data expected 1H 2022

Objectives	Exploratory, signal-seeking study to evaluate safety, tolerability, and pharmacodynamic effects (MRI, biomarkers)
Study design	• 29-day open label • Once-daily CY6463 • Up to 20 adults (targeting 12 completers)
Patient targeting	• Genetically confirmed mitochondrial disease with neurological features of MELAS • Elevated plasma lactate (disease biomarker)
Sites and collaborations	• Study performed at centers of excellence for mitochondrial medicine: CHOP, MGH, Children's National Hospital, Columbia University, Johns Hopkins University • Preclinical collaboration with Dr. Marni Falk at CHOP to elucidate the role of sGC in mitochondrial disease models



Biomarker-guided development strategy: CIAS

CIAS is a debilitating and untreated facet of schizophrenia, with large and growing unmet need

Today	Tomorrow	Future
Exploratory Phase 1b Safety + near-term impact on disease-relevant biomarkers	**Larger, longer studies focused on biomarker-identified populations**	**Standard of care adjunctive therapy** Improve cognitive impairment and functional outcomes

CIAS study ongoing

Objectives	Exploratory, signal-seeking study to evaluate safety, tolerability, and pharmacodynamic effects (qEEG, ERP, digital cognitive performance battery)
Study design	• 14-day in clinic, randomized, placebo-controlled, double-blinded • Once-daily CY6463 • Approximately 60 participants across sequential cohorts
Patient targeting	• Psychiatrically stable adults with schizophrenia • On stable antipsychotic regimen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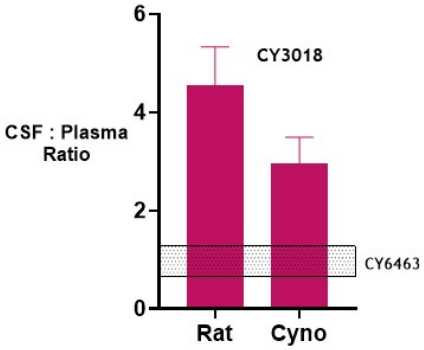
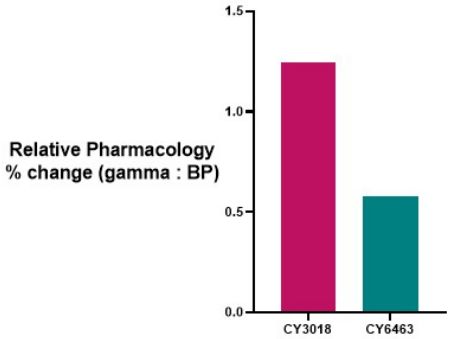
NEXT GENERATION
sGC STIMULATOR
PROGRAM

Next generation sGC stimulator CY3018: selectively targeting the CNS

Greater relative CNS exposure



Greater relative CNS pharmacology



- Greater CSF:plasma ratio for CY3018 translating into greater relative CNS pharmacology
- CY3018 is progressing though IND-enabling development
- Ongoing pharmacology studies to validate amenable CNS indications

Data displayed as mean+ SEM, Relative pharmacology ratio: 1-hour post-dose with vehicle-subtraction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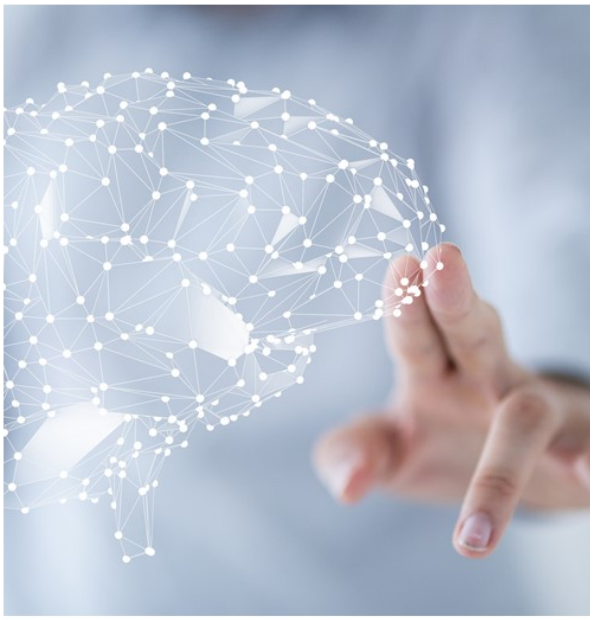
EXECUTING ON
OUR
PRIORITIES

2021: executing on our priorities

Clinical and pre-clinical	• ADv Ph2 study ongoing • MELAS Ph2 study data expected H1 2022 • CIAS Ph1b study ongoing • Advancing CY3018, next-generation development candidate
Partnerships	• Explore CNS collaborations • Praliciguat out-license complete
Capabilities and capital	• Grow external CNS network and augment core team CNS expertise • Reduced monthly cash use to ~50% that of 2020 • Q2 2021 ending cash balance of ~$70M



On a mission to develop treatments that restore cognitive function

Tapping into a fundamental CNS signaling pathway with CY6463, a first-in-class, CNS-penetrant sGC stimulator

Executing biomarker-guided development strategy in well-defined populations with cognitive impairment

Tackling the enormous burden and breadth of cognitive impairment through an innovative portfolio of indications and molecules

APPENDICES

Preclinical, Phase 1 and translational pharmacology studies, references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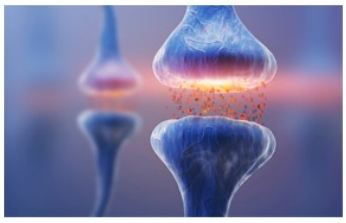
PRECLINICAL
DATA

CY6463 demonstrated beneficial effects in preclinical studies across multiple domains associated with cognitive disease

IMPROVED

Neuronal Function

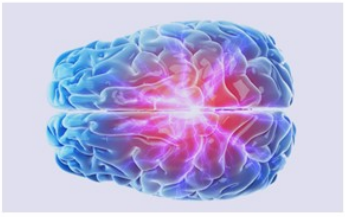
Enhanced memory & spine density in aged animals; increased LTP in neurodegenerative models; affected qEEG spectra



REDUCED

Neuro-inflammation

Decreased markers of LPS-induced neuroinflammation (ICAM1, VCAM1, IL6) *in vitro*



ENHANCED

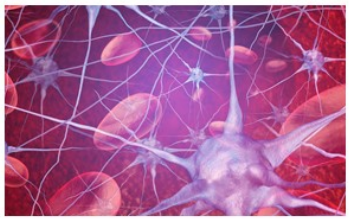
Cellular Bioenergetics

Increased ATP and restored gene expression in cells from patients with mitochondrial diseases

IMPROVED

Cerebral Blood Flow

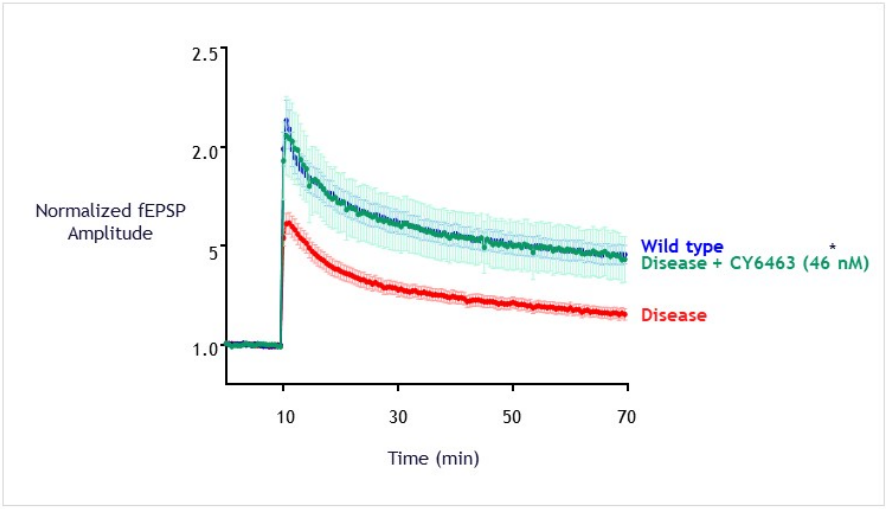
Increased blood flow in areas associated with memory and arousal by fMRI BOLD imaging



CY6463 improved neuronal function

Restored hippocampal long-term potentiation to wild-type levels in a mouse neurodegenerative model

Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow



By acting directly on the neurons, CY6463 could restore impaired neurotransmission

Hippocampal slices from symptomatic Huntington's Disease (R6/2) mice incubated with CY6463 for 25-30 minutes before LTP induction

Extracellular field potentials recordings performed using Multi-Electrode Array; **p<0.01 vs. Disease

CY6463 increased qEEG gamma power

No effect seen with PDE9 inhibitor

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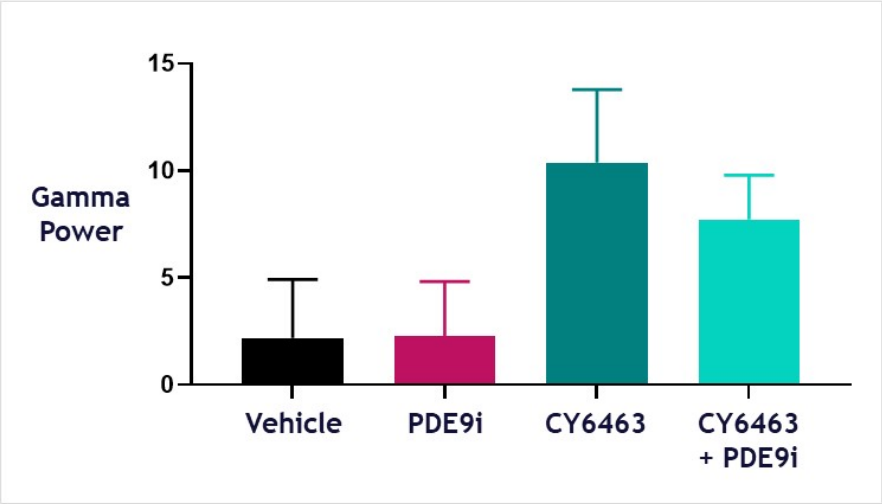
Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow



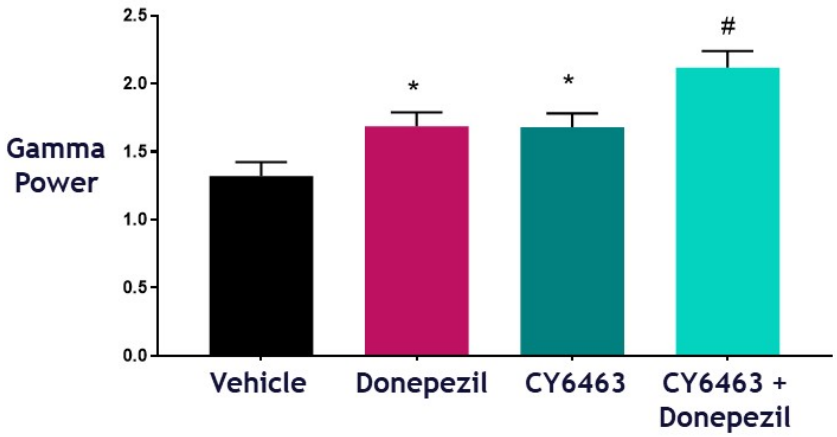
CY6463 is differentiated from PDE9 inhibitor, which showed no effect on gamma power

Healthy awake rats were treated with clinically relevant doses of CY6463 (3 mg/kg) or PDE9 inhibitor (10 mg/kg) Graph displays 1-2h post-dose, mean ± SEM

CY6463 and donepezil act independently to enhance qEEG signal

Combination elicited additive increase in gamma band power in healthy rats

Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow



CY6463 may offer opportunity to enhance attention and cognitive performance alone and on top of standard of care

*p<0.05 vs Veh

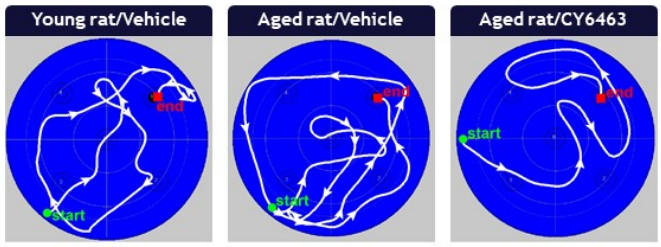
# p<0.05 CY6463 vs CY6463 +Donepezil

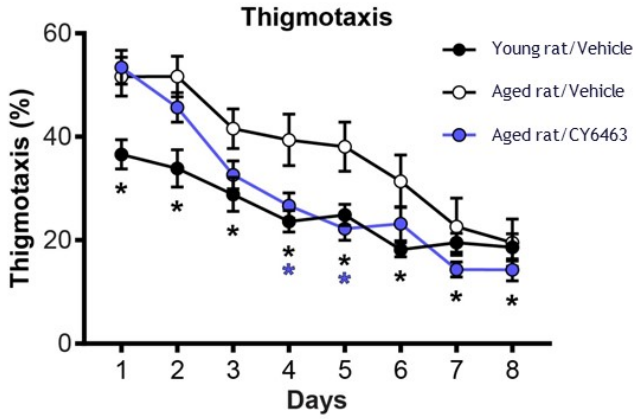
Healthy rats orally administered CY6463 (10mg/kg), Donepezil (1mg/kg), or a combination. Graph displays 1-2h post-dose, mean ± SEM

CY6463 improved learning and memory in aged rats

Increased rate of learning in aged rats treated with CY6463 in Morris Water Maze

Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow

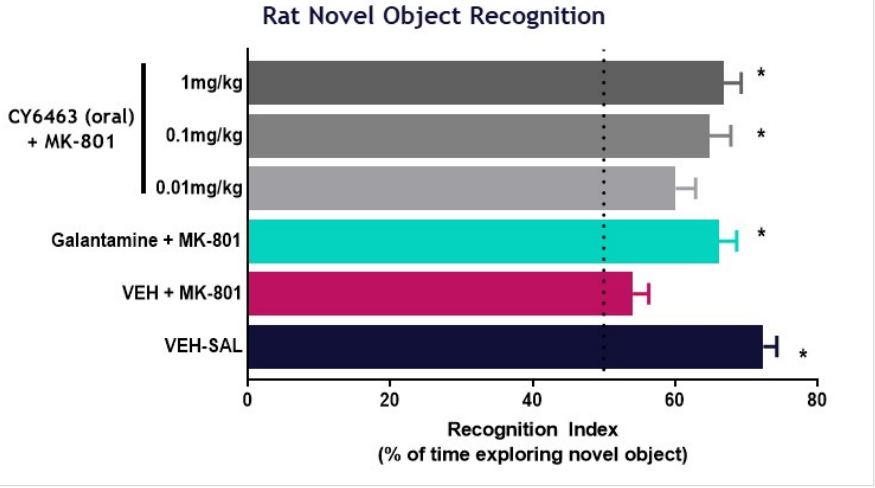




*p<0.05 vs. Aged vehicle-treated

CY6463 improved cognitive function in pharmacologically impaired rats

Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow



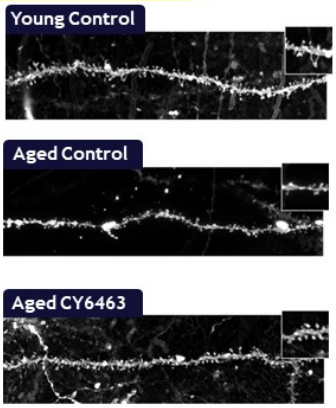
CY6463 acts downstream of NMDA receptor to reverse deficit induced by NMDA antagonist (MK-801)

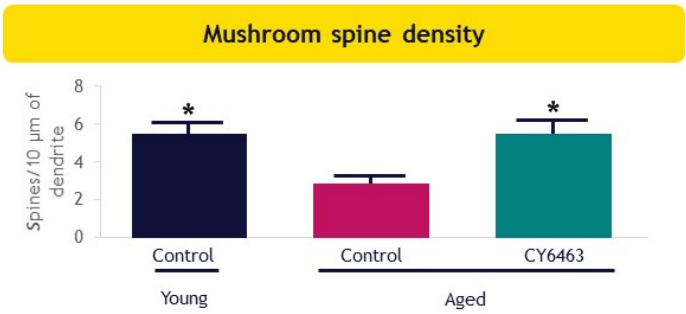
*p<0.05 vs. VEH + MK-801 rats

CY6463 improved neuronal function

Enhanced hippocampal spine density in aged animals treated with CY6463

Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow





Restoration of spine density has potential to provide neuroprotective effects and improve synaptic function in neurodegenerative diseases

**p<0.05 vs. Aged*

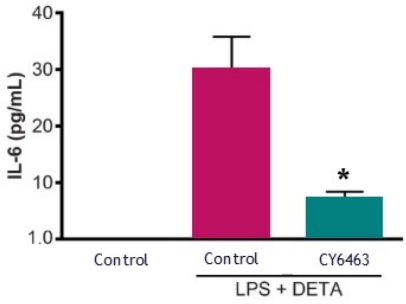
3-month old (young) or 16-month old (aged) healthy mice at study initiation
Aged mice treated for 4 months with 1 mg/kg CY6463

CY6463 reduced neuroinflammation

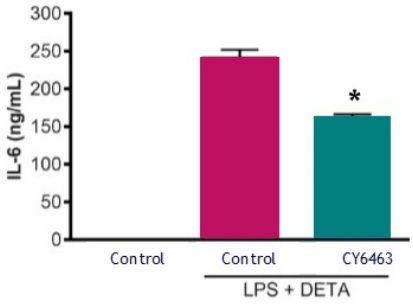
Inhibited in vitro LPS-induction of biomarkers of neuroinflammation

Improve Neuronal Function | **Reduce Neuroinflammation** | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow

Neuroinflammation in rat brain 3D microtissues



Neuroinflammation in mouse microglial cells



*p<0.05 vs. control LPS-treated wells

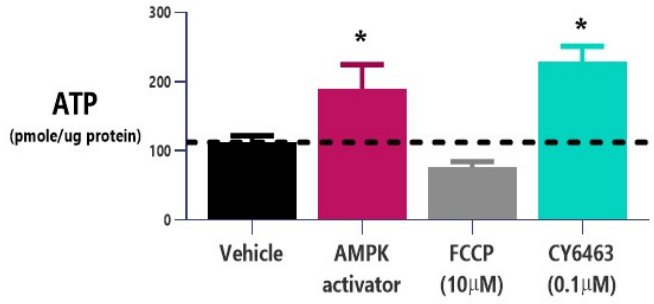
CY6463 (10 µM) and DETA (30 µM) were incubated with SIM-A9 cells or rat brain 3D microtissues for 30 minutes before LPS (100 ng/ml) incubation and further incubated for 18-20h at 37°C before IL-6 quantification in the media

CY6463 enhanced cellular bioenergetics

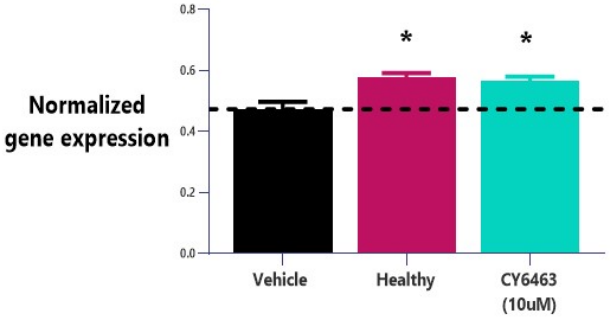
Increased ATP and restored decreased gene expression in cells from patients with mitochondrial diseases

Improve Neuronal Function | Reduce Neuroinflammation | **Enhance Cellular Bioenergetics** | Improve Cerebral Blood Flow

Mitochondrial disease patient cells



TFAM



*p<0.05 vs. vehicle-treated wells

GM13740 Leigh Syndrome patient cells obtained from the Coriell Institute were treated for 24h before ATP quantification

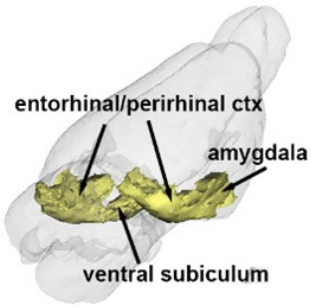
TFAM: mitochondrial transcriptional factor A, a key activator of mitochondrial transcription as well as a participant in mitochondrial genome replication.

CY6463 improved cerebral blood flow

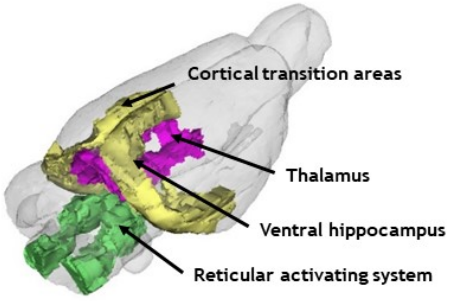
Increased blood flow in areas associated with memory and arousal by fMRI BOLD imaging

Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | **Improve Cerebral Blood Flow**

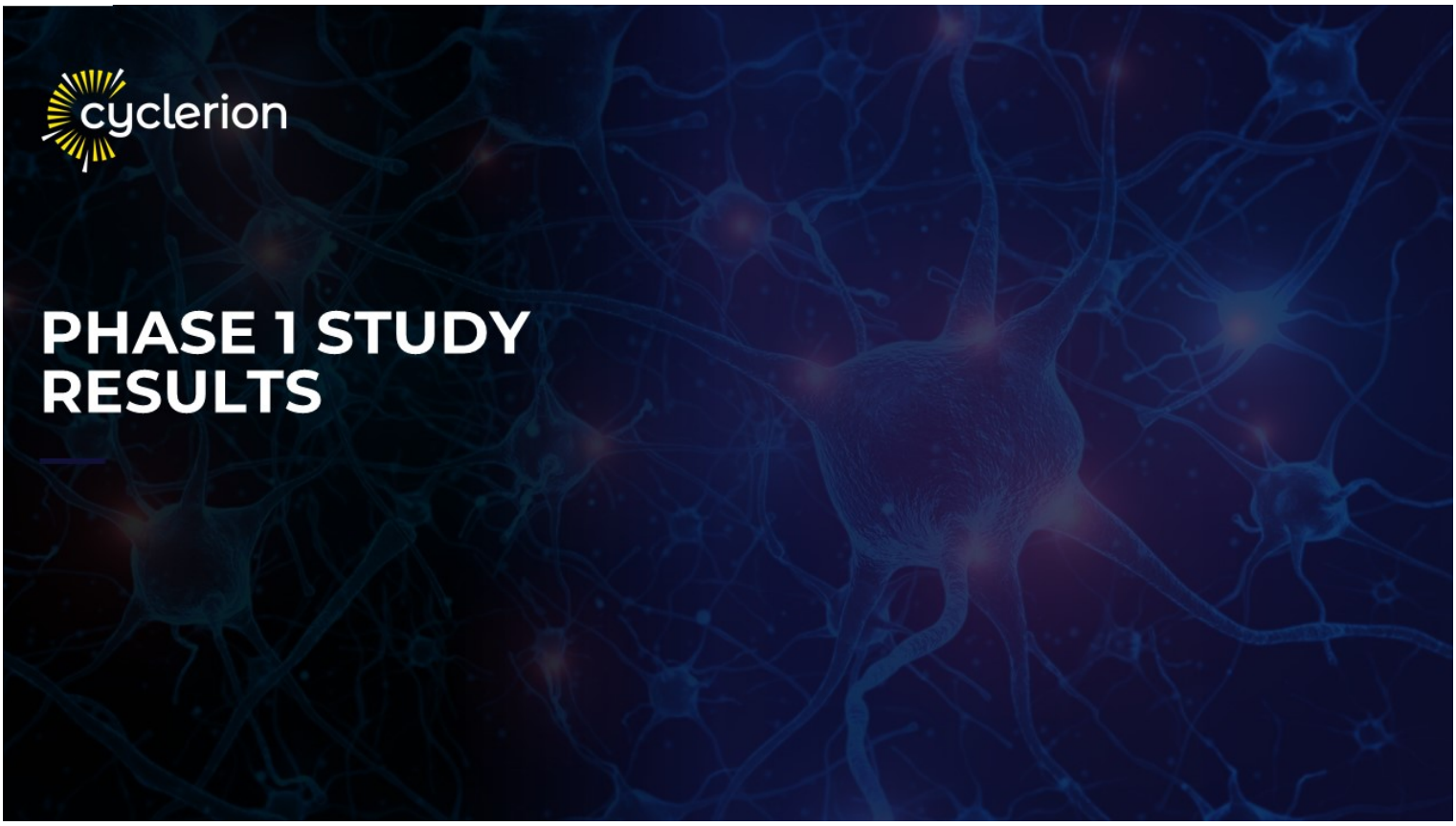
Peripherally restricted sGC stimulator



CNS-penetrant sGC stimulator CY6463



Healthy awake male rats treated with 0.3 mg/kg iv; image quantification 20-30 minutes post-dose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PHASE 1 STUDY
RESULTS

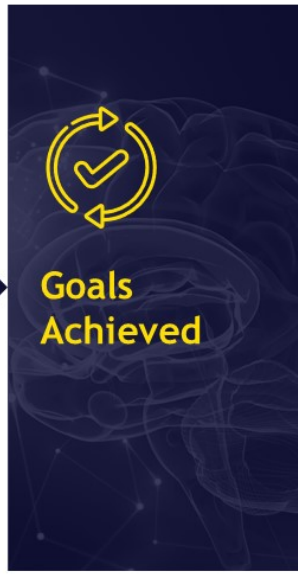
CY6463 phase 1 showed CNS exposure, target engagement, PK, and safety

PHASE 1 (completed)

- **Study design**
  Three stages:
  SAD | MAD | Food Interaction
- 110 healthy young
- Age range 18-63
- Standard safety
- PK (blood & CSF)
- Wide dose range tested

Results

- Identified safe and well-tolerated dose levels with steady-state CNS exposure in therapeutic target range*
- Linear, predictable PK, consistent with QD dosing
- CNS exposure confirmed
- Evidence of target engagement (blood pressure)
- Well tolerated at all dose levels, no safety signals
- May be taken with or without food



*Based on positive CNS pharmacology in multiple preclinical models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TRANSLATIONAL
PHARMACOLOGY
STUDY RESULTS

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 N200 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

Biomarker overview: qEEG frequency bands and their clinical implications

Associated with:

- Cognitive decline in aging and AD
- Genetic risk factors for AD (ApoE4)
- AD pathological protein levels (Aβ, tau)
- Improvement with approved AD treatments

Band	Frequency Hz	associated with
Delta	0-4	Deep sleep
Theta	4-8	Waking/falling asleep, some with cognition
Alpha	8-14	Passive wakefulness Attention and cognitive processing
Beta	14-30	Alert, concentration
Gamma	30-80	Higher cognitive function

Resting-state qEEG:

- subjects sit facing a featureless wall without moving
- recorded with eyes open and closed for 5 minutes each

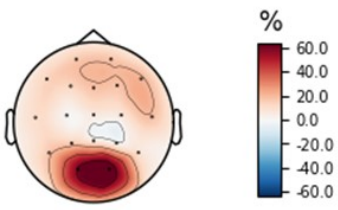
qEEG is quantitative electroencephalography, an objective method that measures electrical activity and brain wave patterns

CY6463 improved qEEG measures: significant increase in alpha power

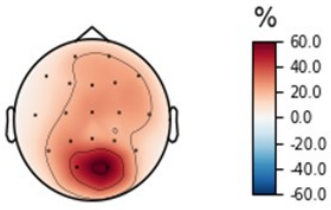
Significant increase in EEG alpha power

No effect of placebo

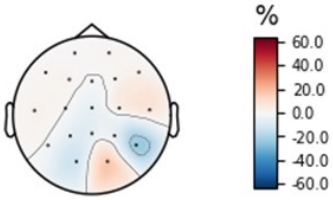
CY6463 vs. baseline



CY6463 vs. placebo



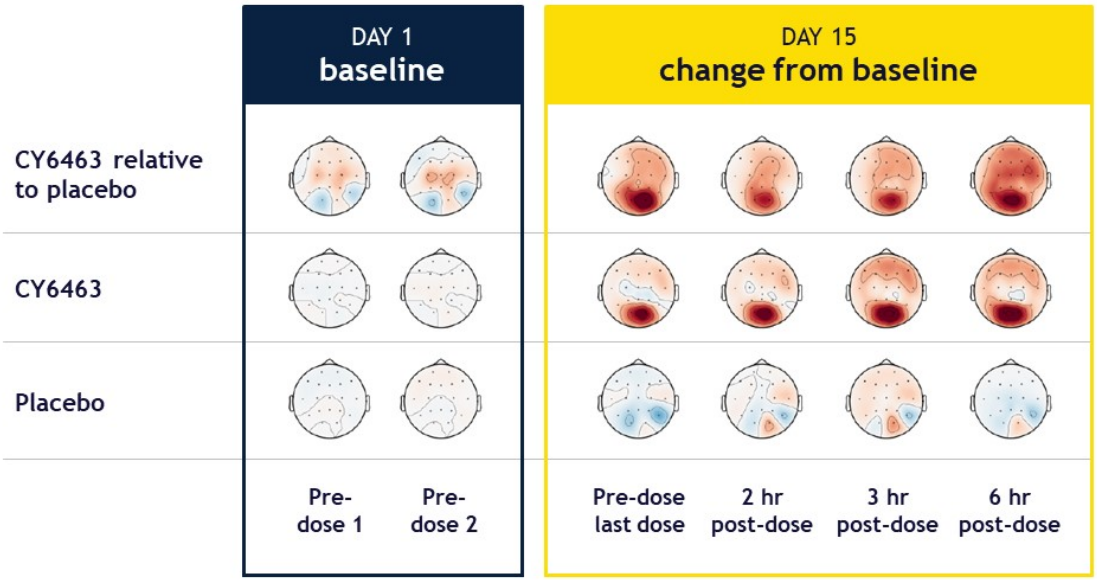
Placebo vs. baseline

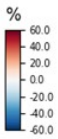


change (%) in alpha power on day 15

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

CY6463's consistent alpha power effects across repeat sessions indicate stable and robust signal



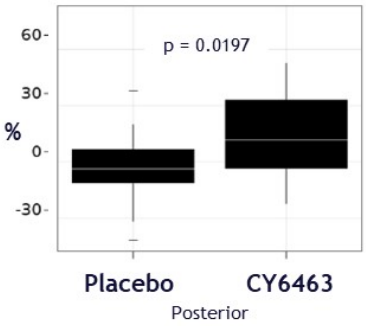


Magnitude of improvement equivalent to decline seen after 2 years of aging

CY6463 increased alpha power with high responder rate (>70%)

Increase in alpha power

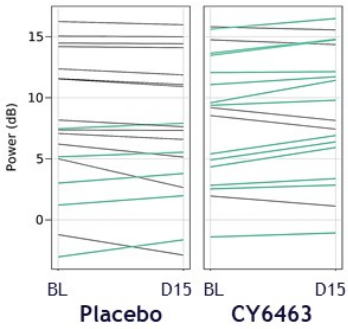
Day 15 change from baseline in mean closed-eye alpha (8-12 Hz) Power



- 17% treatment effect over placebo
- Similar increase in anterior alpha power observed (p=0.0752)

Consistent individual treatment responses

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

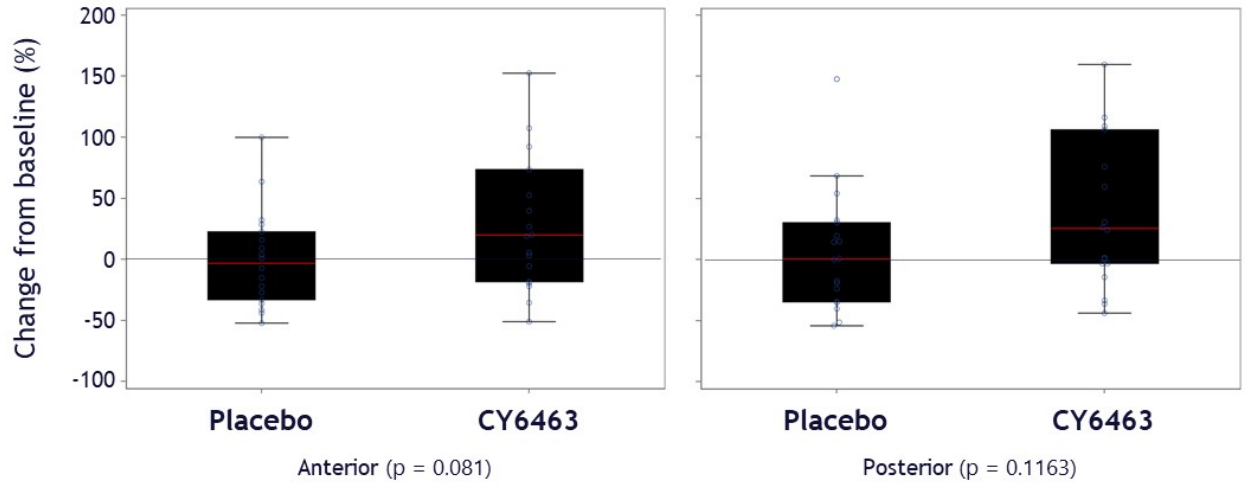


- 13/18 participants increase with CY6463, vs 5/18 with placebo[1]
- Overall effect not driven by outliers

1. Includes all subjects. For CY6463 and pbo each: n=12 for period 1, n=6 for period 2

CY6463 treatment associated with trend improvement in gamma power

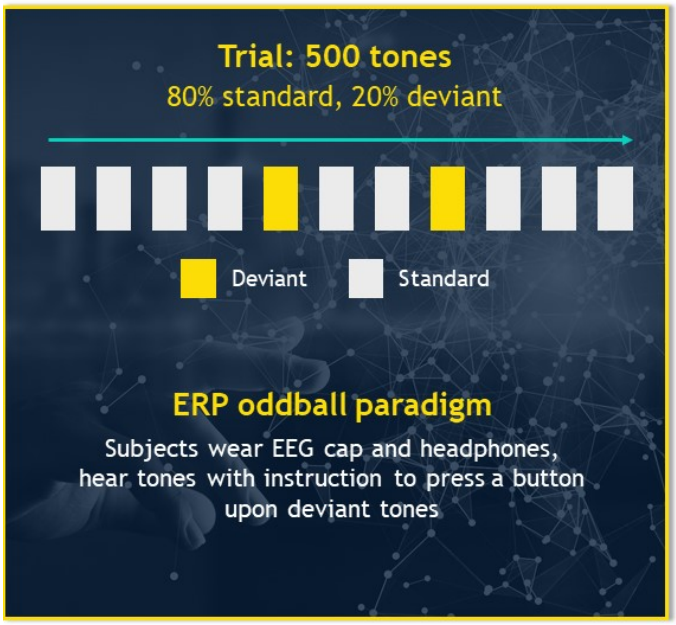
Change in Closed-Eye Gamma (25-45 Hz) Power

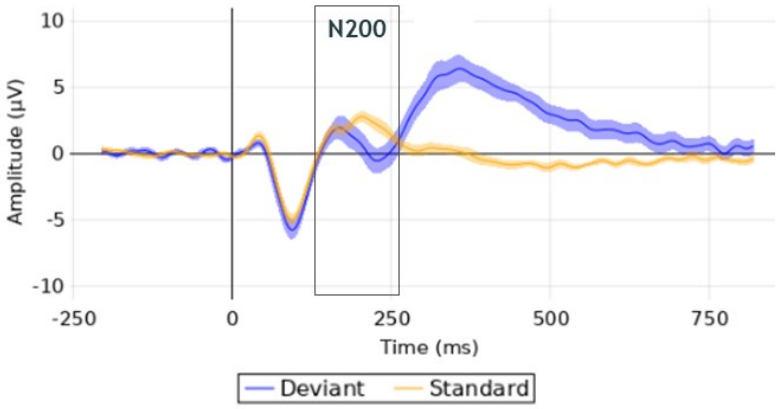


Anterior (p = 0.081)

Posterior (p = 0.1163)

Biomarker overview: event-related potential (ERP)





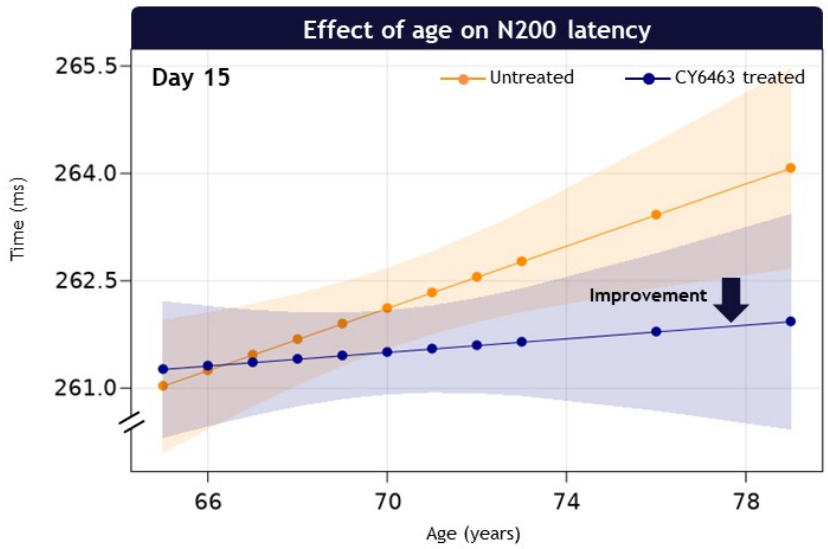
N200

- Stable component of ERP waveform
- Stimulus identification and distinction
- Affected in aging, neurodegenerative and neuropsychiatric diseases with cognitive impairment, and other CNS diseases

Parameters

- **Latency**: time after the stimulus to peak signal
- **Amplitude**: size of peak signal

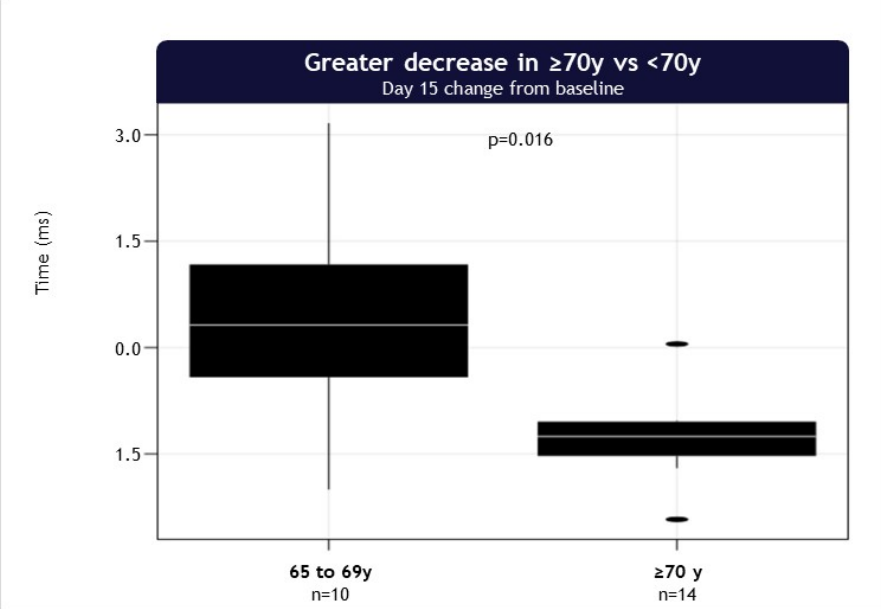
CY6463 improved N200 latency and effect increased with age



Overall decrease in N200 latency for CY6463 treated vs untreated on day 15 ($p<0.02$)

Effect more pronounced in older subjects

CY6463 improved N200 latency, driven by response in older subjects

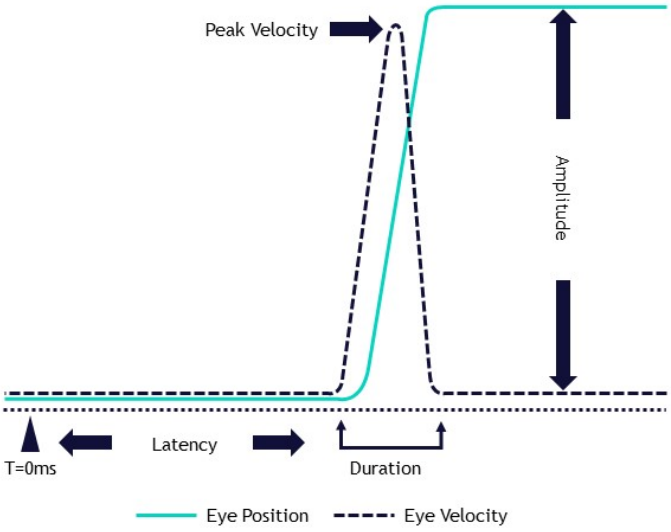


Latency response was greater in subjects ≥70y vs 65-69y (p=0.016)

Narrowing of variance in ≥ 70y supports a drug effect

In ≥ 70y, magnitude of improvement after 2 weeks of treatment with CY6463 represents ~10y age-related change in N200 latency

Biomarker overview: saccadic eye movement as an objective measure of attention and cognition

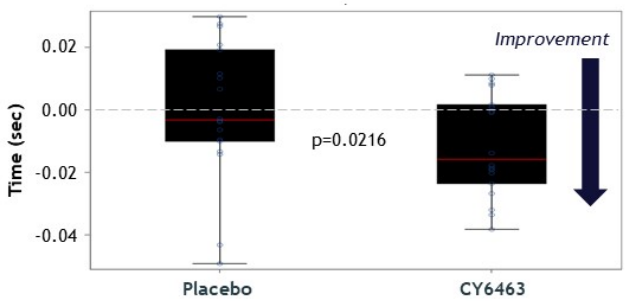


- Short, fast, simultaneous tracking of both eyes in the same direction
- Brain areas involved include the frontal cortex, superior colliculus, substantia nigra, and amygdala
- Considered to be reflective of attention / arousal and influenced by motivation, time on task, and task difficulty
- Sensitive to sedation, fatigue, and CNS depressants and cognitive enhancers, and is affected by aging

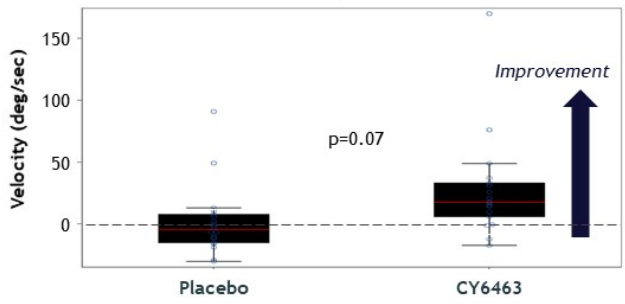
https://www.liverpool.ac.uk/~pcknox/teaching/Eymovs/params.htm

CY6463 improved saccadic eye movement, an objective functional measure

Decrease in saccadic reaction time



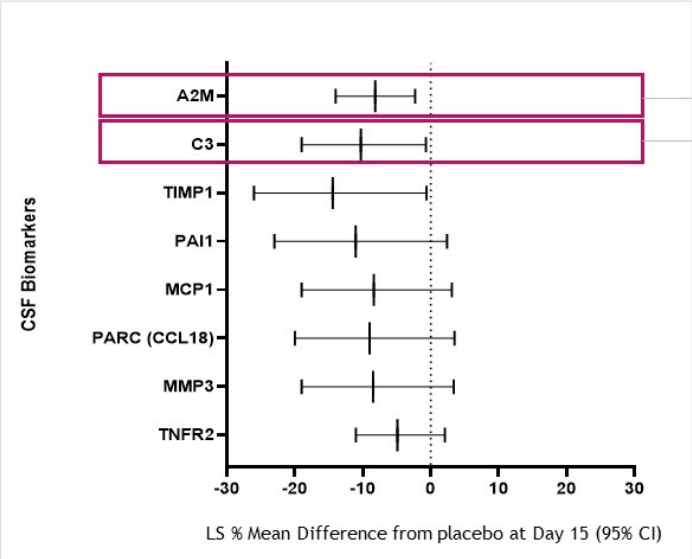
Increase in saccadic peak velocity



- Shorter saccadic reaction times and faster saccadic velocities indicate that CY6463 is improving CNS functional performance - motor output - in addition to CNS neurophysiology
- Cognitive enhancers (e.g., modafinil) also positively impact saccadic eye movements

Mean change from baseline on day 15 post-dose

CY6463 improved neuroinflammatory biomarkers



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

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

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

Relevant reference publications (1 of 2)

NO-sGC-cGMP signaling in the CNS

- Correia S, et al. "The CNS-penetrant soluble guanylate cyclase stimulators CY6463 reveals its therapeutic potential in neurodegenerative diseases." Frontiers in Pharmacology. 2021;12(1014)
- Correia S, et al. "The CNS-penetrant soluble guanylate cyclase stimulators CYR119 attenuates markers of inflammation in the central nervous system." Journal of Neuroinflammation. 2021;18(1)
- Garthwaite, John. "Nitric oxide as a multimodal brain transmitter." Brain and Neuroscience Advances vol. 2 2398212818810683. 4 Dec. 2018
- Kleppisch T, Feil R. cGMP signaling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol. 2009;(191):549-79
- Ben Aissa M, Lee SH, Bennett BM, Thatcher GR. Targeting NO/cGMP Signaling in the CNS for Neurodegeneration and Alzheimer's Disease. Curr Med Chem. 2016;23(24):2770-2788
- Hollas MA, Ben Aissa M, Lee SH, Gordon-Blake JM, Thatcher GRJ. Pharmacological manipulation of cGMP and NO/cGMP in CNS drug discovery. Nitric Oxide. 2019 Jan 1;82:59-74

qEEG spectral frequency analysis

- Ishii et al. Healthy and Pathological Brain Aging: From the Perspective of Oscillations, Functional Connectivity, and Signal Complexity. Neuropsychobiology, 2018
- Babiloni, et al. 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;90:43-59

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Event-related potential (ERP): MMN, N200 and P300

- Bennys K, Portet F, Touchon J. Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment. J Clin Neurophysiol 2007;24:405-12
- Fruehwirt et al. Associations of event-related brain potentials and Alzheimer's disease severity: A longitudinal study. Progress in Neuropsychopharmacology and Biological Psychiatry 92 (2019) 31-38

Saccadic eye movement (SEM)

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- James A. Sharpe & David H. Zackon (1987) Senescent Saccades: Effects of Aging on Their Accuracy, Latency and Velocity, Acta Oto-Laryngologica, 104:5-6, 422-428

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- Cortes-Canteli M, Iadecola C. Alzheimer's Disease and Vascular Aging: JACC Focus Seminar. J Am Coll Cardiol. 2020;75(8):942-951

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- El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab. 2015;116(1-2):4-12

CIAS

- Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. Handb Exp Pharmacol. 2012;(213):11-37