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): **April 27, 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 2.02. Results of Operations and Financial Condition.

On April 27, 2021, Cyclerion Therapeutics, Inc. (the "Company") issued a press release and released an updated corporate presentation ("the Corporate Presentation") as described in Item 7.01 below. The press release and presentation include information that the Company's preliminary unaudited cash, cash equivalents and restricted cash balance as of March 31, 2021 was approximately $45 million and that the Company expects average monthly cash use for the foreseeable future to be approximately 50 percent that of 2020.

The foregoing information constitutes unaudited and preliminary estimates that (i) represent the most current information available to management as of the date of the press release and presentation, (ii) are subject to completion of financial closing and procedures that could result in significant changes to the estimated amounts, and (iii) do not present all information necessary for an understanding of the Company's financial condition as of, and its results of operations for the quarter ended, March 31, 2021. Accordingly, undue reliance should not be placed on such estimates.

The information set forth in this Item 2.02 is being furnished pursuant to Item 2.02 of Form 8-K and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (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, as amended (the "Securities Act"), or under the Exchange Act, whether made before or after the date hereof, except as expressly provided by specific reference in such a filing.

Item 7.01. Regulation FD Disclosure.

On April 27, 2021, the Company provided a corporate update. A copy of the Company's press release of the same date summarizing the corporate update is attached hereto as Exhibit 99.1. The information set forth in the press release is incorporated by reference herein. The press release contains hypertext links to information on the Company's website. The information on the Company's website is not incorporated by reference into this Current Report on Form 8-K and does not constitute a part hereof.

In connection with the corporate update described above, the Company released the Corporate Presentation. Beginning on April 27, 2021, the Company intends to use the Corporate Presentation, or portions thereof, which provides updates on its business activities, in one or more meetings with investors. The Corporate Presentation is attached hereto as Exhibit 99.2, is incorporated by reference herein and is posted on the Company's website, www.cyclerion.com. The Company plans to use its website to disseminate future updates to the presentation and may not necessarily file or furnish a Current Report on Form 8-K alerting investors if the presentation is updated.

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 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 or under 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 Item 7.01 in this report, the press release or the presentation available on the Company's website. The information contained in the press release and presentation 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.

Forward-Looking Statements

This report, the press release and the presentation may contain forward-looking statements within the meaning of Section 27A of the Securities Act 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 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.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release dated April 27, 2021
99.2	Corporate Update Presentation dated April 27, 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: April 27, 2021

By: /s/ Anjeza Gjino

Name: Anjeza Gjino
Title: Chief Financial Officer

Cyclerion Therapeutics Hosted Webinar to Discuss Pipeline Progress

Provided updates on development strategy and execution for CY6463, a first-in-class, CNS-penetrant sGC stimulator, including IND clearance from FDA in ADv and ongoing MELAS program

Introduced new CY6463 clinical program in CIAS with key insights from neuropsychiatric key opinion leader, Andreas Reif, M.D.

Announced new development candidate, CY3018, a differentiated, next-generation CNS-penetrant sGC stimulator

CAMBRIDGE, Mass., April 27, 2021 (GLOBE NEWSWIRE) -- Cyclerion Therapeutics, Inc. (Nasdaq: CYCN), a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function, hosted a webinar today to provide clinical updates for its first-in-class, CNS-penetrant soluble guanylate cyclase (sGC) stimulator CY6463 in Alzheimer's Disease with Vascular pathology (ADv) and Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS). Supported by recent clinical and preclinical data, Cyclerion also discussed the potential for CY6463 to treat Cognitive Impairment Associated with Schizophrenia (CIAS), with key insights from Dr. Andreas Reif on the role of the sGC pathway in the disease. In addition, Cyclerion introduced its latest development candidate CY3018, a differentiated, next-generation, CNS-penetrant sGC stimulator.

"To deliver on our mission to develop treatments that restore cognitive function, we are harnessing the momentum and insights from our preclinical and clinical data on the fundamental role of the NO-sGC-cGMP pathway in central nervous system diseases," said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. "Following the science, we see the potential to unlock significant opportunities across a number of patient populations with cognitive impairment, who are in desperate need of new therapeutic options."

Key Webinar Highlights

- **Modulating a fundamental CNS signaling pathway:** sGC stimulators amplify the power of the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway (NO-sGC-cGMP) signaling to address central aspects of disease pathophysiology. Preclinical data from CY6463 and extensive academic work validate the crucial role of the sGC pathway in brain physiology. Clinical data from the recent translational pharmacology study confirm the ability of CY6463 to impact brain oscillations, neuroinflammation and neurophysiological function.

- **CY6463 Updates**
  - **Disease-relevant, biomarker-guided pipeline strategy:** The company is advancing parallel, signal-seeking, exploratory studies in well-defined patient populations with cognitive impairment including neurodegenerative, neuropsychiatric, and mitochondrial diseases. CY6463 targets sGC, a proven druggable target, in critical brain regions and cell types linked to cognition and has demonstrated an impact on multiple biomarkers associated with cognition in previous Phase 1 studies.
  - **ADv clinical trial initiation:** The U.S. Food and Drug Administration (FDA) cleared the Investigational New Drug (IND) application for CY6463 in ADv, and the Company anticipates beginning to enroll patients in a 12-week Phase 2a clinical trial in patients with ADv by mid-2021, barring any COVID-19 related delays. This exploratory study is designed to evaluate safety, tolerability, and pharmacodynamic effects including impact on disease-relevant biomarkers.
  - **MELAS clinical trial advancement:** This study is enrolling more slowly than initially projected, primarily due to COVID-19. Data from the exploratory 29-day open-label Phase 2a pilot study in patients with MELAS are now expected by year end 2021.
  - **Potential to treat CIAS with novel mechanism:** Neuropsychiatric key opinion leader and expert in the neurobiology of nitric oxide and its relation to psychiatric disorders, Andreas Reif, M.D., Chair, Department of Psychiatry, University Hospital Frankfurt, discussed the sGC pathway and its role in cognitive function and CIAS. Reduced NO-sGC-cGMP signaling is linked to cognitive dysfunction in schizophrenia. Stimulation of sGC by CY6463 to amplify NO-sGC-cGMP signaling is a potential first-in-class approach for the treatment of CIAS. Cyclerion is planning to initiate a Phase 1b signal-seeking study in CIAS to evaluate safety and near-term impact on disease-relevant biomarkers.
- **CY3018, a differentiated, next-generation CNS-penetrant sGC stimulator:** Cyclerion shared information on the latest development candidate, CY3018. Preclinical data show increased CNS-exposure, with significantly increased cerebrospinal fluid (CSF) to plasma ratio, compared to CY6463. This increased CNS distribution is mirrored by a higher level of pharmacological activity in the CNS relative to the periphery. The company is advancing CY3018 through IND-enabling development.

“We are using insights from our preclinical and clinical data to tap into a fundamental CNS signaling pathway with CY6463 – our first-in-class, CNS-penetrant sGC stimulator,” said Andy Busch, Ph.D., Chief Scientific Officer at Cyclerion. “We are excited by the data from our CY6463 translational pharmacology study that demonstrated rapid improvement in biomarkers associated with cognition and reflect CY6463’s multidimensional pharmacology. These data are leading us to explore opportunities in cognition through the sGC pathway.”

Cash, cash equivalents, and restricted cash balance on March 31, 2021 was approximately $45 million, as compared to approximately $58 million on December 31, 2021. As of April 2021, Cyclerion has substantially streamlined its operating model to invest more fully in its priority opportunities in cognition and expects average monthly cash use for the foreseeable future to be approximately 50 percent that of 2020.

Webinar Replay Information

A replay of the event can be accessed by visiting the investors’ section of the Cyclerion website at https://ir.cyclerion.com/news-events/event-calendar.

About Cyclerion Therapeutics

Cyclerion Therapeutics is a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function. Cyclerion’ is advancing novel, first-in-class, CNS-penetrant, sGC stimulators that modulate a key node in a fundamental CNS signaling pathway. The multidimensional pharmacology elicited by the stimulation of sGC has the potential to impact a broad range of CNS diseases. The most advanced compound, CY6463 has shown rapid improvement in biomarkers associated with cognitive function and is currently in clinical development for Alzheimer’s Disease with Vascular pathology (ADv) and Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS) and Cognitive Impairment Associated with Schizophrenia (CIAS). Cyclerion is also advancing CY3018, a next generation sGC stimulator.

For more information about Cyclerion, please visit https://www.cyclerion.com/ and follow us on Twitter (@Cyclerion) and LinkedIn (www.linkedin.com/company/cyclerion).

Forward Looking Statement

This press release 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 press release, and Cyclerion undertakes no obligation to update these forward-looking statements, except as required by law.

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Exhibit 99.2


cyclerion
ON A MISSION TO DEVELOP TREATMENTS THAT RESTORE COGNITIVE FUNCTION
CORPORATE PRESENTATION
APRIL 2021

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.

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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

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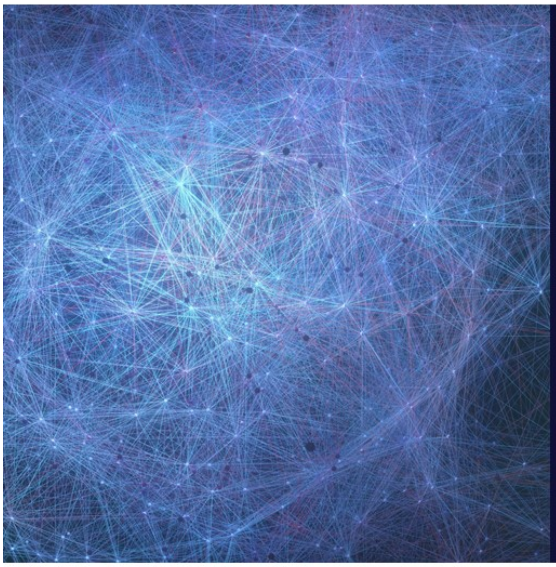
Contents



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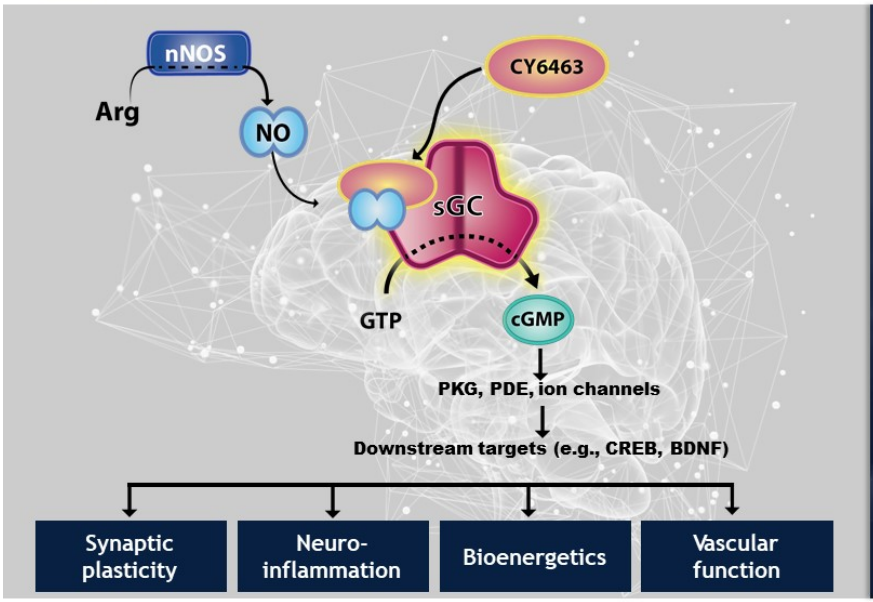
NO-sGC-cGMP IS A FUNDAMENTAL CNS SIGNALING PATHWAY

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

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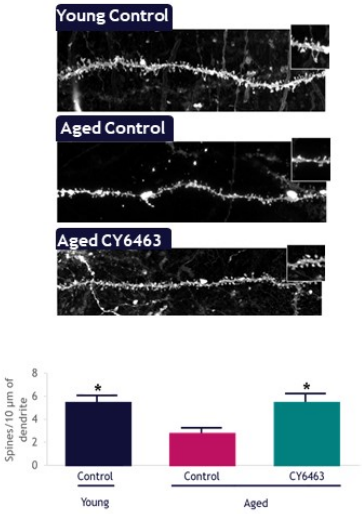
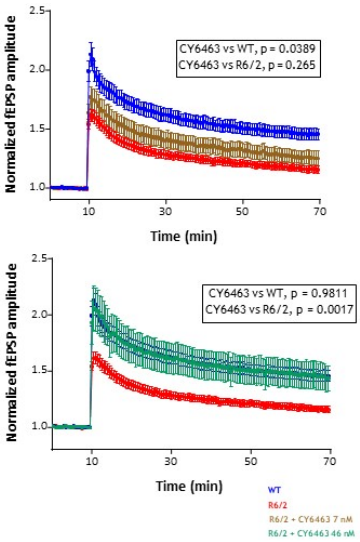
CY6463 improves endpoints relevant to cognition

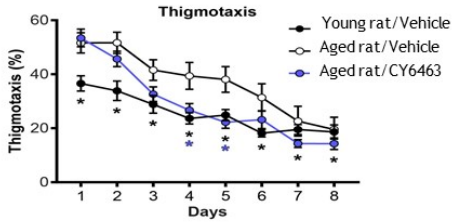
Morphological plasticity



Ex-vivo LTP



In-vivo learning and memory



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

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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
- reduction in neuroinflammatory biomarkers

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

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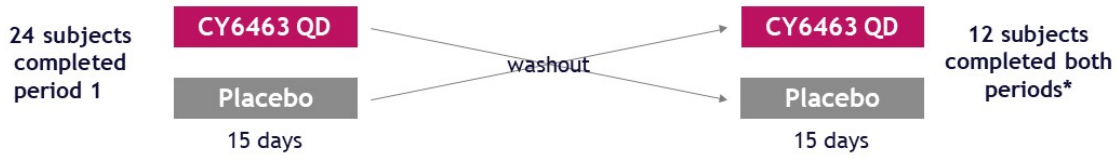
Phase 1b translational pharmacology study designed to evaluate CNS activity

Healthy elderly population (≥65 years)



Objectives

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

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

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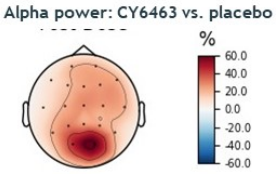
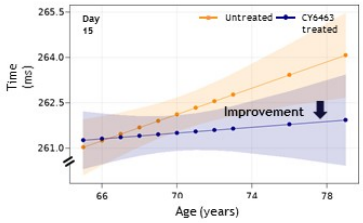
CY6463 showed rapid improvement in biomarkers of cognition

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

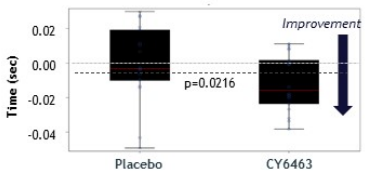
Increased alpha and gamma power



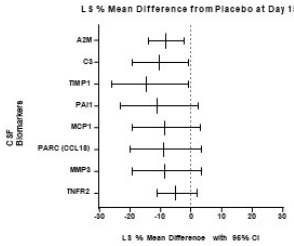
Improved N200 latency



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

=

In a 15-day study in 24 healthy elderly subjects

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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

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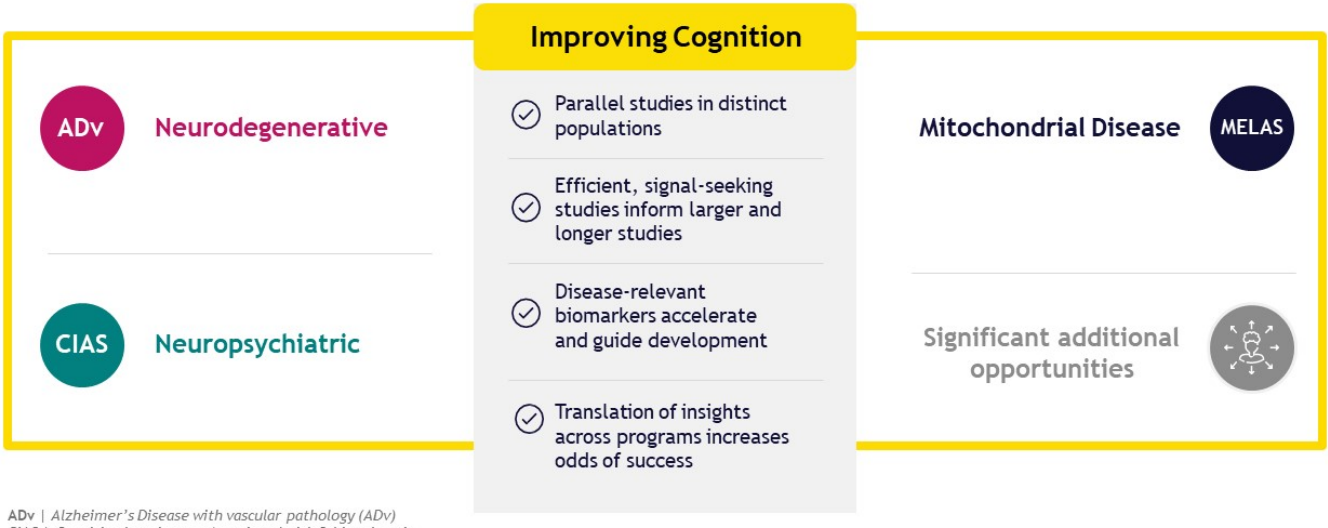
Biomarker-guided development strategy in well-defined populations with cognitive impairment



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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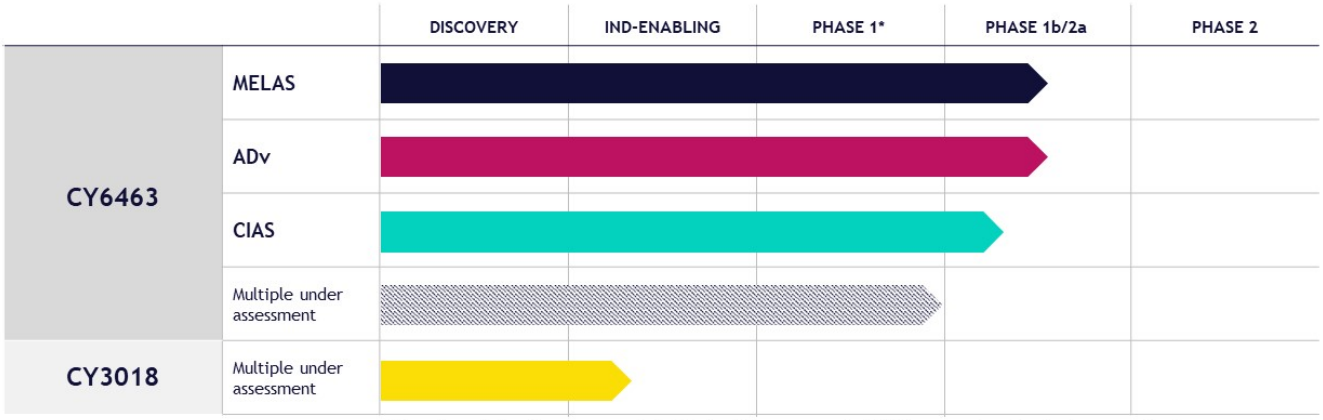
POTENTIAL FOR PATIENT IMPACT: OUR PRIORITY INDICATIONS

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*

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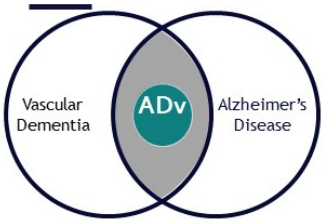
Biomarker-guided development strategy: ADv



Growing patient population, devastating impact, limited treatments

Today

Exploratory Phase 2

Near-term impact on disease-specific biomarkers and cognition

Tomorrow

Larger, longer studies 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

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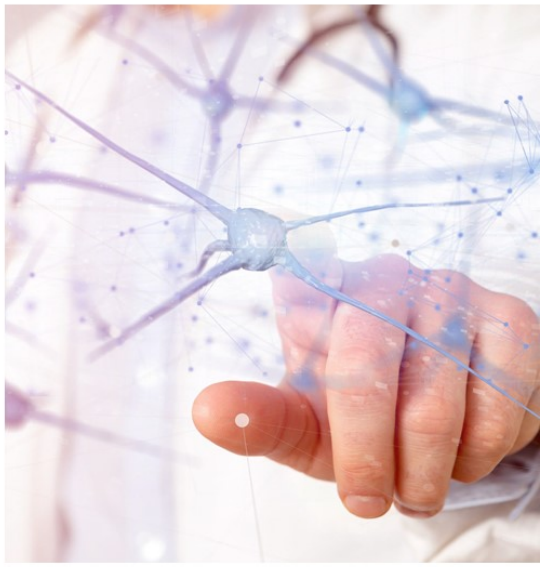
ADv study expected to initiate in mid-2021

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



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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

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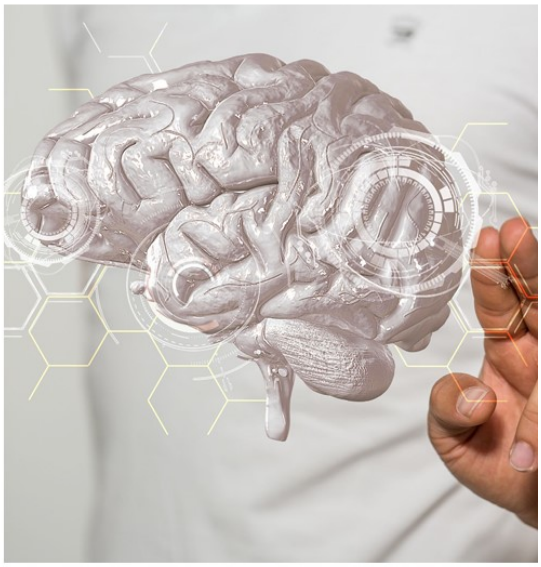
MELAS study underway; data expected late 2021

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



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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

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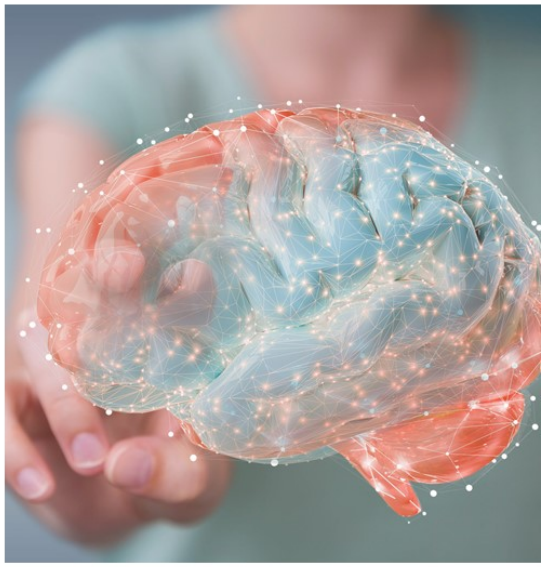
CIAS study expected to initiate in 2H 2021

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 50 participants across sequential cohorts
Patient targeting	• Psychiatrically stable adults with schizophrenia • On stable antipsychotic regimen



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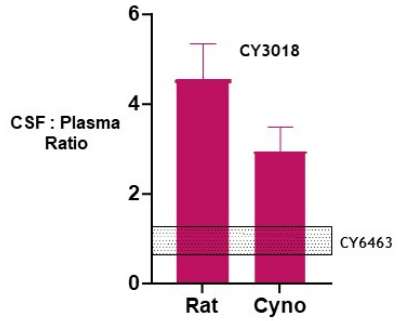
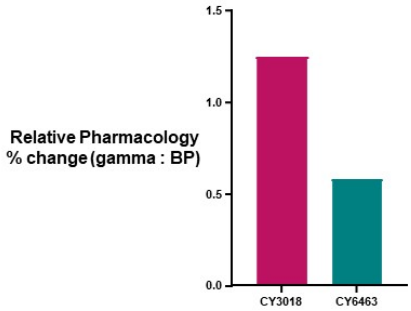
NEXT GENERATION sGC STIMULATOR PROGRAM

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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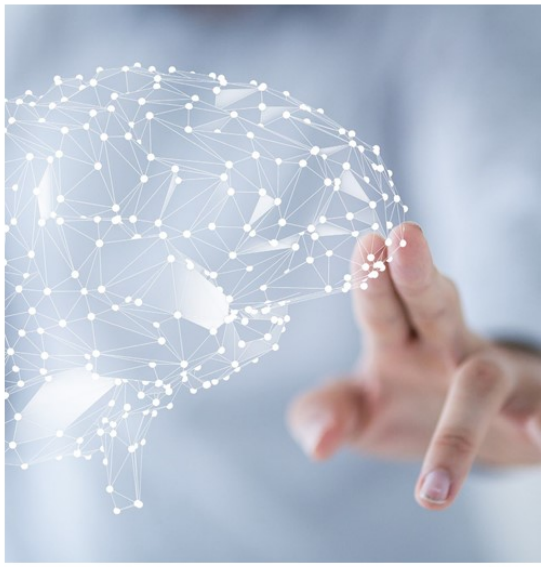
EXECUTING ON OUR PRIORITIES

2021: executing on our priorities

Clinical and pre-clinical	• ADv Ph2 study start mid-2021 • MELAS Ph2 study data by year end 2021 • CIAS Ph2b study start in 2H 2021 • Advancing CY3018, NextGen development candidate
Partnerships	• Explore CNS collaborations • Praliciguat out-license
Capabilities and capital	• Grow external CNS network and augment core team CNS expertise • Reduced monthly cash use to ~50% that of 2020 • Q1 2021 ending cash balance of ~$45M*



* Preliminary, unaudited unrestricted cash, cash equivalents and restricted cash balance as of March 31, 2021

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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

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APPENDICES

Preclinical, Phase 1 and translational pharmacology studies, references

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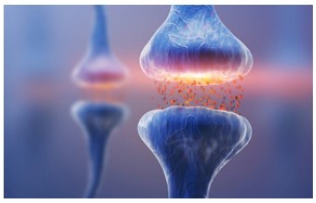
PRECLINICAL DATA

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

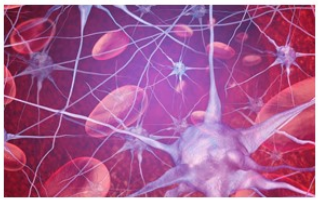
Cellular Bioenergetics

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



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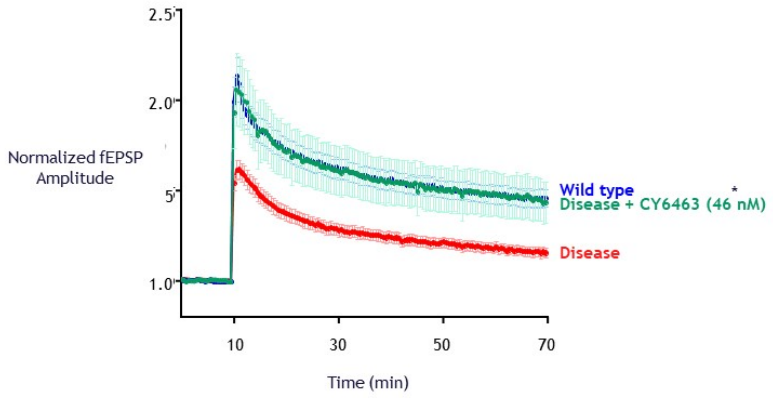
CY6463 improved neuronal function

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

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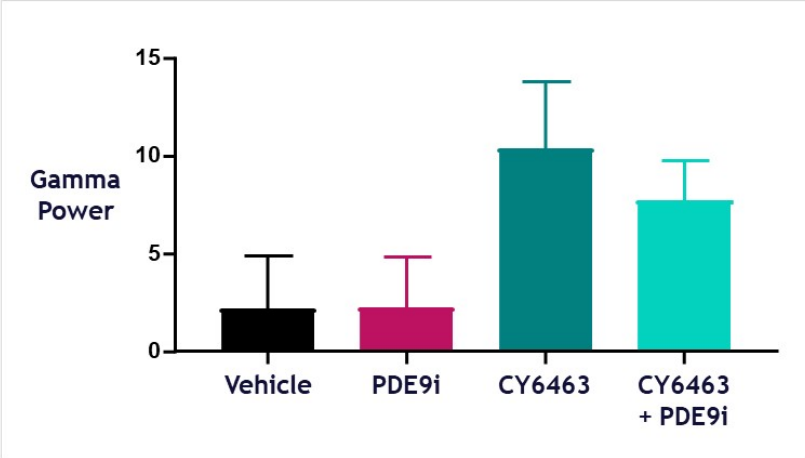
CY6463 increased qEEG gamma power

No effect seen with PDE9 inhibitor

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

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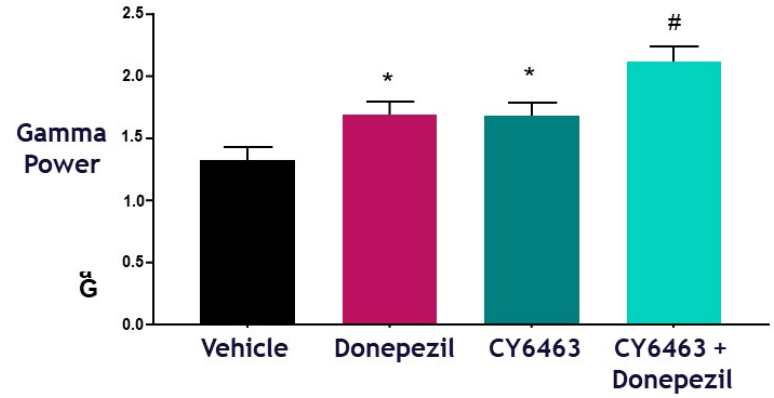
CY6463 and donepezil act independently to enhance qEEG signal

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

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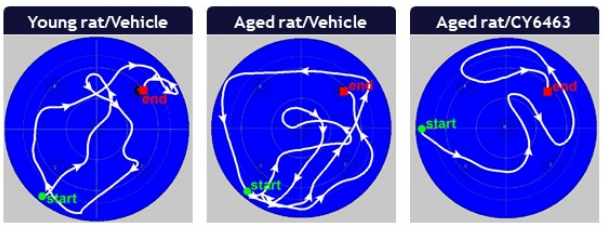
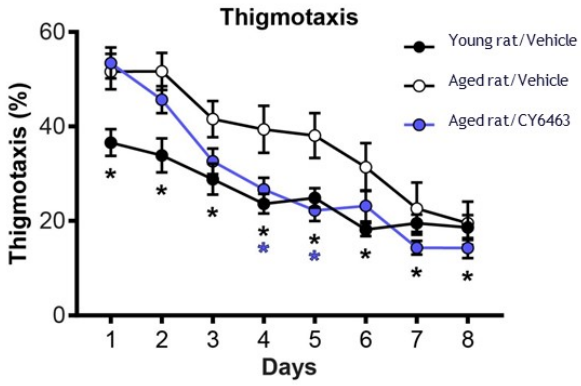
CY6463 improved learning and memory in aged rats

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

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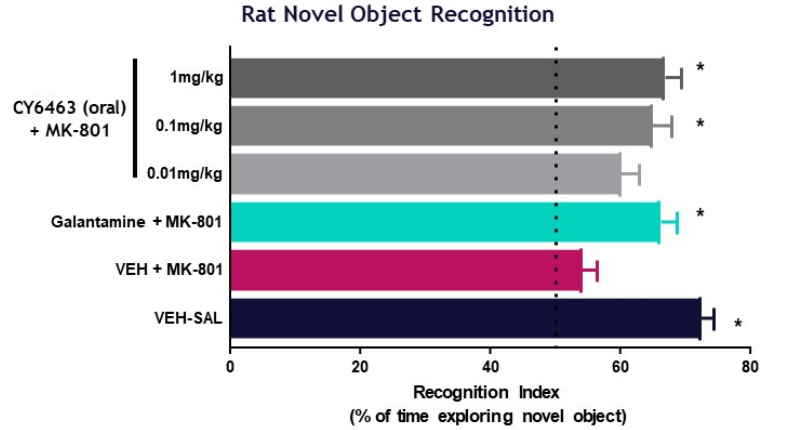
CY6463 improved cognitive function in pharmacologically impaired rats

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

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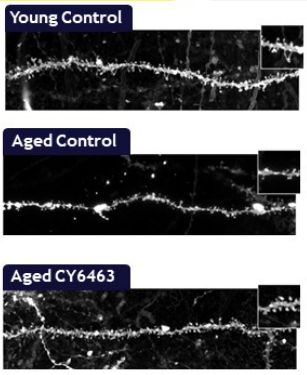
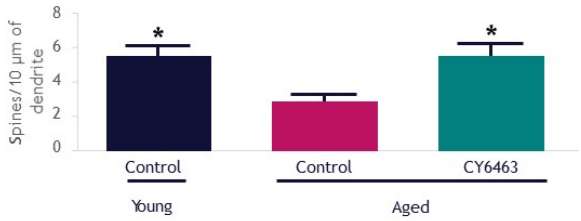
CY6463 improved neuronal function

Enhanced hippocampal spine density in aged animals treated with CY6463

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



Mushroom spine density



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

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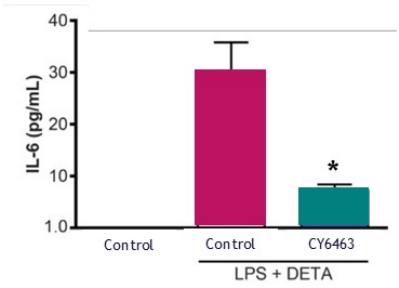
CY6463 reduced neuroinflammation

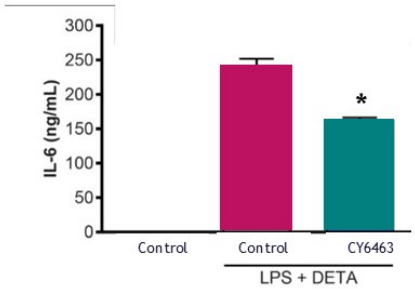
Inhibited in vitro LPS-induction of biomarkers of neuroinflammation

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

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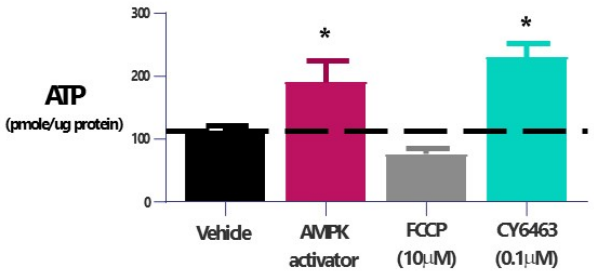
CY6463 enhanced cellular bioenergetics

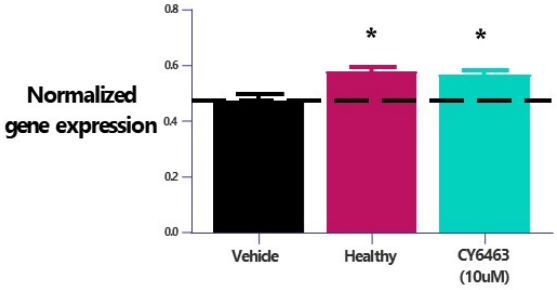
Increased ATP and restored decreased gene expression in cells from patients with mitochondrial diseases

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.

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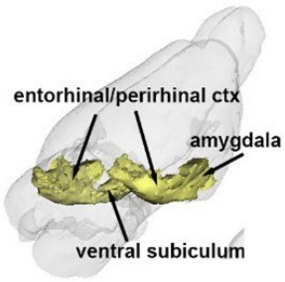
CY6463 improved cerebral blood flow

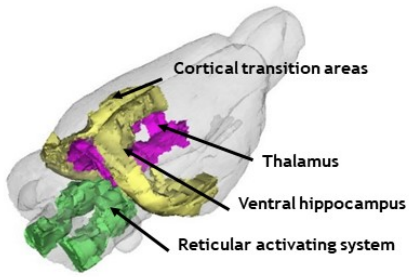
Increased blood flow in areas associated with memory and arousal by fMRI BOLD imaging

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

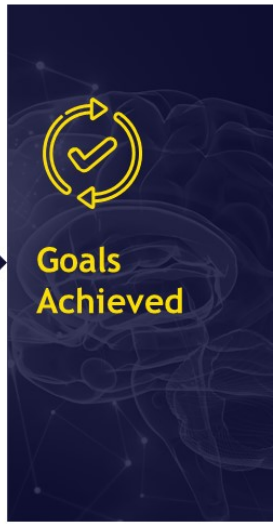
CY6463 phase 1 showed CNS exposure, target engagement, PK, and safety

PHASE 1 (completed Jan. 2020)

- **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

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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

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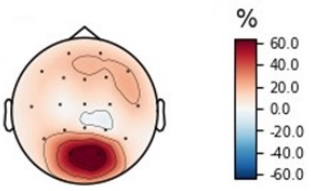
CY6463 improved qEEG measures: significant increase in alpha power

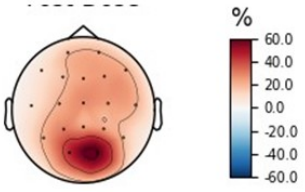
Significant increase in EEG alpha power

No effect of placebo

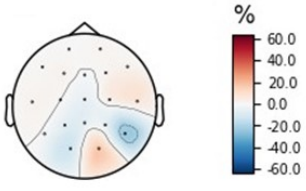
CY6463 vs. baseline



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

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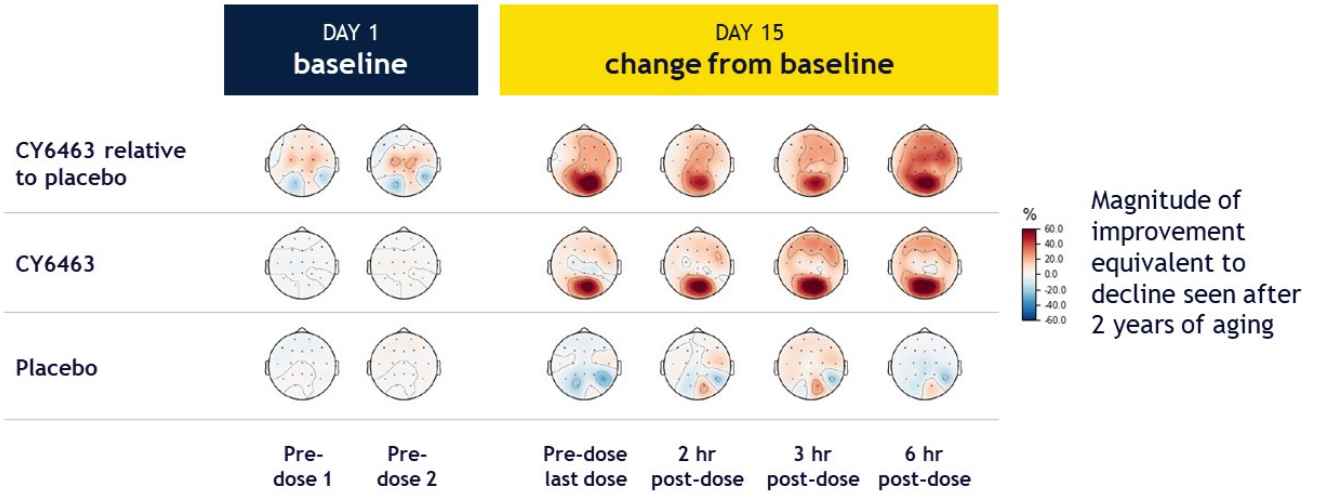
CY6463's consistent alpha power effects across repeat sessions indicate stable and robust signal



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

Footer

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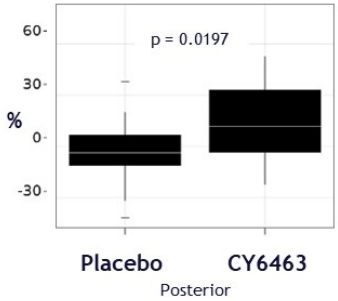
CY6463 increased alpha power with high responder rate (>70%)

Increase in alpha power

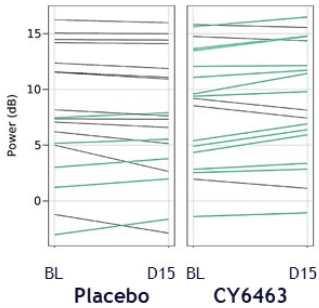
Day 15 change from baseline in mean closed-eye alpha (8-12 Hz) Power



- 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

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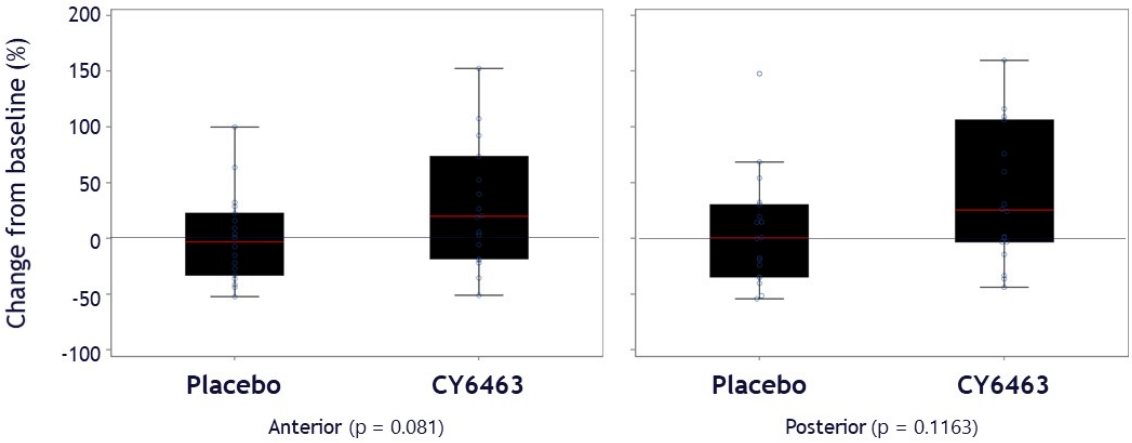
CY6463 treatment associated with trend improvement in gamma power

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



Anterior (p = 0.081)

Posterior (p = 0.1163)

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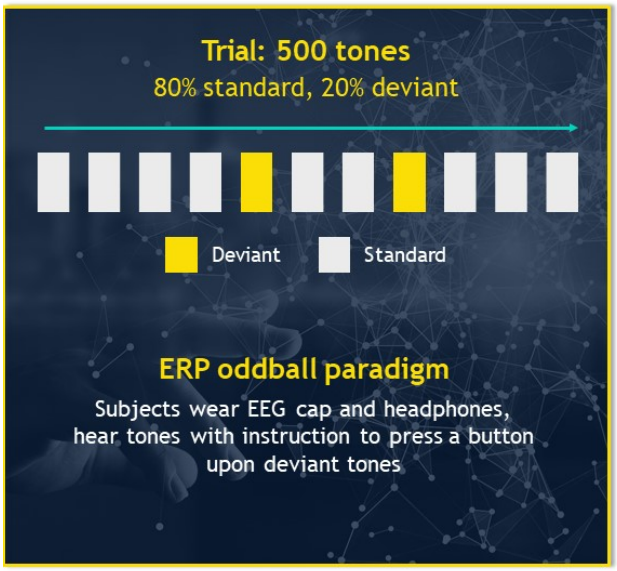
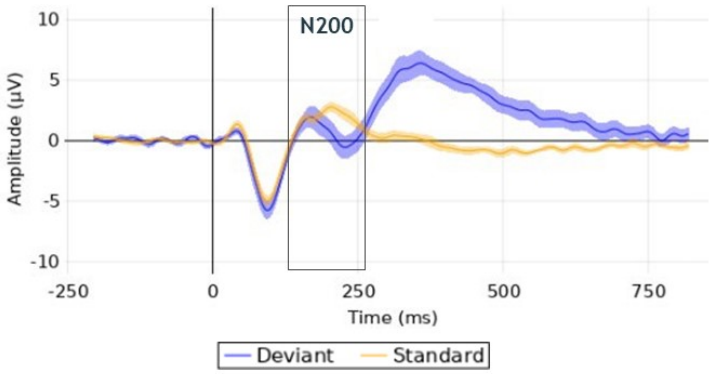
Biomarker overview: event-related potential (ERP)





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

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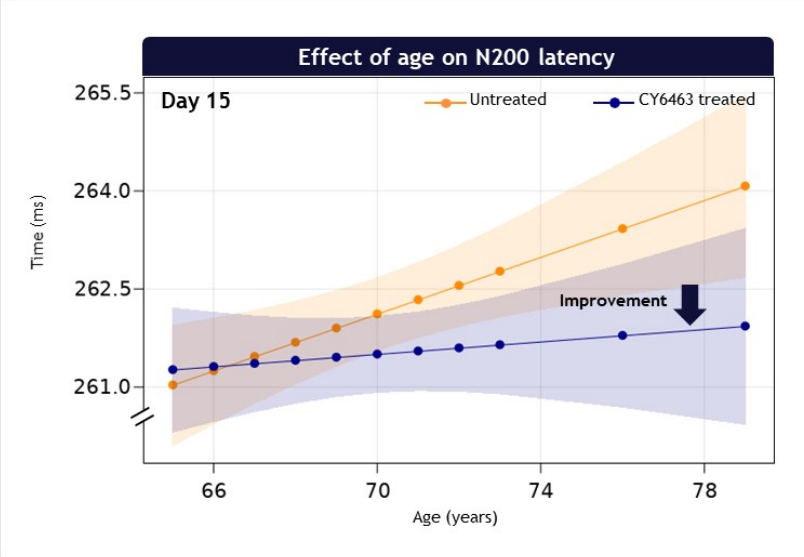
CY6463 improved N200 latency and effect increased with age



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

Effect more pronounced in older subjects

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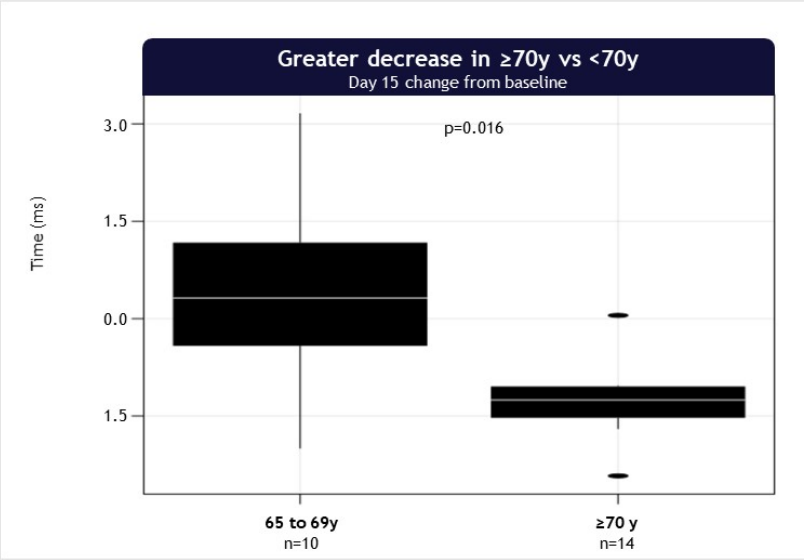
CY6463 improved N200 latency, driven by response in older subjects



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

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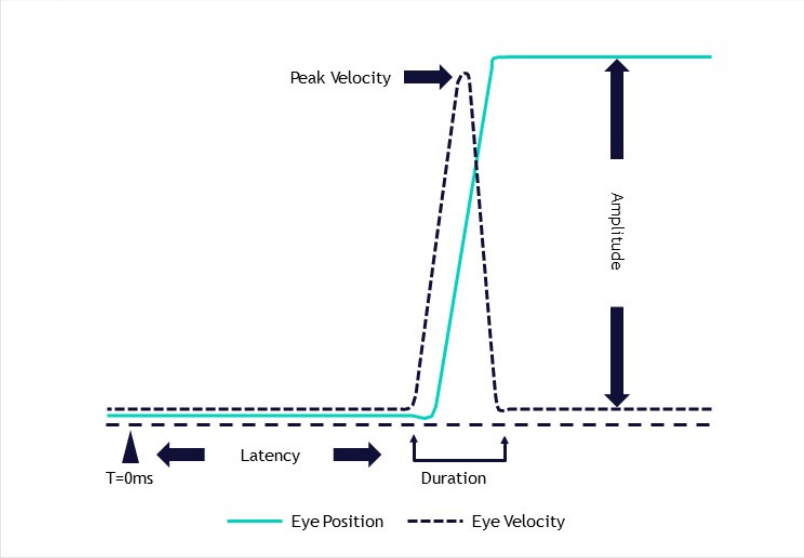
Biomarker overview: saccadic eye movement as an objective measure of attention and cognition



- 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

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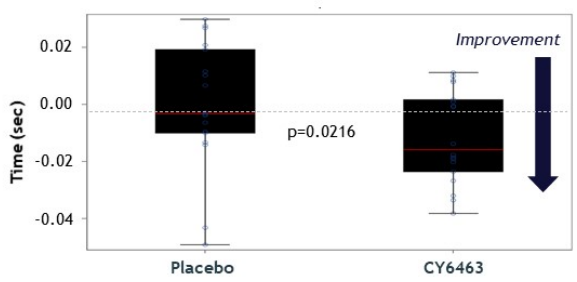
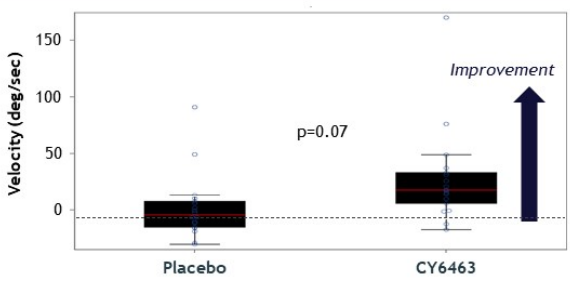
CY6463 improved saccadic eye movement, an objective functional measure

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

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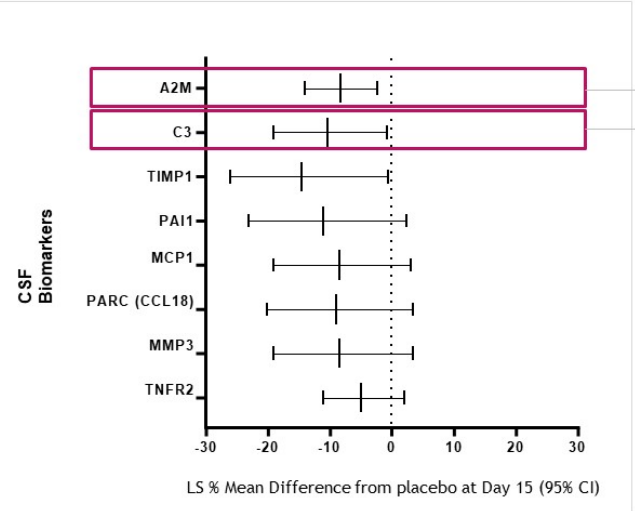
CY6463 improved neuroinflammatory biomarkers



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

- 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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Relevant reference publications (2 of 2)

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)

- Wilcockson et al. Abnormalities of saccadic eye movements in dementia due to Alzheimer's disease and mild cognitive impairment. Aging 2019, Vol.11, No.15
- 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

ADv

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

MELAS

- 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

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