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): **June 10, 2022**

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 June 10, 2022, Cyclerion Therapeutics, Inc. (the "Company") announced topline data from its CY6463 Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes (”MELAS”) study. Copies of the press release and corporate presentation are being furnished as Exhibit 99.1 and Exhibit 99.2, respectively to this Current Report on Form 8-K.

The information contained in Item 7.01 of this Current Report on Form 8-K, Exhibit 99.1 and Exhibit 99.2 attached hereto is intended to be furnished and shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934 (the “Exchange Act”) or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description
99.1	Press Release of Cyclerion Therapeutics, Inc. dated June 10, 2022
99.2	Corporate presentation of Cyclerion Therapeutics, Inc., dated June 10, 2022
104	Cover Page Interactive Data File

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: June 10, 2022

By: /s/ Anjeza Gjino
Name: Anjeza Gjino
Title: Chief Financial Officer

Cyclerion Therapeutics Announces Positive Topline Clinical Data for CY6463 in MELAS Patients at UMDF Mitochondrial Medicine 2022 Symposium

Data from an eight-patient, open-label study demonstrate improvements across multiple biomarkers of mitochondrial function, inflammation, cerebral blood flow, and functional connectivity

CY6463 was well tolerated, with no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs); oral, once-daily administration provided expected CNS exposure

Data support further development of CY6463 in CNS diseases with mitochondrial dysfunction

Cambridge, Mass., June 10, 2022 – Cyclerion Therapeutics, Inc. (Nasdaq: CYCN), a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function, today announced positive topline data in its signal-seeking clinical study of CY6463, for the potential treatment of Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS). Chad Glasser, Pharm.D., Director of Clinical Research at Cyclerion Therapeutics, will present results from this clinical study today during the *Clinical Trial Updates Panel* at the United Mitochondrial Disease Foundation (UMDF) Mitochondrial Medicine 2022 Symposium, taking place June 8-11, 2022, in Phoenix, Arizona.

CY6463 is a positive allosteric modulator of soluble guanylate cyclase (sGC), which amplifies endogenous NO signaling, a pathway that has been linked to mitochondrial biogenesis and function. In this open-label, single-arm study of the oral, once-daily sGC stimulator in eight MELAS patients, improvements were seen across a range of biomarkers, including mitochondrial disease-associated biomarkers such as lactate and GDF-15, a broad panel of inflammatory biomarkers, cerebral blood flow, and functional connectivity between neural networks. These positive effects after 29 days of dosing were supported by correlations across several endpoints and were more pronounced in patients with greater baseline disease burden. A return toward baseline levels after discontinuation of CY6463 dosing across several biomarkers was also observed.

CY6463 was well tolerated with no adverse events leading to treatment discontinuation, and pharmacokinetics (PK) were consistent with the Phase 1 study in healthy volunteers. The positive data from this study further support the potential of CY6463, the first and only CNS-penetrant sGC stimulator in clinical development, to provide therapeutic benefit to people living with MELAS.

“MELAS patients currently have no approved treatment options for a devastating orphan disease that affects multiple organs, including the CNS, skeletal muscle, and eyes,” said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. “We are excited by the strength of these data and consistency across disease domains, which support the further advancement of CY6463 as a potential treatment option.”

Study Highlights:

- The single-arm, open-label study enrolled eight participants who spanned a range of disease burden; 6 of the 8 (75%) were also taking a daily regimen of oral arginine or citrulline, precursors to nitric oxide that are current standard of care for MELAS patients.
- CY6463 was well tolerated; there were no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs).
- The PK profile and concentrations in the cerebrospinal fluid (CSF) and plasma were consistent with exposures observed in Phase 1 healthy volunteer studies.
- Effects were observed across multiple domains of disease activity:
    - Improvements in biomarkers associated with mitochondrial function including lactate and GDF-15. These changes correlated with each other and with CY6463 plasma concentrations
    - Improvements across a broad panel of inflammatory biomarkers
    - Increases in cerebral blood flow across all brain regions. These changes correlated with clinical improvement as assessed by the patient global impression of change (PGIC) scale
    - Increases in functional connectivity between brain regions and activation of occipital brain regions in response to the visual stimulus as measured by fMRI BOLD

“In this study we saw positive impacts on important biomarkers associated with MELAS and other mitochondrial disease following 29 days of once-daily dosing with CY6463,” said Andreas Busch, Ph.D., Chief Scientific Officer at Cyclerion Therapeutics. “These findings are exciting as we think

about the potential of our mechanism in mitochondrial disease and more broadly about the effects of CY6463 on mitochondrial function, which is relevant to numerous CNS diseases, including schizophrenia and Alzheimer's Disease."

A video presentation of the topline data is available on the Investor page of the Cyclerion website. Additional data from the MELAS clinical study will be shared in the coming weeks.

About CY6463

CY6463 is the first CNS-penetrant sGC stimulator to be developed as a symptomatic and potentially disease-modifying therapy for serious CNS diseases. The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway is a fundamental mechanism that precisely controls key aspects of physiology throughout the body. In the CNS, the NO-sGC-cGMP pathway regulates diverse and critical biological functions including neuronal function, neuroinflammation, cellular bioenergetics, and vascular dynamics. Although it has been successfully targeted with several drugs in the periphery, this mechanism has yet to be fully leveraged therapeutically in the CNS, where impaired NO-sGC-cGMP signaling is believed to play an important role in the pathogenesis of many neurodegenerative and neuropsychiatric diseases and other disorders associated with cognitive impairment. As an sGC stimulator, CY6463 acts as a positive allosteric modulator to sensitize the sGC enzyme to NO, increase the production of cGMP, and thereby amplify endogenous NO signaling. By compensating for deficient NO-sGC-cGMP signaling, CY6463 and other sGC stimulators may have broad therapeutic potential as a treatment to improve cognition and function in people with serious CNS diseases.

About the Study

The Phase 2a study was an open-label, single-arm study of oral, once-daily CY6463 in eight adults aged 18 or older with MELAS. The primary objective of the study was to assess the safety and tolerability of a 15 milligram, once-daily, oral dose of CY6463 over 29 days. The secondary objectives included pharmacokinetics, and exploratory pharmacodynamic effects, with the goal of identifying which biomarkers to carry forward into additional studies. The study was not powered for hypothesis testing.

About MELAS

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) is a devastating orphan disease affecting multiple organ systems, including the CNS, with no approved

therapies. It is the most common form of primary mitochondrial diseases (PMD). MELAS is phenotypically and genetically defined by a mutation in mitochondrial tRNA. It is estimated that about 1 in 4,300 individuals has a mitochondrial disease, and ~80% of individuals with mitochondrial disease have CNS symptoms. The unmet need in MELAS is immense, symptoms include, chronic fatigue, muscle weakness, and pain in addition to neurological manifestations. Life expectancy is estimated at ~17 years from onset of CNS symptoms. The disease impedes the individual's ability to live independently, leads to social isolation, and overall reduced quality of life.

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 Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS), Cognitive Impairment Associated with Schizophrenia (CIAS) and Alzheimer's Disease with Vascular pathology (ADv). Cyclerion is also advancing CY3018, a next-generation sGC stimulator.

Forward Looking Statement

Certain matters discussed in this press release are "forward-looking statements". We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should", "positive" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company's statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing or future clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials, futility analyses and receipt of interim results, which are not necessarily indicative of or supported by the final results of our ongoing or subsequent clinical trials; any results of clinical studies, including in particular single-arm open-label studies involving a number of patients that is not statistically significant such as described in this release, not necessarily being indicative of or supported by the final results of our ongoing or subsequent clinical trials; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory

authority approval of, or other action with respect to, our product candidates; the potential for the CY6463 clinical trial to provide a basis for approval for treatment of MELAS; the Company's ability to successfully defend its intellectual property or obtain necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the success of the Company's license agreements; the acceptance by the market of the Company's product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within the Company's control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

For more information about Cyclerion, please visit cyclerion.com and follow us on Twitter and LinkedIn.

Investors
Carlo Tanzi, Ph.D.
Kendall Investor Relations
ctanzi@kendallir.com

Media
Amanda Sellers
Verge Scientific Communications
asellers@vergescientific.com

Exhibit 99.2

THINKING DIFFERENTLY ABOUT COGNITION

CORPORATE PRESENTATION
JUNE 2022

Safe harbor statement

This presentation is for informational purposes only and is not an offer to sell nor a solicitation of an offer to buy any securities of Cyclerion Therapeutics, Inc. (the "Company"). This presentation includes or may include certain information obtained from trade and statistical services or sources, third party publications and other sources. The Company has not independently verified such information and there can be no assurance as to its accuracy.

Certain matters discussed in this presentation are "forward-looking statements". We may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "positive," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company's statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing or future clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials, futility analyses and receipt of interim results, which are not necessarily indicative of or supported by the final results of our ongoing or subsequent clinical trials; any results of clinical studies, including in particular single-arm open-label studies involving a number of patients that is not statistically significant such as described in this presentation, not necessarily being indicative of or supported by the final results of our ongoing or subsequent clinical trials; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory authority approval of, or other action with respect to, our product candidates; the potential for the CY6463 clinical trial to provide a basis for approval for treatment of MELAS; the Company's ability to successfully defend its intellectual property or obtain necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the success of the Company's license agreements; the acceptance by the market of the Company's product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within the Company's control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

Other important factors that could cause actual results to differ from those reflected in any forward-looking statements herein are described in the Company's most recent Form 10-K as well as the Company's subsequent filings with the Securities and Exchange Commission (the "SEC"). All of the Company's development plans may be subject to adjustment depending on funding, recruitment rate, regulatory review, preclinical and clinical results, and other factors any of which could result in changes to the Company's development plans and programs or delay the initiation, enrollment, completion, or reporting of clinical trials.

In addition to the risks described above and in the Company's filings with the SEC, other unknown or unpredictable factors could affect the Company's results. No froward-looking statements can be guaranteed, and actual results may materially differ from such statements. The information in this presentation is provided only as of June 10, 2022, and the Company undertakes no obligation to update any forward-looking statements contained in this presentation on account of new information, future events, or otherwise, except as required by law.

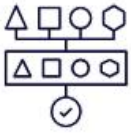
Developing therapies to restore cognitive function

Experienced team of scientific leaders, drug hunters, company builders, and CNS experts

- Developed and launched first-in-class therapies
- Raised billions in capital
- Built leading strategic partnerships

Neuroinnovation engine enables faster, more precise drug development

- Identifying most promising patient populations early
- Developing disease and mechanism specific translational biomarkers
- Continuously refining signal-to-noise



Advancing CY6463, potential breakthrough, first-in-class CNS therapy

- Improvement trends in MELAS patients across biomarkers of mitochondrial function, inflammation, cerebral blood flow and functional connectivity
- CIAS study results expected in Q3'22; ADv study actively enrolling
- Evaluating collaborative development opportunities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NEUROINNOVATION
ENGINE

Efficiently developing drugs that matter

Leverage **deep understanding** of brain biology, pathobiology of cognitive dysfunction and small molecule mechanisms

Partner with academic and industry leaders to access leading-edge data and technologies

Apply **advanced analytics** to robust multimodal nonclinical and clinical data sets to extract actionable insights

Identify most promising patient populations early, increase signal-to-noise ratio

Cyclerion neuroinnovation engine de-risks development at every stage

Scientific insights & unmet need

MOA & biomarker-driven non-clinical validation
Identify mechanism- and disease-relevant biomarkers

Late-stage development and approval
Select the right patient, right dose, right endpoint

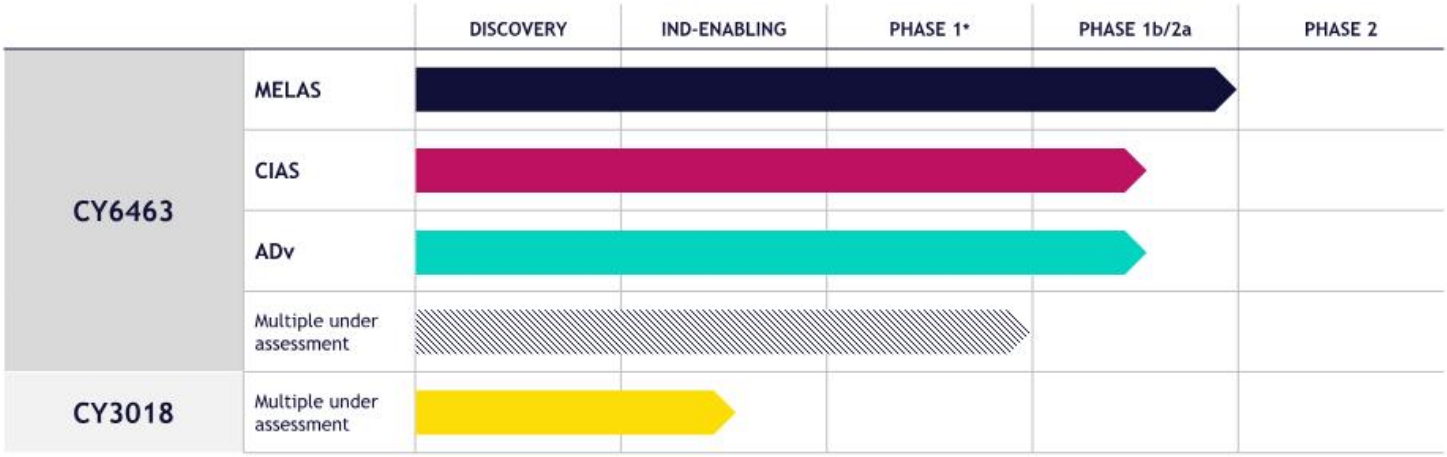
Proof of principle; first-in-human biomarker translation
Validate homologous physiological response to drive clinical development

Proof of concept; Accelerate and de-risk
Inform larger, longer studies

Proof of mechanism; biomarker-guided, signal-seeking studies in patients
Refine indication and patient selection aided by advanced analytics


cyclerion
DEPLOYING OUR
NEUROINNOVATION ENGINE

Advancing parallel clinical studies in priority populations



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

CY6463 amplifies the fundamental NO-sGC-cGMP signaling pathway

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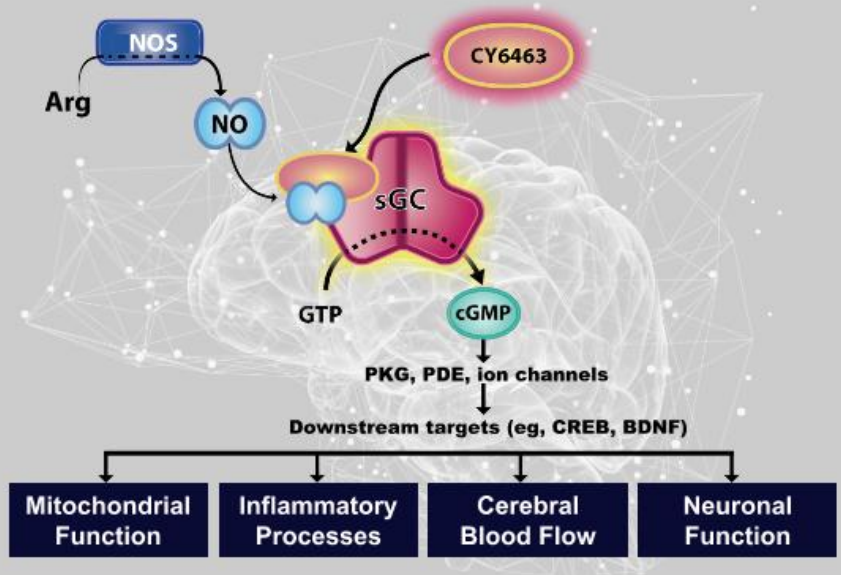
Scientific insights & unmet need | MOA & biomarker-driven non-clinical validation | First-in-human biomarker translation | Biomarker-guided, signal-seeking studies in patients



CY6463

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

sGC stimulators clinically validated in several non-CNS indications

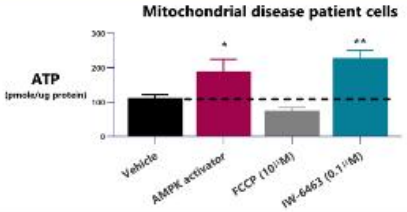
Preclinical data and extensive academic work validate the crucial role of the NO-sGC-cGMP pathway in brain physiology

Important role in learning and memory

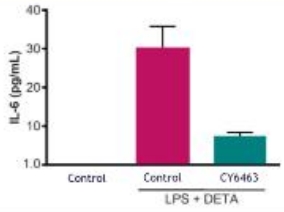
CY6463 improves processes relevant to cognition in preclinical models

Scientific insights & unmet need | **MOA & biomarker-driven non-clinical validation** | First-in-human biomarker translation | Biomarker-guided, signal-seeking studies in patients

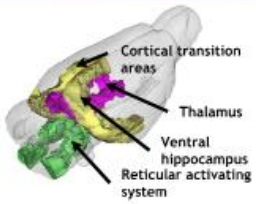
Mitochondrial Function



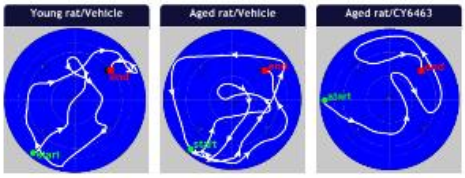
Inflammatory Processes



Cerebral Blood Flow



Neuronal/Cognitive Function



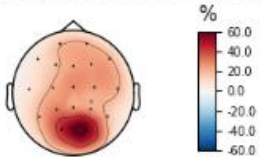
CY6463 showed rapid improvement in biomarkers associated with cognitive function

Scientific insights & unmet need | MOA & biomarker-driven non-clinical validation | **First-in-human biomarker translation** | Biomarker-guided, signal-seeking studies in patients

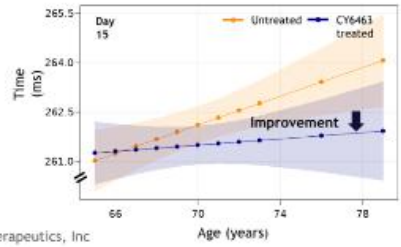
In a 15-day study in 24 healthy elderly subjects, CY6463 demonstrated:

Increased alpha and gamma power

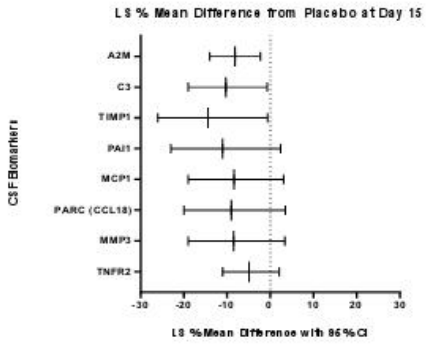
Alpha power: CY6463 vs. placebo



Improved N200 latency



Reduced neuroinflammatory biomarkers



Biomarker-guided strategy to refine target populations with cognitive impairment

Scientific insights & unmet need | MOA & biomarker-driven non-clinical validation | First-in-human biomarker translation | **Biomarker-guided, signal-seeking studies in patients**

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

MELAS — Mitochondrial Disease

CIAS — Neuropsychiatric

Neurodegenerative — ADv

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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MELAS
STUDY RESULTS

MELAS clinical data demonstrate that CY6463 has potential as breakthrough CNS therapeutic

MELAS

- Devastating genetically and phenotypically defined mitochondrial disease (MD) with no approved therapies

CY6463

- Positive allosteric modulator of sGC which amplifies endogenous NO signaling

Study design

- Open label, 29-day study of once-daily, oral, CY6463 (n=8)

Improvement observed across important biomarkers associated with MELAS after CY6463 treatment

- Well tolerated with no serious adverse events or treatment discontinuation
- Oral once-daily administration provided expected CNS exposure
- Improvements observed across multiple domains of disease activity:
  - Biomarkers associated with **mitochondrial function**, including lactate and GDF-15
  - Broad panel of **inflammatory biomarkers** with the potential to translate to CNS diseases with mitochondrial dysfunction
  - **Cerebral blood flow (CBF)** across all brain regions
  - **Functional connectivity** between brain regions and **activation of occipital brain regions** in response to the visual stimulus as measured by fMRI BOLD
- Supported by correlations across several endpoints and more pronounced in patients with heavier baseline disease burden
- Return toward baseline levels observed across several biomarkers after dosing discontinuation

MELAS*: devastating orphan disease affecting multiple organ systems, no approved therapies

Orphan disease

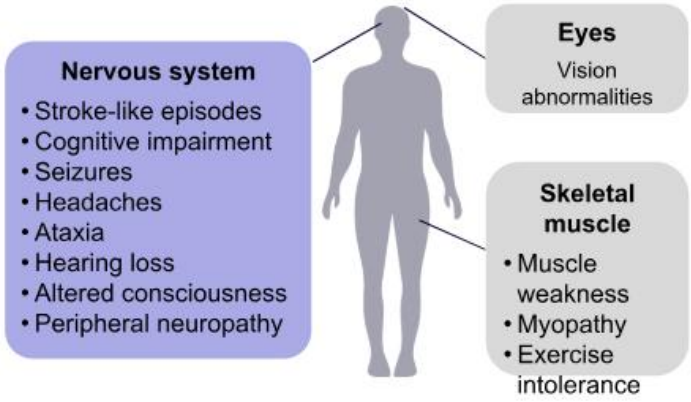
- MELAS is most common form of primary mitochondrial disease (PMD)
- Phenotypically and genetically defined (mutation in mitochondrial tRNA)
  - ~10-20k MELAS patients (US)
  - ~65k PMD patients (US)

Tremendous unmet need

- Life expectancy ~17 years from onset of CNS symptoms
- Chronic fatigue, muscle weakness, and pain in addition to neurological manifestations
- Impedes ability to live independently
- Social isolation, and reduced quality of life

Multisystem involvement

>80% of patients have CNS symptoms



*MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis, & Stroke-like Episodes

Strong therapeutic rationale for stimulating NO-sGC-cGMP pathway to treat mitochondrial disease

- CY6463 is a positive allosteric modulator of sGC and amplifies endogenous NO signaling
- Literature links NO-sGC-cGMP pathway to mitochondrial biogenesis and function
- NO deficiency in mitochondrial disease has been linked to impaired blood flow, inflammation, angiopathy, and endothelial dysfunction
- Use of NO precursors recommended by Mitochondrial Medicine Society
- CYCN preclinical data demonstrate CY6463 affects multiple aspects of mitochondrial disease pathophysiology

Open-label, 29-day study of CY6463 in MELAS patients to assess safety, PK, PD and impact on important domains of mitochondrial disease

Study population (n=8)	Genetically confirmed with history of CNS symptoms such as stroke, seizure, headache Stable medications including NO precursors (e.g., arginine and citrulline) permitted (6 of 8)
Safety	Safety and tolerability profile with 15-mg QD dosing Safety on top of NO precursors and other stable medications
PK	Plasma and, when available, cerebrospinal fluid (CSF) concentrations of CY6463
CNS/PD	**Measures of key domains of MELAS** • Mitochondrial function • Inflammatory processes • Cerebral blood flow • Neuronal/cognitive function • Patient-reported outcomes (PROs)

Strong safety/tolerability and once-daily profile extended to participants with MELAS

CY6463 well tolerated with and without NO precursors (L-arginine and L-citrulline)

- Mostly mild adverse events (AEs), no severe AEs
- No SAEs, no discontinuations due to AEs
- Most common AE was headache, all but 1 mild
- No signals on clinical labs, vital signs, ECGs, or suicidal rating scale

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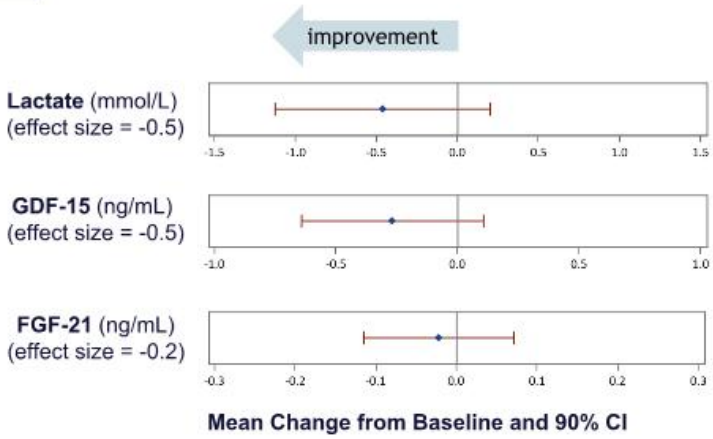
Once-daily dosing with consistent pharmacokinetics

- Pharmacokinetics (AUC_{tau}, C_{max}, and C_{trough}) in MELAS participants consistent with PK studies in healthy volunteers
- Confirmed CNS exposure with CSF:plasma ratio consistent with that observed in healthy volunteers

Improvement in biomarkers of mitochondrial function that are affected in MELAS disease



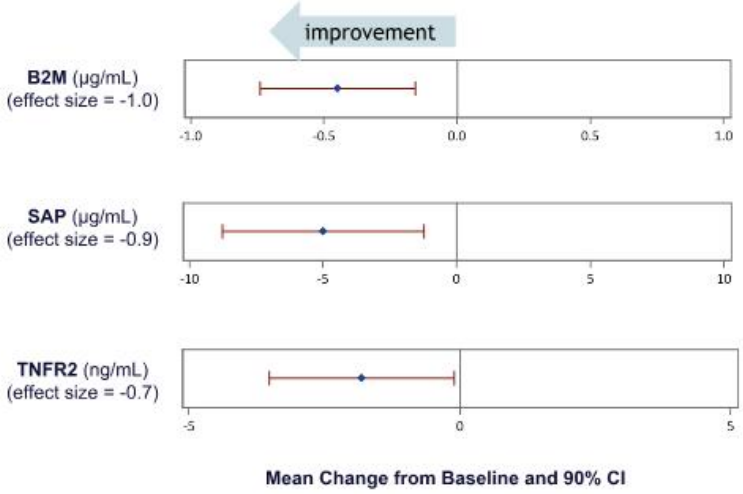
Mitochondrial function effects

- Blood biomarkers linked to mitochondrial function were elevated at baseline across participants (mean)
- Improvement after 29-day dosing supported by correlations between blood biomarkers and CY6463 plasma concentrations

GDF-15: Growth/Differentiation Factor-15; FGF-21: Fibroblast Growth Factor-21

Broad improvement of inflammatory biomarkers

Biomarkers with effect size |value|≥0.7



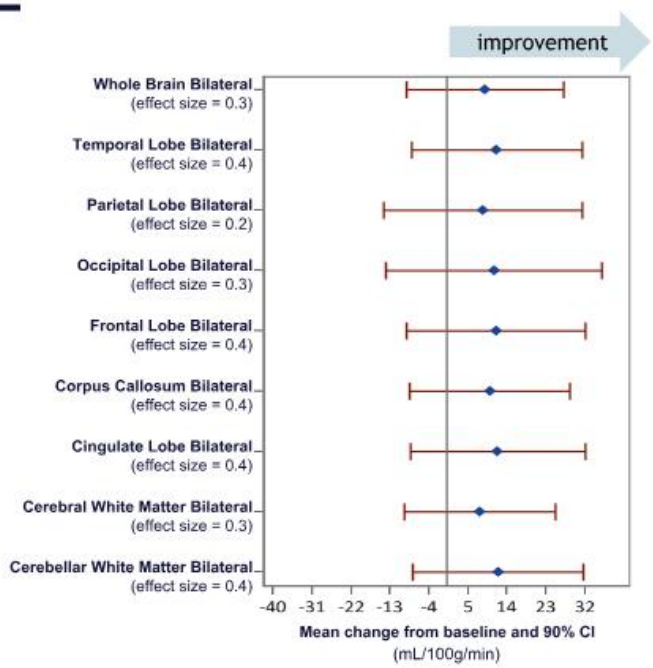
Mean Change from Baseline and 90% CI

Anti-inflammatory effects

- ~65% of 40 inflammatory biomarkers with effect sizes |value|≥0.3
- Central and peripheral inflammation is upregulated in patients with mitochondrial dysfunction

B2M: Beta-2-Microglobulin; SAP: Serum Amyloid P-Component; TNFR2: Tumor Necrosis Factor Receptor 2

Increased cerebral blood flow across all regions analyzed



Blood flow effects

- Neuronal and/or glial injury due to mitochondrial failure, nitric oxide deficiency and cerebrovascular angiopathy reduce cerebral blood flow
- Dysregulated cerebral blood flow is linked to stroke-like episodes and CNS symptoms

CY6463 enhanced functional connectivity and visual activation in CNS, which is impaired in MELAS

Task-free fMRI (resting state) shows enhanced functional connectivity: Increased signals across several resting state networks including those involved in:

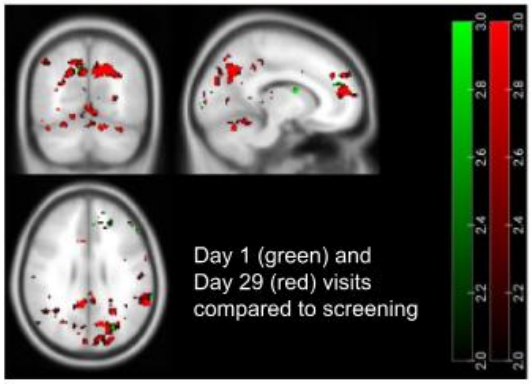
- executive function
- sensorimotor processing

Task-based fMRI (visual activation) shows occipital region activation by CY6463

- fMRI BOLD response to visual stimulus is markedly reduced in symptomatic MELAS compared to controls (Rodan et al 2020)
- CY6463 increased activation of occipital brain regions in response to the visual stimulus, with greater activation at Day 29 compared to screening and Day 1

Additional analyses of imaging data ongoing
n=6 (fMRI data collected at one site were not analyzable)

Task-based fMRI visual activation



Whole-brain voxelwise statistical parametric maps (SPM) of task-fMRI visual activation at day 1 (green) and day 29 (red) visits compared to screening. Maps thresholded a t = 2.0 for exploratory visualization.

Improvements after 29-day dosing supported by correlation across endpoints

Correlations (r) between changes in blood biomarkers and plasma concentrations

Biomarker parameters	Fibroblast growth factor 21	Growth differentiation factor 15	Lactate	Trough plasma concentration
Fibroblast growth factor 21	1.00			
Growth differentiation factor 15	0.86	1.00		
Lactate	0.74	0.87	1.00	
Trough plasma concentration	-0.75	-0.68	-0.41	1.00

Correlations (r) between CBF and clinical improvement as assessed by the patient global impression of change (PGIC)

ASL parameters	CEREBELLAR WHITE MATTER	CEREBRAL WHITE MATTER	CINGULATE LOBE	CORPUS CALLOSUM	FRONTAL LOBE	OCCIPITAL LOBE	PARIETAL LOBE	TEMPORAL LOBE	WHOLE BRAIN
PGIC	-0.65	-0.85	-0.90	-0.78	-0.82	-0.75	-0.79	-0.85	-0.84

Darker greens are correlations ≥0.8 (very strong)
Lighter greens are correlations ≥0.6 but <0.8 (strong)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ONGOING
CLINICAL TRIALS

CIAS study ongoing; data expected Q3 2022

Scientific insights & unmet need | MOA & biomarker-driven non-clinical validation | First-in-human biomarker translation | **Biomarker-guided, signal-seeking studies in patients**

Objectives	Exploratory, signal-seeking study to evaluate safety, tolerability, and pharmacodynamic effects (qEEG, ERP, digital cognitive performance battery)
Study design	• In-clinic, randomized, placebo-controlled, double-blind, multiple-ascending-dose design • 14-day treatment with Once-daily CY6463 or placebo • 48 participants across 4 sequential cohorts
Patient targeting	• Psychiatrically stable adults with schizophrenia, no more than moderate symptoms • On stable, single antipsychotic regimen
Collaborations	• Study conducted at experienced, partner sites: Hassman Research Institute and Collaborative Neuroscience • Exploratory, AI-driven, integrated analysis of data with Ariana Pharma

ADv study ongoing

Scientific insights & unmet need | MOA & biomarker-driven non-clinical validation | First-in-human biomarker translation | **Biomarker-guided, signal-seeking studies in patients**

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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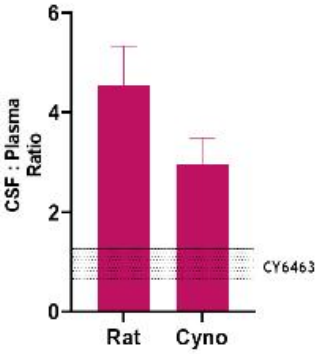
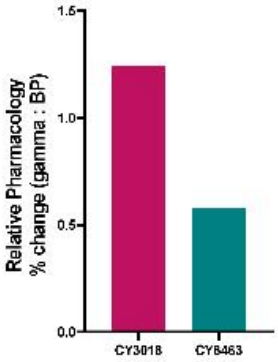
NEXT-GENERATION
sGC STIMULATOR
PROGRAM

Applying the neuroinnovation engine to CY3018 – a differentiated sGC stimulator

Greater relative CNS exposure



Greater relative CNS pharmacology



Scientific insights & unmet need

- Demonstrated a positive effect on cognition in primates
- Currently exploring the impact of CY3018 in preclinical models
- Expected to be a once-daily oral therapy

MOA & biomarker-driven non-clinical validation

- In mice, rats, and non-human primates, CY3018 has greater partitioning into the brain than CY6463
- CY3018 elicited unique patterns of activation and deactivation in rodent imaging studies demonstrating differentiation from other sGC stimulators
- IND-enabling activities are on track for end-of-year completion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TRACK RECORD OF
SUCCESS

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Vice President, Clinical Strategy

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Vice President, Information Technology & Facilities

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Vice President, Pharmaceutical Development

Chris Winrow, PhD
Vice President, Translational Medicine & Development Program Lead

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Lyrica Pregabalin

Belsomra (suvorexant) IV

bridion (sugammadex) injection

Nayzilam (midazolam) nasal spray

GEMTESA (vibegron) 75 mg tablets

Zyprexa IntraMuscular Olanzapine for Injection

technivie ombitasvir, paritaprevir and ritonavir tablets

Adempas riociguat

Verquvo vericiguat

Experienced Board of Directors and Scientific Advisors

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University of Rome

Andrew E. Budson, MD

VA Boston Healthcare System

Boston University

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Mark Currie, PhD

Ironwood Pharmaceuticals

Science Exchange

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AavantiBio

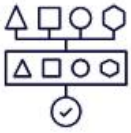
Developing therapies to restore cognitive function

Experienced team of scientific leaders, drug hunters, company builders, and CNS experts

- Developed and launched first-in-class therapies
- Raised billions in capital
- Built leading strategic partnerships

Neuroinnovation engine enables faster, more precise drug development

- Identifying most promising patient populations early
- Developing disease and mechanism specific translational biomarkers
- Continuously refining signal-to-noise



Advancing CY6463, potential breakthrough, first-in-class CNS therapy

- Improvement trends in MELAS patients across biomarkers of mitochondrial function, inflammation, cerebral blood flow and functional connectivity
- CIAS study results expected in Q3'22; ADv study actively enrolling
- Evaluating collaborative development opportunities

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APPENDICES

Preclinical, Phase 1 and translational pharmacology studies, references


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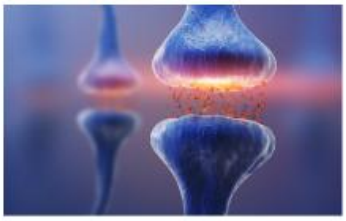
PRECLINICAL
DATA

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

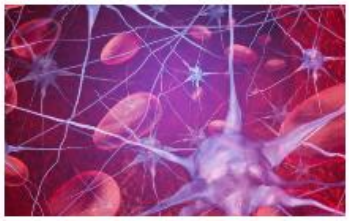
Cellular Bioenergetics

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



CY6463 improved neuronal function

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

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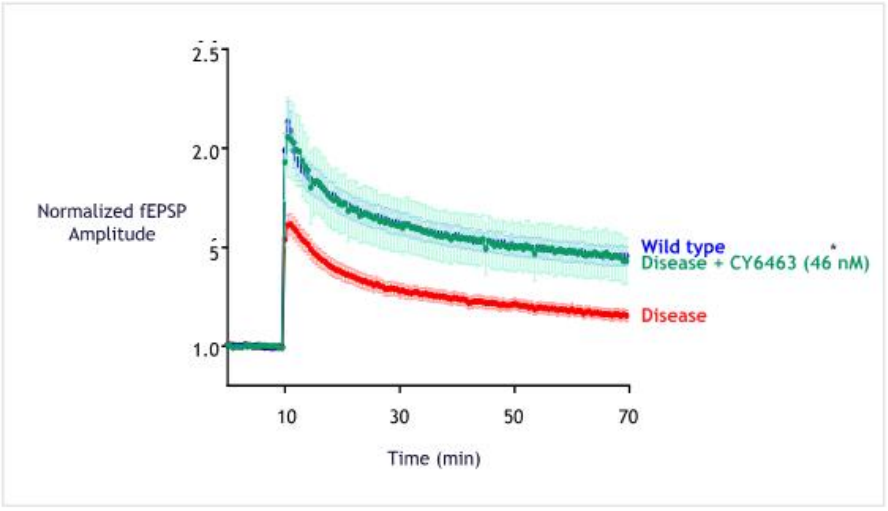
Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | Improve Cerebral Blood Flow



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

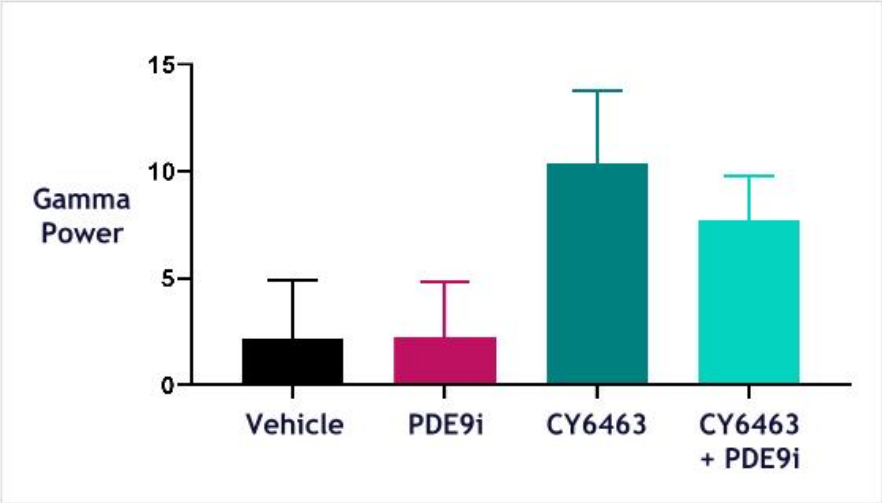
Hippocampal slices from symptomatic Huntington's Disease (R6/2) mice incubated with CY6463 for 25-30 minutes before LTP induction

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

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



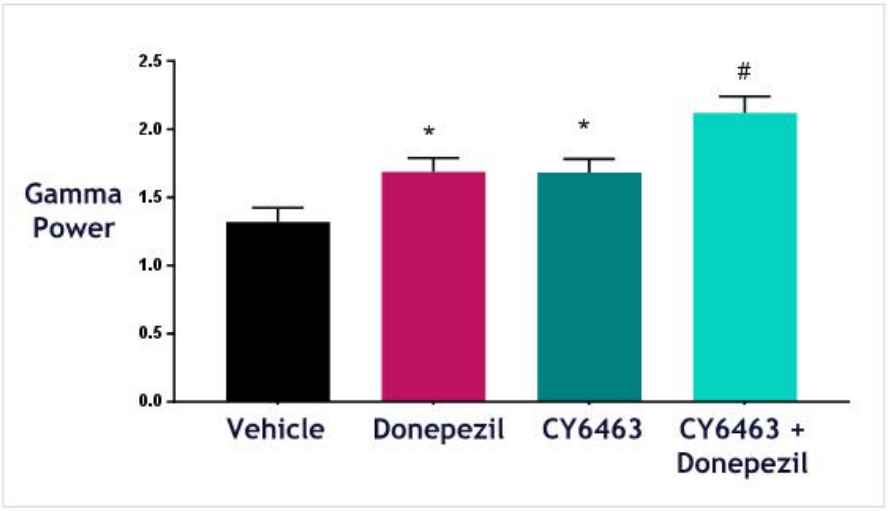
CY6463 is differentiated from PDE9 inhibitor, which showed no effect on gamma power

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

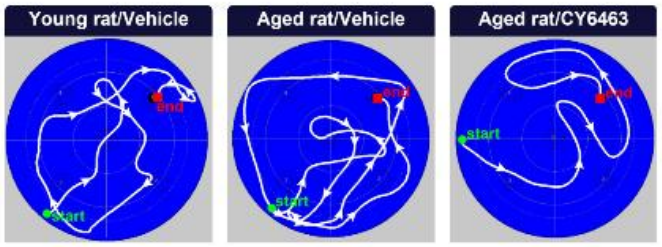
# p<0.05 CY6463 vs CY6463 +Donepezil

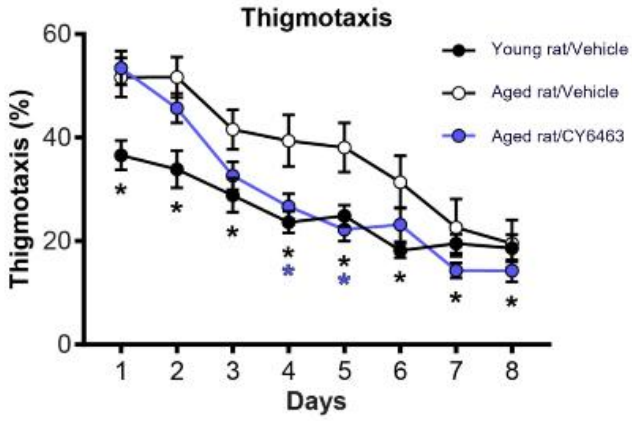
Healthy rats orally administered CY6463 (10mg/kg), Donepezil (1mg/kg), or a combination. Graph displays 1-2h post-dose, mean ± SEM

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

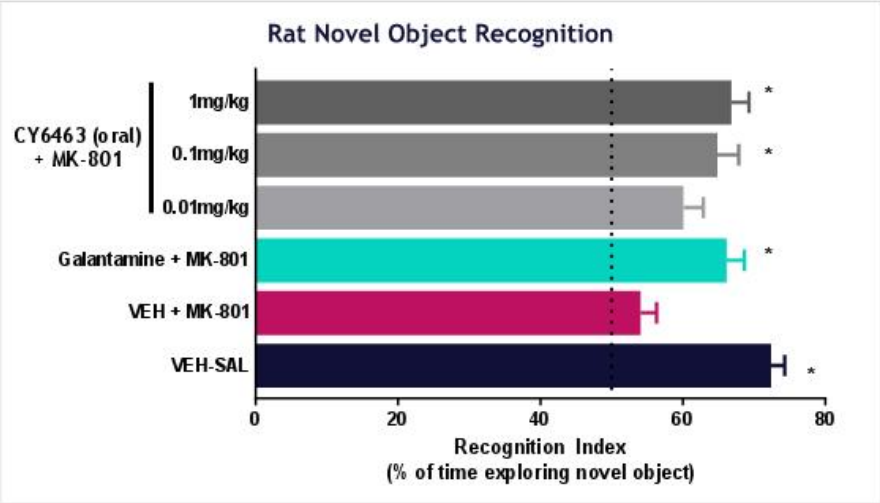




*p<0.05 vs. Aged vehicle-treated

CY6463 improved cognitive function in pharmacologically impaired rats

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



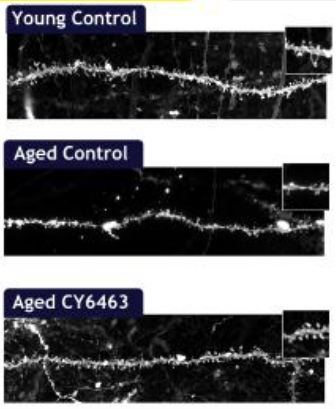
CY6463 acts downstream of NMDA receptor to reverse deficit induced by NMDA antagonist (MK-801)

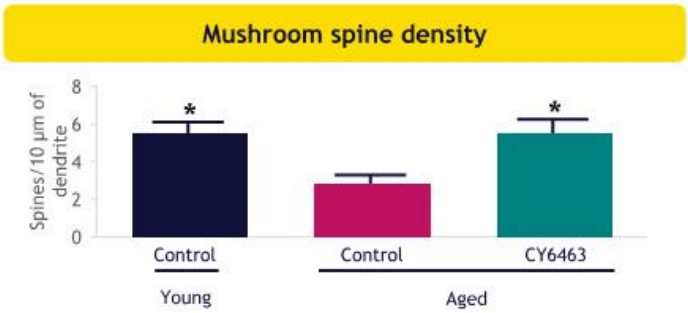
*p<0.05 vs. VEH + MK-801 rats

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*

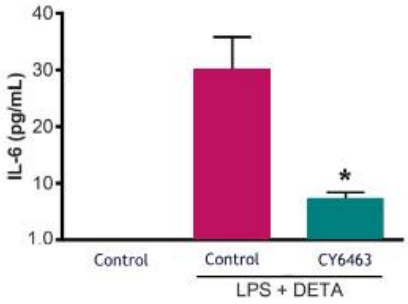
3-month old (young) or 16-month old (aged) healthy mice at study initiation
Aged mice treated for 4 months with 1 mg/kg CY6463

CY6463 reduced neuroinflammation

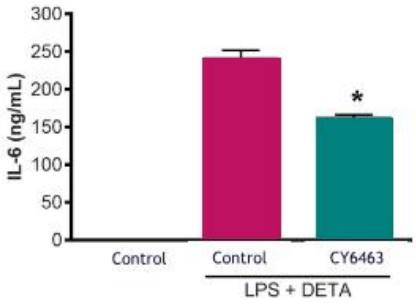
Inhibited in vitro LPS-induction of biomarkers of neuroinflammation

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

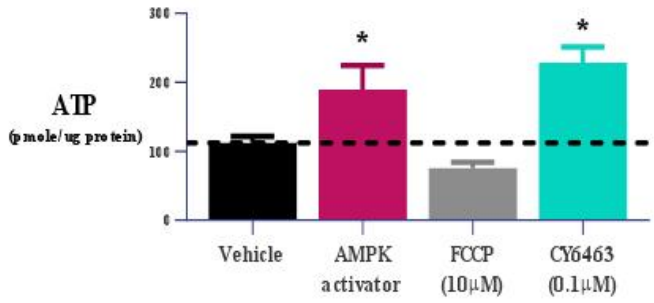
CY6463 (10 µM) and DETA (30 µM) were incubated with SIM-A9 cells or rat brain 3D microtissues for 30 minutes before LPS (100 ng/ml) incubation and further incubated for 18-20h at 37 °C before IL-6 quantification in the media

CY6463 enhanced cellular bioenergetics

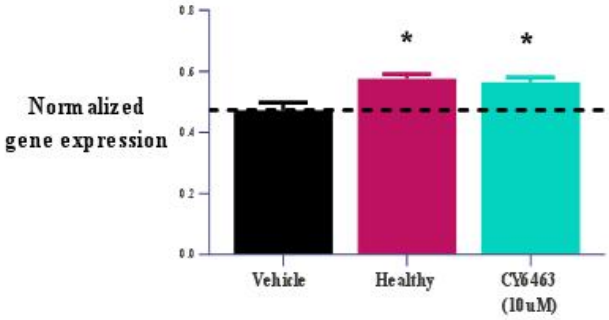
Increased ATP and restored decreased gene expression in cells from patients with mitochondrial diseases

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

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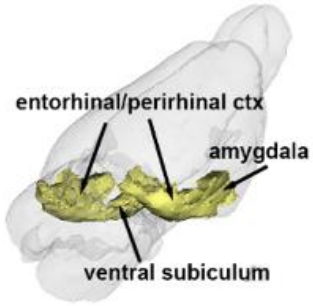
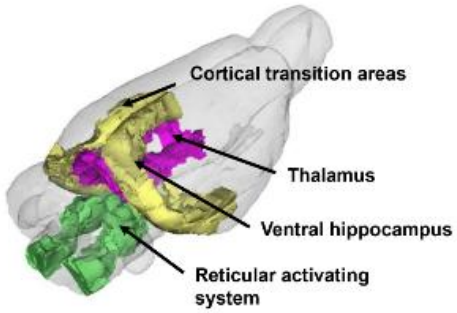
Improve Neuronal Function | Reduce Neuroinflammation | Enhance Cellular Bioenergetics | **Improve Cerebral Blood Flow**

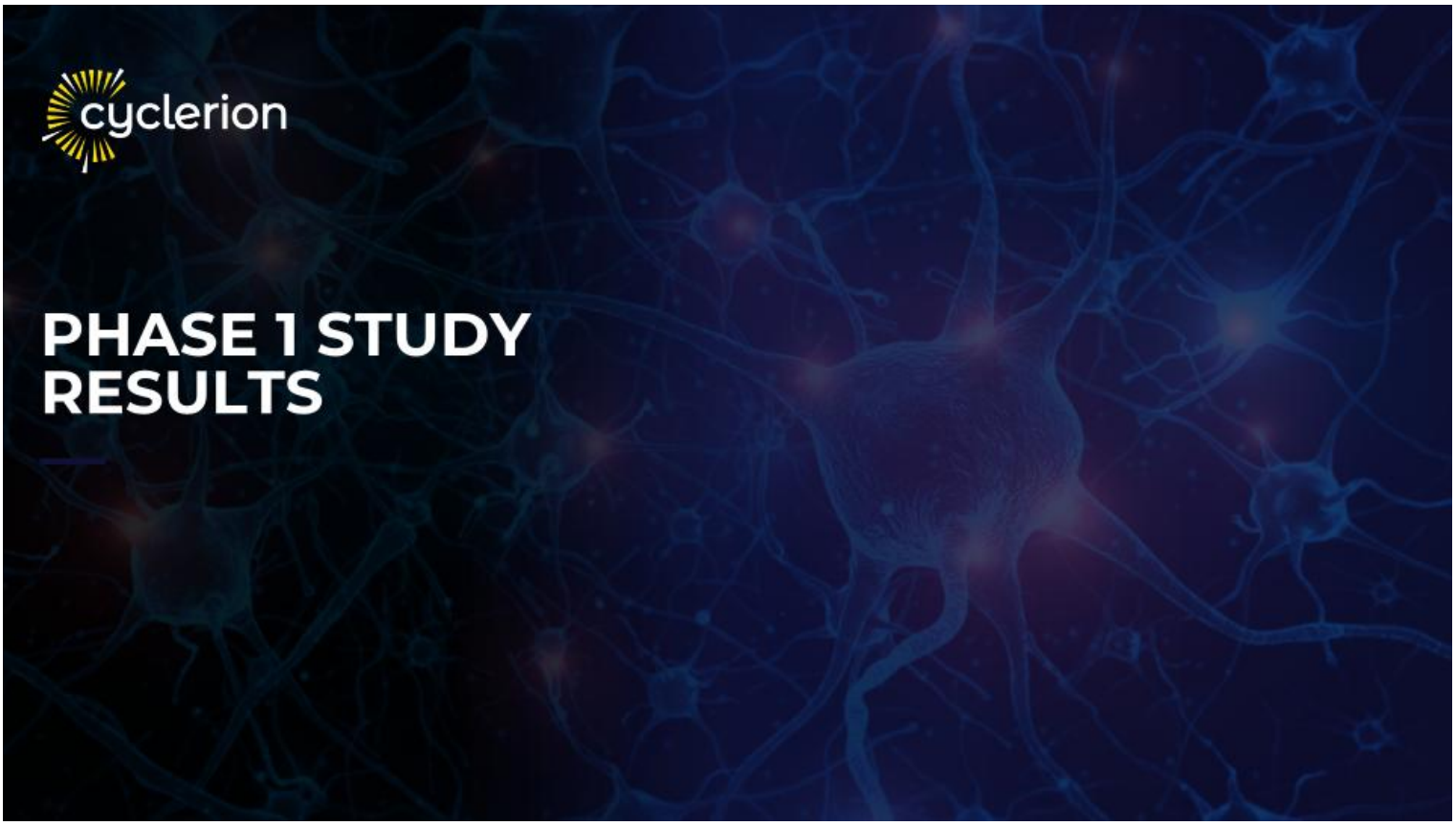
Peripherally restricted sGC stimulator



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

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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 ~~co~~gnitive 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 (Aß, 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

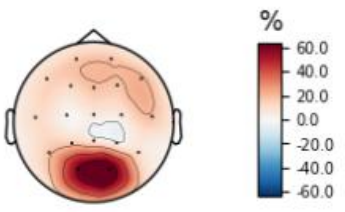
qEEG is quantitative electroencephalography, an objective method that measures electrical activity and brain wave patterns

CY6463 improved qEEG measures: significant ~~inc~~rease in alpha power

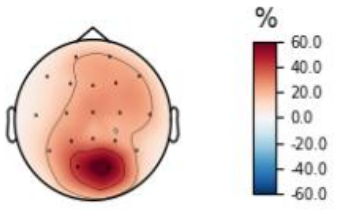
Significant increase in EEG alpha power

No effect of placebo

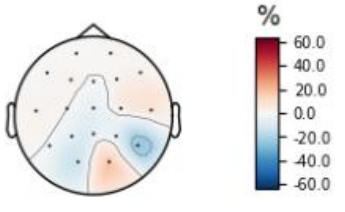
CY6463 vs. baseline



CY6463 vs. placebo



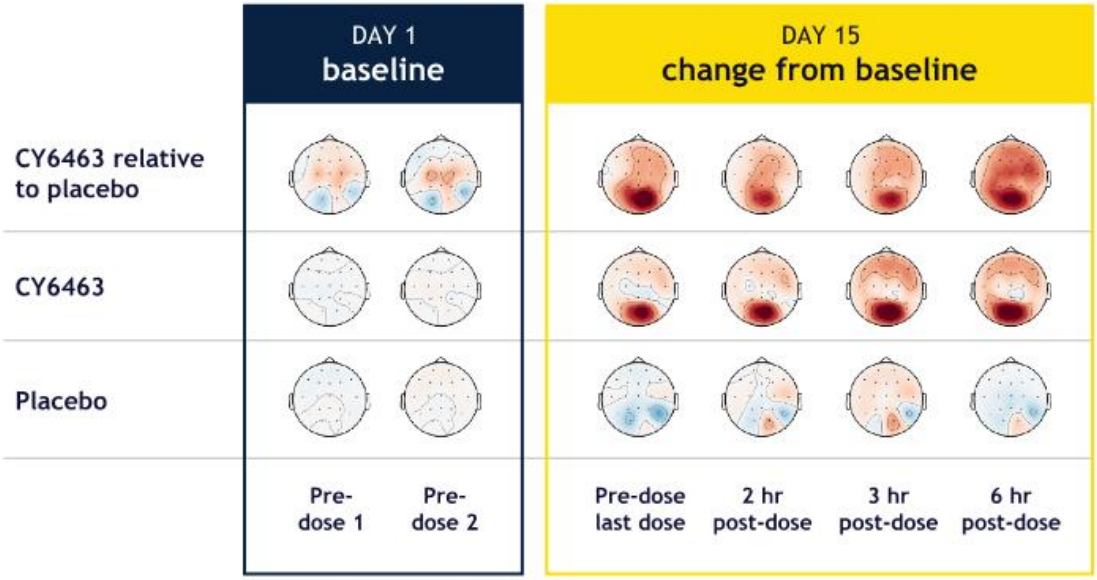
Placebo vs. baseline

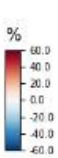


change (%) in alpha power on day 15

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





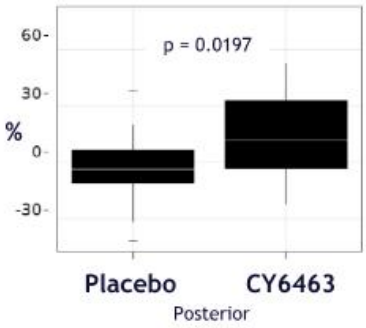
Magnitude of improvement equivalent to decline seen after 2 years of aging

Footer

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

Increase in alpha power

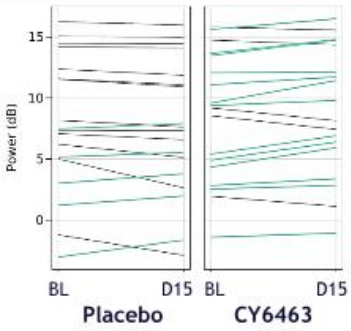
Day 15 change from baseline in mean closed-eye alpha (8-12 Hz) Power



- 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

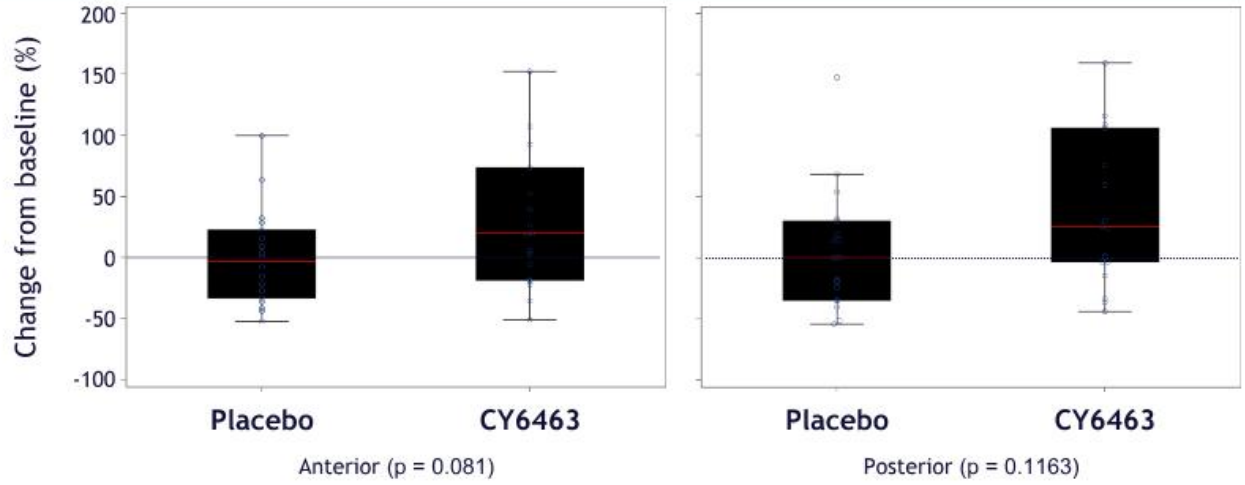


- 13/18 participants increase with CY6463, vs 5/18 with placebo[1]
- Overall effect not driven by outliers

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

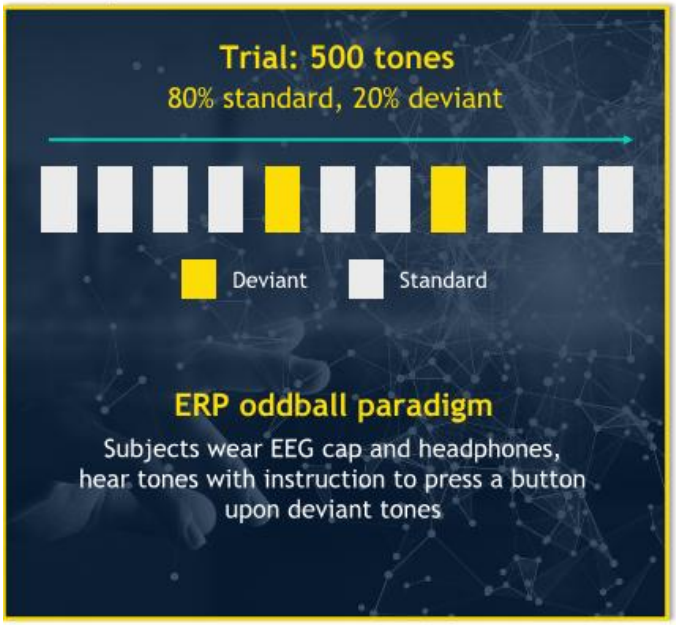
Change in Closed-Eye Gamma (25-45 Hz) Power

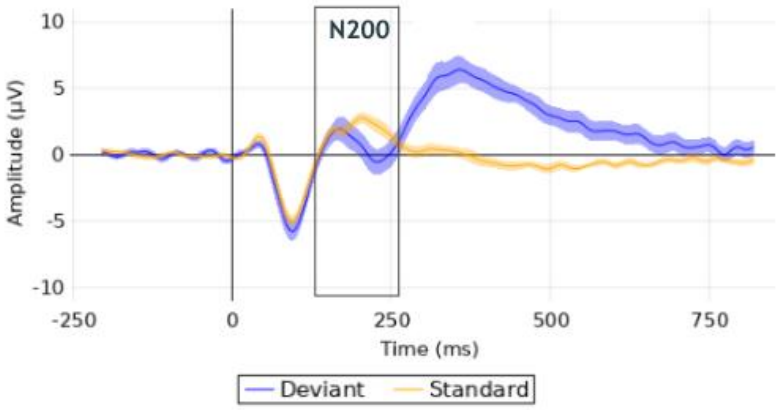


Anterior (p = 0.081)

Posterior (p = 0.1163)

Biomarker overview: event-related potential (ERP)





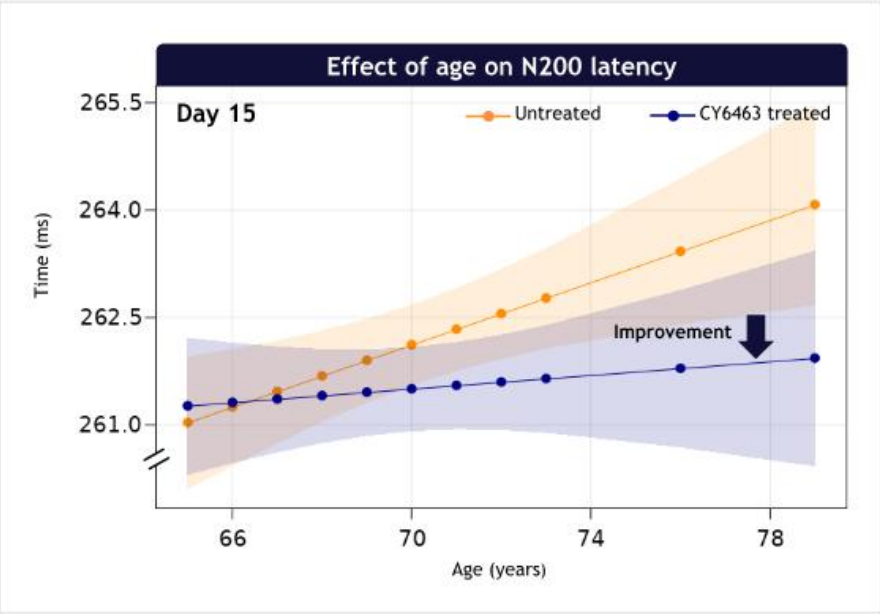
N200

- 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

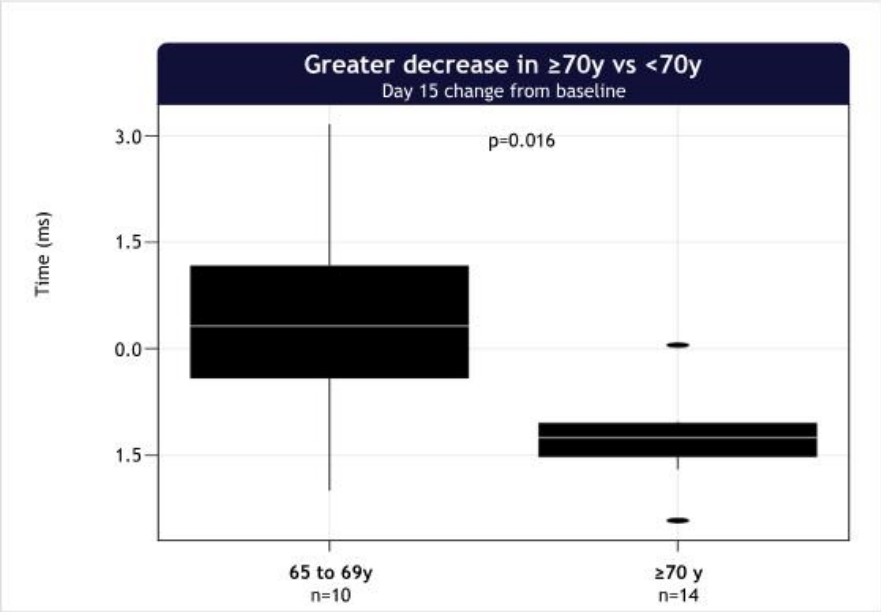
CY6463 improved N200 latency and effect increased with age



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

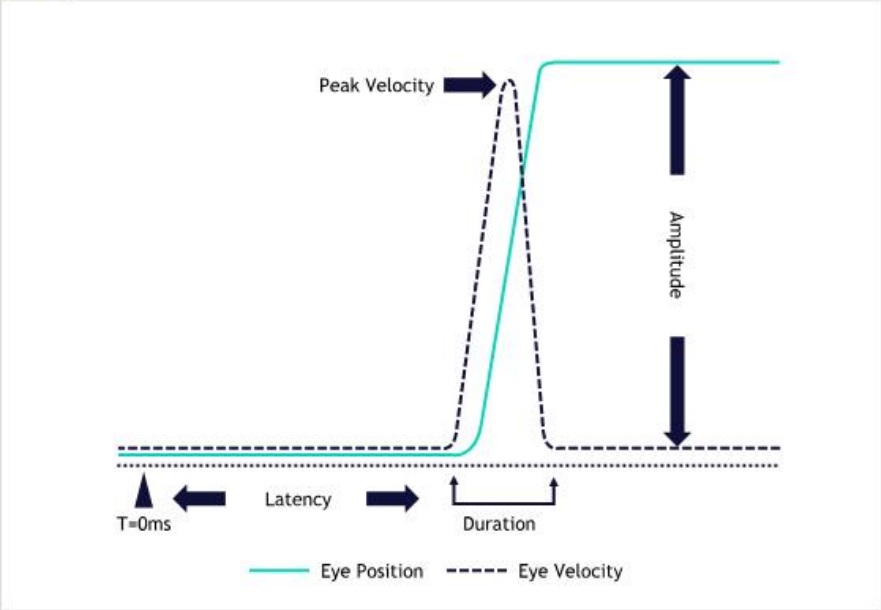


Latency response was greater in subjects ≥70y vs 65-69y (p=0.016)

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

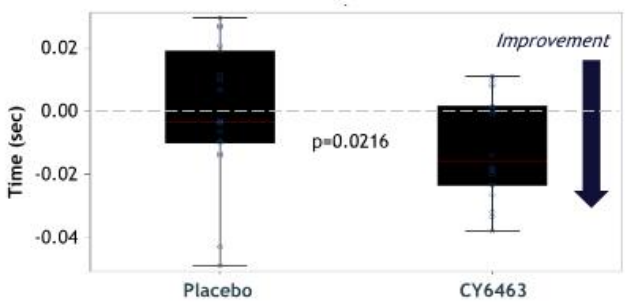


- Short, fast, simultaneous tracking of both eyes in the same direction
- Brain areas involved include the frontal cortex, superior colliculus, substantia nigra, and amygdala
- Considered to be reflective of attention / arousal and influenced by motivation, time on task, and task difficulty
- Sensitive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

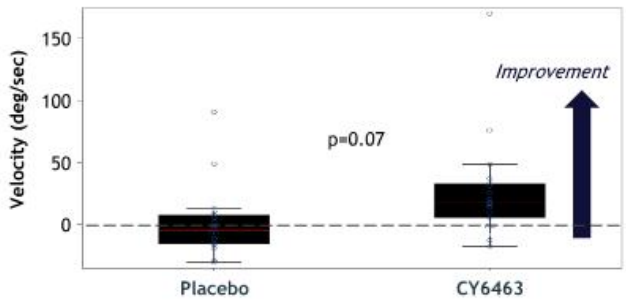
https://www.liverpool.ac.uk/~pcknox/teaching/Eymovs/params.htm

CY6463 improved saccadic eye movement, an objective functional measure

Decrease in saccadic reaction time



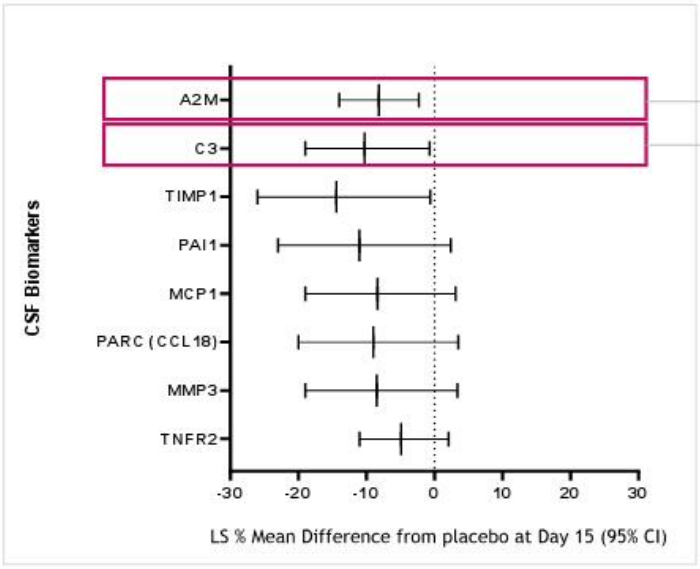
Increase in saccadic peak velocity



- 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

- 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

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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