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): **July 28, 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 July 28, 2022, Cyclerion Therapeutics, Inc. (the "Company") announced topline data from its CY6463 Cognitive Impairment Associated with Schizophrenia (”CIAS”) study. Copies of the press release and CIAS clinical data 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 July 28, 2022
99.2	CIAS Clinical Data Presentation of Cyclerion Therapeutics, Inc., dated July 28, 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: July 28, 2022

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

Cyclerion Therapeutics Announces Positive Topline Clinical Data for CY6463 in Patients with Cognitive Impairment Associated with Schizophrenia (CIAS)

Study data demonstrate positive effects of CY6463 on cognition and inflammation after two weeks of dosing in patients with stable schizophrenia on standard of care

Oral, once-daily CY6463 was well tolerated, with no reports of serious adverse events (SAEs) or treatment discontinuation due to adverse events (AEs)

Data demonstrate the translation of sGC multi-dimensional pharmacology and the therapeutic potential of amplifying sGC signaling in the CNS and support the further development of oral, once-daily CY6463

Company to discuss data during live webinar today at 8:00 a.m. EDT

CAMBRIDGE, Mass., July 28, 2022 (GLOBE NEWSWIRE) -- 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 from its clinical study of CY6463 for the treatment of Cognitive Impairment Associated with Schizophrenia (CIAS) in individuals with stable schizophrenia on a stable, single, atypical antipsychotic regimen. Data from the 14-day, double-blind, randomized, placebo-controlled, multiple-ascending-dose study demonstrate that once-daily CY6463 was safe and well tolerated, with no reports of serious adverse events (SAEs), severe adverse events (AEs), or treatment discontinuation due to AEs. Study data demonstrate a strong effect on cognitive performance after two weeks of 15mg once-daily dosing. A broad positive movement on inflammatory biomarkers was also observed. These signals on exploratory endpoints provide further evidence of the pro-cognitive and anti-inflammatory effects of CY6463 observed in preclinical studies and prior clinical trials.

“Cognitive impairment is a central debilitating, and untreated facet of schizophrenia, and there is a significant need for a treatment option that improves cognition,” said Steven E. Hyman, M.D., Core Member of the Broad Institute, Director of the Stanley Center for Psychiatric Research at the Broad Institute, and new member of Cyclerion’s Board of Directors. “I am encouraged by the promising

cognition signals observed after only two weeks of CY6463 dosing in patients with stable schizophrenia. These data demonstrate the therapeutic potential of amplifying sGC signaling in the CNS, including positive effects on cognition and inflammation, and support further development of CY6463 in diseases characterized by cognitive impairment."

CY6463 is a positive allosteric modulator of soluble guanylate cyclase (sGC) that amplifies endogenous nitric oxide (NO) signaling, a pathway that has been linked to schizophrenia.

The clinical study enrolled 48 participants with stable schizophrenia with no more than moderate positive symptoms and on a stable, single, atypical antipsychotic regimen. Topline results include:

- CY6463 was safe and well tolerated. There were no reports of SAEs, severe AEs, or treatment discontinuation due to AEs. All AEs were transient.
- The pharmacokinetic profile of once-daily CY6463 is consistent with earlier clinical studies in healthy volunteers and MELAS patients, and demonstrated linear, dose-proportional exposure and low intersubject variability.
- The general cognition composite score from the Cogstate Schizophrenia Battery increased with 14 days of once-daily dosing with CY6463 15 mg, compared to placebo, with an effect size of 0.60. An effect size of approximately 0.3 is generally considered clinically relevant in neuropsychiatry.
- Favorable changes were observed in a broad panel of plasma inflammatory biomarkers, including biomarkers with links to schizophrenia and cognition, after 14 days of once-daily dosing with CY6463 15 mg. These anti-inflammatory effects extend results observed in preclinical and earlier clinical studies of CY6463.
- Analysis of data from exploratory EEG assessments (resting state, qEEG, ERP, sleep EEG,) are ongoing. Data from these assessments will be shared in future scientific forums.
- At the two higher dose levels evaluated in this multiple-ascending-dose study (30 and 60 mg), CY6463 was observed to be safe and well tolerated; however, higher doses did not demonstrate an effect on the general cognition composite at Day 14, a finding consistent with preclinical experiments.

"This is the second clinical study successfully demonstrating safety, pharmacokinetics, and therapeutic activity in a patient population where previous drug development has been very challenging," said Andreas Busch, Ph.D., Chief Scientific Officer at Cyclerion Therapeutics. "These exciting results confirm previous clinical and preclinical findings, adding to a strong data package that supports the advancement of CY6463 in CNS diseases where cognition is impaired, including CIAS and MELAS. We are eager to build on the momentum from these positive data and continue to assess opportunities to accelerate development, refine patient selection, and improve endpoint assessment."

“The data emerging from this CIAS study, coupled with the recently reported CY6463 MELAS clinical study data, demonstrate positive multi-dimensional therapeutic activity and favorable safety and tolerability in two distinct patient populations,” said Peter Hecht, Ph.D., Chief Executive Officer of Cyclerion. “These data present a path and opportunity forward for Cyclerion’s first-in-class, CNS-penetrant sGC stimulator to yield multiple breakthrough CNS therapeutics across patient populations in need of novel treatment options. We continue to explore potential partnerships with parties who share our vision for the broad therapeutic potential of sGC in treating CNS disorders.”

Webinar Information

The Company will discuss these positive topline clinical data during a live webinar on Thursday, July 28th at 8:00 a.m. EDT, including a live Q&A. The live event can be accessed by visiting the investors' section of the Cyclerion website at https://ir.cyclerion.com/news-events/event-calendar. An archived replay will also be available on the Cyclerion website.

About the CIAS Study

The CIAS trial (NCT04972227) was an in-center, randomized, placebo-controlled, multiple-ascending-dose study of oral, once-daily CY6463 in 48 adults aged 18-50 who were diagnosed with stable schizophrenia with no more than moderate positive symptoms and on a stable, single, atypical antipsychotic regimen. The primary objective of the study was to assess the safety and tolerability of 15, 30 and 60 milligram, once-daily, oral doses of CY6463 over 14 days. The secondary objectives included pharmacokinetics and exploratory pharmacodynamic effects. The study was not powered for hypothesis testing.

About Schizophrenia and CIAS

Schizophrenia is a chronic brain disorder that affects how patients think, feel, and behave, which may result in hallucinations, delusions and/or disordered behavior that impairs daily functioning. Cognitive impairment is a core, debilitating, and untreated symptom of schizophrenia, with nearly all patients suffering from some cognitive deficits. There are currently no approved therapies that specifically improve cognitive deficits.

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

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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 Cyclerion Therapeutics

Cyclerion Therapeutics is a clinical-stage biopharmaceutical company on a mission to develop treatments that restore cognitive function. Cyclerion's lead molecule is CY6463, a novel, first-in-class, CNS-penetrant, sGC stimulator that modulates a key node in a fundamental CNS signaling network. The multidimensional pharmacology elicited by the stimulation of sGC has the potential to impact a broad range of CNS diseases. 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

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 the potential for CY6463 in the treatment of CNS diseases, including CIAS and MELAS, the potential for any successful development of CY6463, the sufficiency of our resources and other abilities to pursue the development of CNS, and other 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, our ability to continue with sufficient liquidity and capital resources to pursue our business plan regarding CY6463 or any other product (including without limitation our ability to fund additional clinical trials); our ability to successfully demonstrate the efficacy, safety and therapeutic effectiveness of CY6463; 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 not necessarily being indicative of or supported by the final results of our ongoing or subsequent clinical trials;; the timing of and our ability to pursue, 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 and CIAS; 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.

Investors

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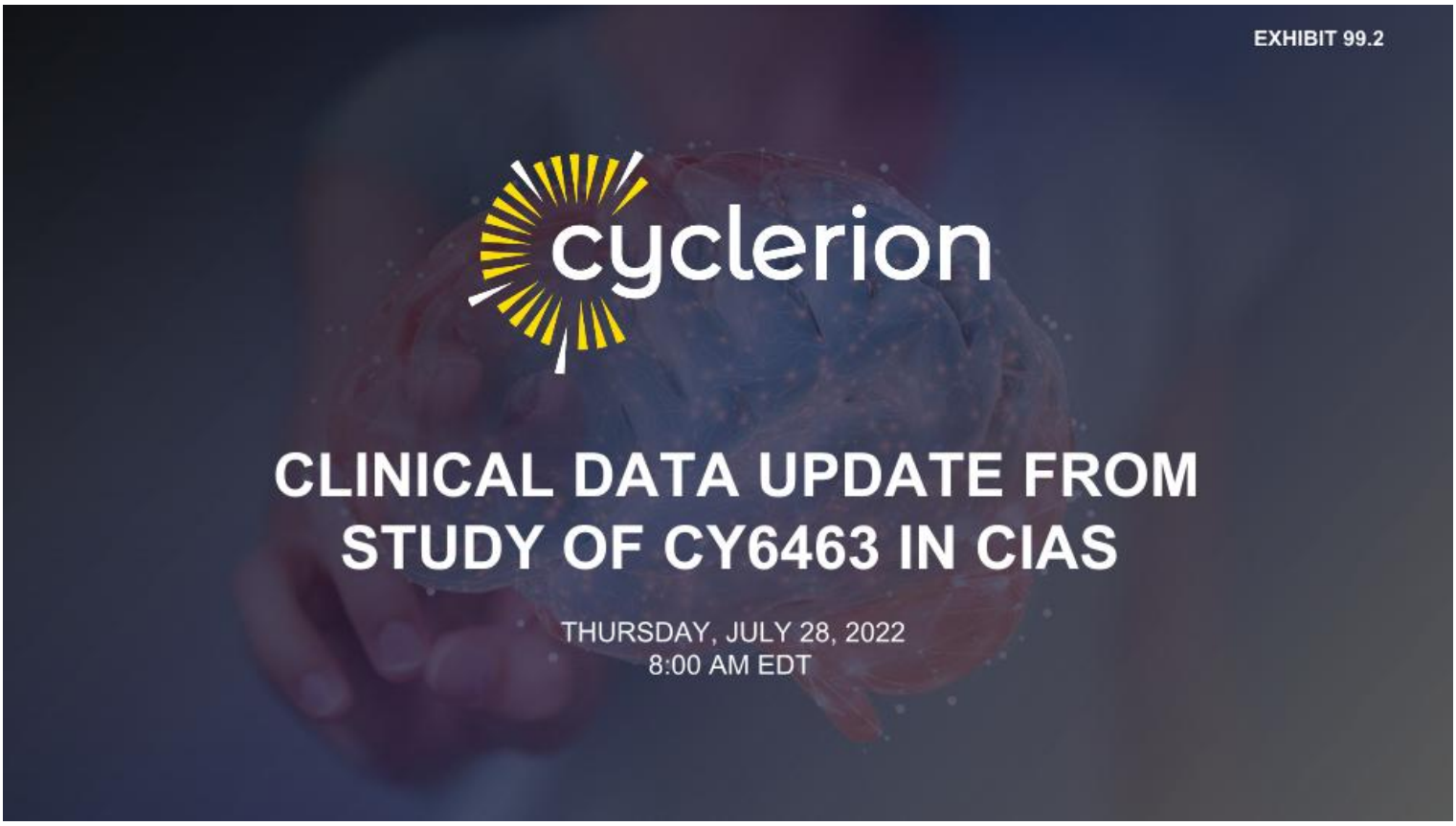
EXHIBIT 99.2



CLINICAL DATA UPDATE FROM STUDY OF CY6463 IN CIAS

THURSDAY, JULY 28, 2022
8:00 AM EDT

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 the potential for CY6463 in the treatment of CNS diseases, including CIAS and MELAS, the potential for any successful development of CY6463, the sufficiency of our resources and other abilities to pursue the development of CNS, and other 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, our ability to continue with sufficient liquidity and capital resources to pursue our business plan regarding CY6463 or any other product (including without limitation our ability to fund additional clinical trials); our ability to successfully demonstrate the efficacy, safety and therapeutic effectiveness of CY6463; 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, not necessarily being indicative of or supported by the final results of our ongoing or subsequent clinical trials; the timing of and our ability to pursue, 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 and CIAS; 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.

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 July 28, 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.

Speakers & Agenda

Steven Hyman, MD

Director, The Stanley Center for Psychiatric Research, Broad Institute

Board Member, Cyclerion

Peter Hecht, Ph.D.

Chief Executive Officer, Cyclerion

Jennifer Chickering, PhD

Vice President, Clinical Strategy, Cyclerion

Bruce Kinon, MD

Vice President, Clinical Development, Cyclerion

1. Welcome & introductions
2. A brief overview of CIAS and CY6463
3. CY6463 clinical data overview
   - Clinical study design
   - Clinical data summary
4. Perspective on CY6463
5. Q&A

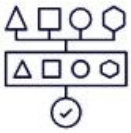
Developing therapies to restore cognitive function

NO-sGC-cGMP is a fundamental CNS signaling pathway

- Regulates mitochondrial function, inflammation, neuronal function, and cerebral blood flow
- Deficits in pathway linked to multiple CNS diseases

CY6463 is a positive allosteric modulator of sGC; oral, QD, small molecule with CNS exposure

- Strong safety and tolerability profile established in >150 participants
- Durable intellectual property with exclusivity to early 2040s

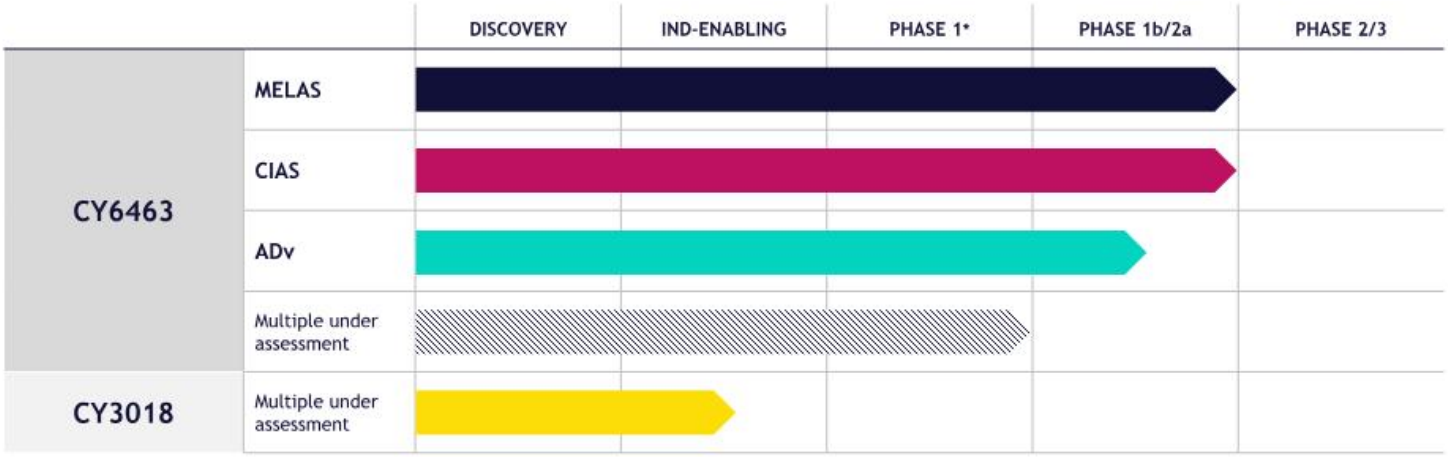


Promising signals observed in two distinct patient populations

- In **CIAS***: strong positive effect size on cognition; improvement in broad panel of inflammatory biomarkers
- In **MELAS****: improvement in markers of mitochondrial function and inflammation, cerebral blood flow, and CNS functional connectivity

*Cognitive impairment associated with schizophrenia (CIAS)
**Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

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*

OVERVIEW OF CIAS AND CY6463

Bruce Kinon, MD
Vice President, Clinical Development, Cyclerion

Schizophrenia is one of the top 15 leading causes of disability worldwide[1]

21M worldwide, 2.7M in US with schizophrenia and growing

Over three quarters of the estimated US annual cost of schizophrenia ($281B in 2020) is attributable to indirect costs including costs due to unemployment and productivity loss[2]

Schizophrenia is associated with significant health, social, and economic concerns

Financial costs associated with schizophrenia are disproportionately high relative to other chronic mental and physical health conditions[3]

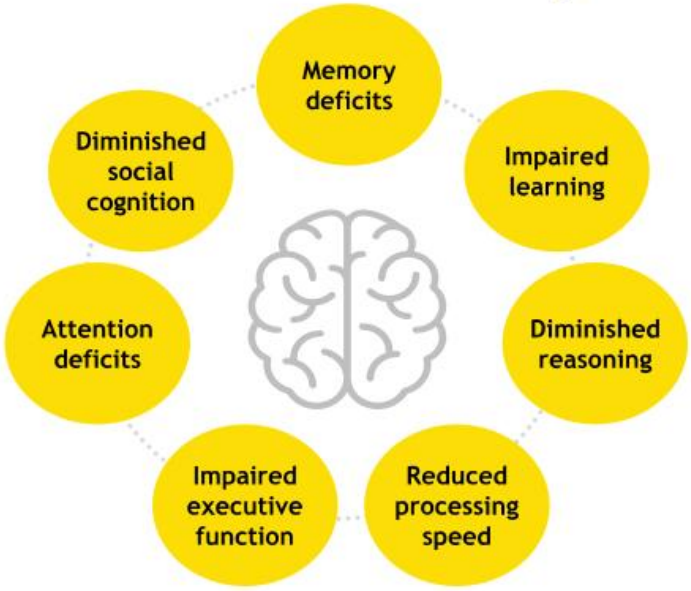
[1] McGrath et al. Epidemiol Reviews 2008, [2] Societal Costs of Schizophrenia White Paper Schizophrenia & Psychosis Action Alliance 2021, [3] Global Burden of Disease Study The Lancet 2017

Core cognitive deficits are chief determinant of long-term disability in schizophrenia

Vast majority of schizophrenia patients suffer with cognitive deficits

- Deficits overlap with measures of intelligence or IQ[1]
- Cognitive function in schizophrenia may decline at rate of 1 IQ point every 1-2 years [2]
- As a group, patients with schizophrenia perform significantly worse than controls on almost all neuropsychological tests [3, 4]

Impairments in memory, attention, reasoning and problem solving are worse in schizophrenia compared to bipolar disorder and major depressive disorder [5]:



[1] Kahn and Keefe JAMA Psychiatry 2013; [2] Jonas et al. JAMA Psychiatry; [3] Wilk et al. Schiz Res 2004; [4] Keefe et al. Schiz Res 2011; [5] Buchanan et al Schiz Bull 2005

Cognitive deficiencies are "neurocognitive rate-limiting factors" to optimal social and vocational functioning [1]

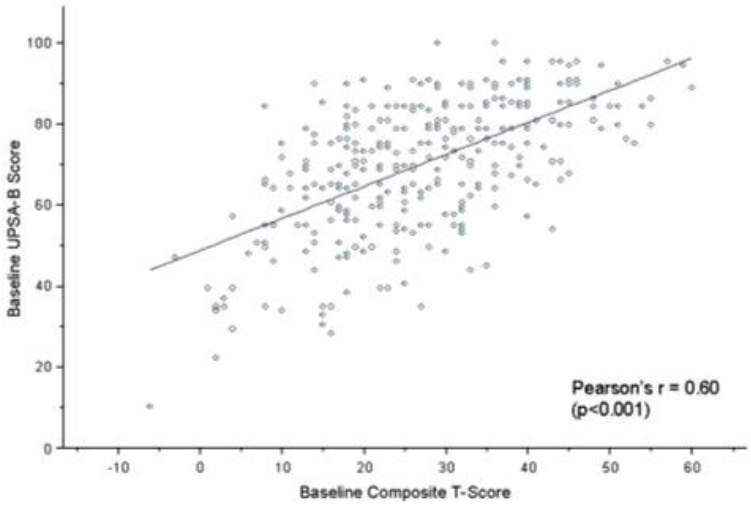


Fig. 3. Cross-sectional relationship between MCCB composite *T*-score and UPSA-B composite score.

- Substantial correlation between functional capacity and cognitive performance in schizophrenia [2]
- Cognitive impairments, negative symptoms but not positive symptoms, are predictive, both cross-sectionally and longitudinally, of adaptive life skills in persons with schizophrenia [3]

[1] Green Am J Psychiat 1996; [2] Keefe et al. Schiz Res 2011; [3] McGurk et al. Schiz Res 2000

Current antipsychotic treatment does little to improve cognitive impairment

No pharmacologic approaches to improve cognition have yet been successful to yield approved treatments

Treatment innovation may depend on search for new disease targets that may mediate CIAS

Improving cognition

Functional recovery

Increasing ability to participate fully in the community and live independently

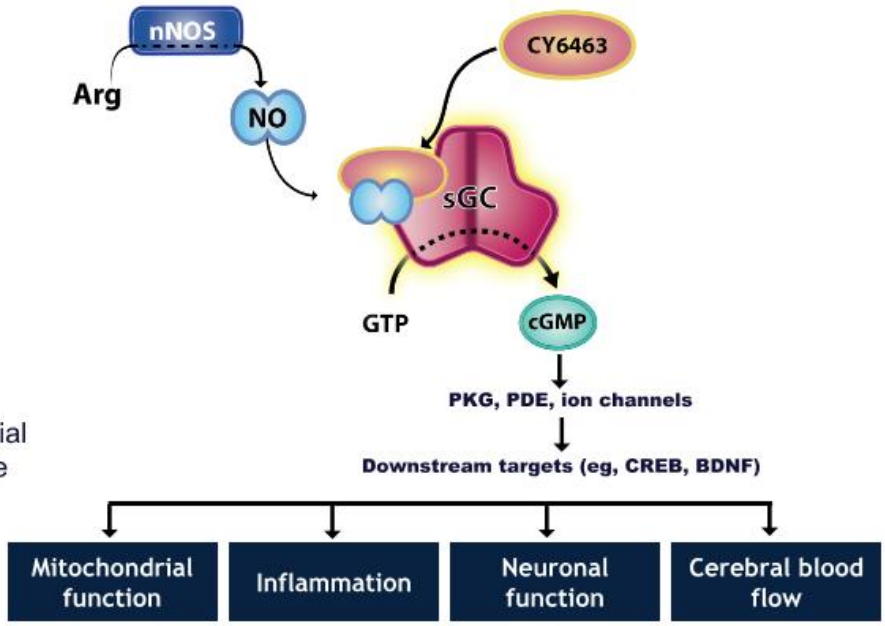
CY6463 is an sGC stimulator that amplifies endogenous NO-sGC-cGMP signaling

NO-sGC-cGMP is a fundamental CNS signaling pathway

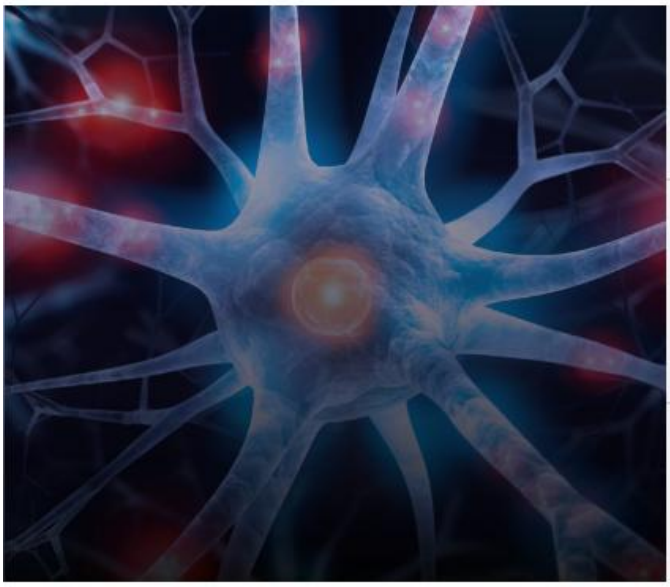
- Pathway machinery is broadly expressed (neurons, glial cells, and vasculature)
- Deficits linked to multiple CNS diseases

CY6463 is a positive allosteric modulator (PAM) that amplifies endogenous NO signaling

- Robust preclinical data demonstrate potential to address multiple aspects of CNS disease



NO-sGC-cGMP dysfunction is implicated in CIAS pathophysiology



Network analysis of pathways, protein-protein interactions, and genetics link NO-sGC-cGMP signaling to schizophrenia[1,2,3,4,5,6,7]

Compromised prefrontal and hippocampal NO signaling is implicated in cognitive deficits in schizophrenia[8]; reduced cGMP in CSF observed in schizophrenia[9,10]

CY6463 improved dendritic spine morphology, increased LTP, increased gamma EEG power, and improved cognitive performance in preclinical models[11]

[1]Docherty 2015, [2]Freudenberg 2015, [3]Shinkai 2002, [4]Bernstein 2011, [5]Reif 2006, [6]O'Donovan 2008, [7]Weber 2014, [8]Issy 2018, [9]Gattaz 1983, [10]Ebstein 1976, [11]Correia 2021

Targeting sGC is a promising therapeutic approach in CIAS where new therapies are greatly needed

Nearly all people with schizophrenia (98%) have **cognitive deficits**

Core cognitive deficits are chief determinant of **long-term disability** in schizophrenia

NO-sGC-cGMP is a **fundamental CNS signaling pathway** with dysfunction implicated in CIAS pathophysiology

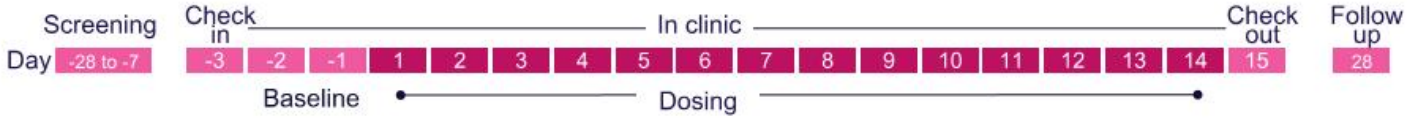
CY6463 is a positive allosteric modulator of sGC that amplifies endogenous signaling, offering a **promising therapeutic approach** to the treatment of CIAS

CY6463 CIAS CLINICAL STUDY

Jennifer Chickering, PhD
Vice President, Clinical Strategy, Cyclerion

Study to assess effects of once-daily CY6463 on safety, PK, PD, and cognition in CIAS on standard of care

Randomized, double-blind, placebo-controlled, multiple-ascending-dose, in-clinic study



Eligibility

- 18-50y with DSM-5 schizophrenia
- Stable, moderate symptomatology
- On stable, single atypical antipsychotic background regimen

4 dose cohorts (12 participants/cohort)

- Randomized 8 active/4 placebo
- Escalation based on safety
- 15 mg, 30mg, and 60 mg (2 cohorts)
- Placebo pooled for analyses

Assessments of safety, PK, cognition, and PD

Safety	• Adverse events, BP/HR, ECGs, PANSS, clinical labs • Extrapyramidal sx (AIMS, BARS, SAS), C-SSRS, other vitals, PEs
PK	• Plasma concentrations of CY6463 and associated pharmacokinetics
Cognition	• Cognitive performance battery
CNS/PD	• Inflammation biomarkers (plasma) • EEG: resting-state qEEG, ERPs, sleep

Conducted at Hassman Research Institute, Dr. Elan Cohen (PI), and Collaborative Neuroscience, Dr. David Walling (PI)

BP, blood pressure; HR, heart rate; ECG, electrocardiography; PANSS, Positive and Negative Syndrome Scale; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; SAS, Simpson Angus Scale; C-SSRS, Columbia Suicide Severity Rating Scale; PE, physical exam; qEEG, quantitative electroencephalography; ERP, event-related potential

Enrolled cognitively impaired, chronic schizophrenia population on standard of care

Cognitively impaired at baseline consistent with chronic schizophrenia

- Means ~0.5 to 2 SDs lower than those of age-matched controls from normative database

Single, antipsychotic background regimen, stable ≥ 8w; n (%)

- Risperidone 21 (43.8)
- Aripiprazole 13 (27.1)
- Quetiapine 9 (18.8)
- Paliperidone 3 (6.3)
- Olanzapine 2 (4.2)

Baseline characteristics	Total study population (N=48)
Sex – male, n (%)	47 (97.9)
Race, n (%)	
Black/African-American	38 (79.2)
White	10 (20.8)
Hispanic/Latino, n (%)	11 (22.9)
Age in years, mean (SD)	36.7 (7.75)
BMI, mean (SD)	29.5 (5.06)
Years since diagnosis, mean (SD)	15.1 (7.83)
PANSS, mean (SD)	54.9 (7.19)

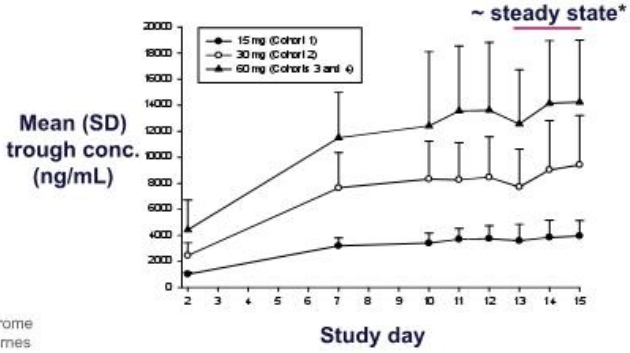
Strong safety, tolerability, and PK profile extended in participants with schizophrenia on standard of care

Well tolerated across all dose levels on top of antipsychotic regimen

- Mostly mild adverse events (AEs), all AEs resolved
- No SAEs, no severe AEs, no dropouts due to AEs
- Most common AE was headache, all but 1 mild
- No signals on clinical labs, vital signs, ECGs, PANSS, SAS, AIMS, BARS, C-SSRS

Once-daily pharmacokinetics as expected, consistent with previous studies

- Approximately dose proportional exposure
- Low intersubject variability
- Accumulation (~3x) similar across dose levels
- At or near steady state by Day 13

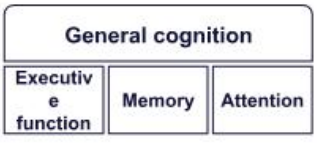


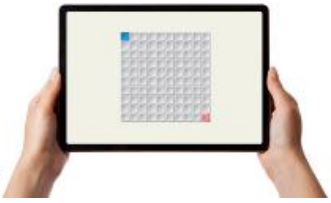
SAE, serious adverse event; ECG, electrocardiography; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson Angus Scale; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; C-SSRS, Columbia Suicide Severity Rating Scale

*Based on visual assessment

Characterizing effects of CY6463 on cognitive performance

Cogstate Schizophrenia Battery

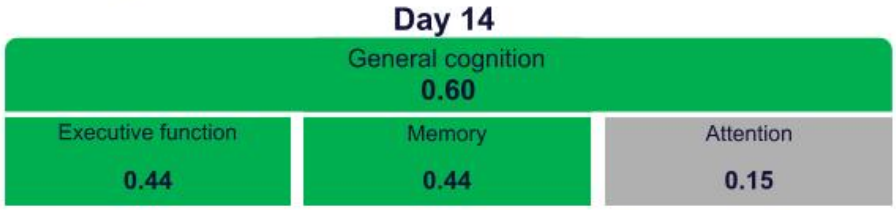




- **Content validity vs MCCB with reduced burden**
- **Composite scores for general cognition and cognition domains**
- **Analysis – change from baseline CY6463-treated vs placebo-treated**
- **Focus - effect size (standardized mean difference) CY6463 vs placebo**

MCCB; Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery
Effect size=(Mean CFB CY6463 – mean CFB placebo)/pooled SD
MMRM (mixed-effect model repeated measure) analysis with change from baseline as the response variable, treatment, time point, and treatment-by-visit interaction as fixed effects and the respective baseline value as the covariate with an appropriate variance-covariance structure.

Promising cognition signal after only 2 weeks of once-daily dosing with 15mg CY6463



- **Strong positive effect on general cognition at steady-state**
- **Effect size of ≥0.3 considered clinically relevant in the context of neuropsychiatry[1,2]**
- **Higher doses did not show an effect on general cognition on Day 14**
- **15mg results on cognition supported by sensitivity analyses**
- **15mg dose also showed broad positive effects in recently completed MELAS study**

Effect size = (Mean CFB CY6463 – mean CFB placebo)/pooled SD; means are least square means fromMMRM (mixed-effect model repeated measure) analysis with change from baseline as the response variable, treatment, time point, and treatment-by-visit interaction as fixed effects and the respective baseline value as the covariate with an appropriate variance-covariance structure.

[1]Angst 2017, [2]Leucht 2012

Increase in cognition signal over time

Effect size

≥0.30
≥.20 to .29
-.19 to .19
-.29 to -.20
<=-0.30

Legend

Day 2			Day 7			Day 14		
General cognition 0.16			General cognition 0.31			General cognition 0.60		
Exec fn	Memory	Attn	Exec fn	Memory	Attn	Exec fn	Memory	Attn
0.27	0.18	-0.32	0.12	0.54	0.06	0.44	0.44	0.15

Increasing effect size with time on treatment

Consistent with pharmacokinetics of CY6463

Benefit expected to be durable and increase with chronic treatment based on:

- Experience with approved, peripherally active sGC stimulators
- Multi-dimensional sGC stimulator pharmacology

Effect size = (Mean CFB CY6463 – mean CFB placebo)/pooled SD; means are least square means fromMMRM (mixed-effect model repeated measure) analysis with change from baseline as the response variable, treatment, time point, and treatment-by-visit interaction as fixed effects and the respective baseline value as the covariate with an appropriate variance-covariance structure.

CY6463 shows strong cognition signal over placebo after only 2 weeks of dosing

Intervention	N	Treatment duration	Test	Effect size	Reference
CY6463 15mg sGC stimulator	8 active, 16 placebo	2 weeks	CSB	**0.60**	Current study
BI 425809 10mg GlyT1 inhibitor	~85 active, 170 pbo	12 weeks	MCCB	**0.34**	Fleishhacker et al, 2021, Phase 3 ongoing
Encenicline 0.27mg α7 partial agonist	~ 105/arm	12 weeks	CSB	**0.26**	Keefe et al, 2015
GSK239512 H3R antag./inverse agon.	~20/arm	7 weeks	CSB	**0.29**	Jarskog et al, 2015

Characterizing effects of CY6463 on plasma biomarkers of inflammation

InflammationMAP® biomarker panel

- **Multi-Analyte Profile (MAP) – multiplexed immunoassay for a panel of inflammatory biomarkers**
- **Anti-inflammatory effects are well established for CY6463, preclinically and clinically**
- **Inflammation implicated in schizophrenia**
- **Analysis – change from baseline CY6463 group vs placebo group**
- **Focus – effect size (standardized mean difference) CY6463 vs placebo**

InflammationMAP® v. 1.1, RBM
Effect size = (Mean CFB CY6463 – mean CFB placebo)/pooled SD where means are from anANCOVA (analysis of covariance) with change from baseline as the response variable, treatment group as the main effect, and the respective baseline value as the covariate

Disease-relevant, anti-inflammatory effects for CY6463 15mg, consistent with CY6463 pharmacology

Biomarker	Abbrev	Effect size
Brain-Derived Neurotrophic Factor	BDNF	-0.83
Interleukin-2	IL-2	0.81
Interleukin-6	IL-6	-0.66
Interleukin-8	IL-8	-0.59
Interleukin-10	IL-10	-0.60
Interleukin-18	IL-18	-0.72
Stem Cell Factor	SCF	0.73
T-Cell-Specific Protein-RANTES	RANTES	-0.62
Tissue Inhibitor of Metalloproteinases 1	TIMP-1	-0.59

Biomarkers highlighted showed:

- Change from baseline in CY6463 group
- Effect size >|0.5|
- Nominal p-value <0.2

All effects represent favorable directional improvement[1-14]

Effect size = (Mean CFB CY6463 – mean CFB placebo)/pooled SD where means are from anANCOVA (analysis of covariance) with change from baseline as the response variable, treatment group as the main effect, and the respective baseline value as the covariate; p-value not controlled for multiplicity
RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted)
[1]Asevedo 2014; [2]Carnossa 2022; [3]Domenici 2019; [4]Frydecka 2015; [5]Frydecka 2018; [6]Fu 2019; [7]Lee 2017; [8]Miller 2021; [9]Miranda 2019; [10]Momtazmanesh 2018; [11]Peng, 2018; [12]Potvin 2008; [13]Stuart 2014; [14]Syed 2021

CY6463 shows cognition signal over placebo after only 2 weeks of dosing in CIAS

Well tolerated, no safety signals, on top of stable, single antipsychotic regimen

Dose-proportional, **once-daily PK** profile

Robust cognition signal measured on instrument suitable for registration

Disease-relevant, **anti-inflammatory** pharmacology

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PERSPECTIVE ON CY6463

Steven Hyman, MD
Director, The Stanley Center for Psychiatric Research, Broad Institute
Member, Cyclerion Board of Directors

SUMMARY

Peter Hecht, PhD
Chief Executive Officer, Cyclerion

CY6463 pharmacology translating from preclinical to clinical, now in two patient populations

	Known aspects of sGC pharmacology			
CY6463 studies	Mitochondrial function	Inflammation	Neuronal function	Cerebral blood flow
Preclinical	✓	✓	✓	✓
Healthy elderly (CY6463 15mg)		✓	✓	
MELAS (CY6463 15mg)	✓	✓	✓	✓
CIAS (CY6463 15mg)		✓	✓	
ADv (CY6463 15mg)		TBD	TBD	TBD

Not assessed
Assessed, no effect observed

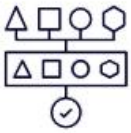
Developing therapies to restore cognitive function

NO-sGC-cGMP is a fundamental CNS signaling pathway

- Regulates mitochondrial function, inflammation, neuronal function, and cerebral blood flow
- Deficits in pathway linked to multiple CNS diseases

CY6463 is a positive allosteric modulator of sGC; oral, QD, small molecule with CNS exposure

- Strong safety and tolerability profile established in >150 participants
- Durable intellectual property with exclusivity to early 2040s



Promising signals observed in two distinct patient populations

- In **CIAS***: strong positive effect size on cognition; improvement in broad panel of inflammatory biomarkers
- In **MELAS****: improvement in markers of mitochondrial function and inflammation, cerebral blood flow, and CNS functional connectivity

*Cognitive impairment associated with schizophrenia (CIAS)
**Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

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Q&A

Moderated by
Cheryl Gault,
Chief Operating Officer,
Cyclerion

Key Takeaways

- NO-sGC-cGMP is a fundamental CNS signaling pathway
- CY6463 is a positive allosteric modulator of sGC; oral, QD, small molecule with CNS exposure, strong safety profile and durable IP
- Promising signals observed in two distinct patient populations with CY6463
  - In CIAS: strong positive effect size on cognition; improvement in broad panel of inflammatory biomarkers
  - In MELAS: improvement in markers of mitochondrial function and inflammation, cerebral blood flow, and CNS functional connectivity