SCD and CNS:
creating breakthrough treatments
harnessing the power of soluble guanylate cyclase (sGC)

Anjeza Gjino, Head of Finance and Corporate Secretary

H.C.WAINWRIGHT & CO 22nd Annual Global Investment Conference

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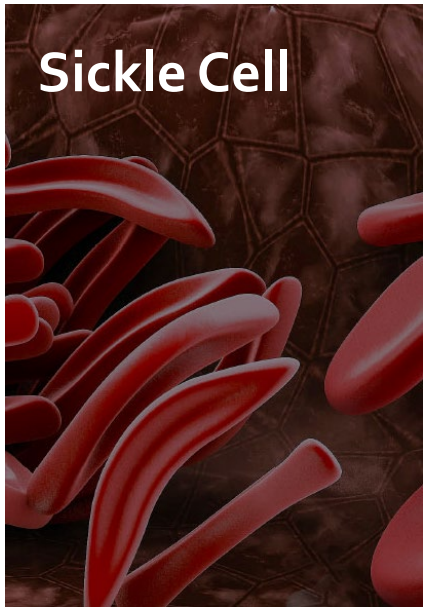
Safe Harbor Statement

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

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

Applicable risks and uncertainties include the risks listed under the heading "Risk Factors" and elsewhere in our 2019 Form 10-K filed on March 12, 2020, and in Cyclerion's subsequent SEC filings, including the Forms 10-Q filed on May 4, 2020 and August 3, 2020. Investors are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Cyclerion undertakes no obligation to update these forward-looking statements, except as required by law.

Cyclerion's value creation momentum



Building a company:
our sGC science, pipeline and our team

- two important upcoming clinical catalysts
- priority disease areas: sickle cell and CNS
- capital efficient, bio-marker guided fast to POC trial approach reduces risk
- cash position of $62M* fortified with $24M PIPE on July 30
- seasoned team with successful track record in drug hunting and company building

* *unrestricted cash, cash equivalents and restricted cash balance as of June 30, 2020*

Clinical program snapshot

Approaching catalysts

OLINCIGUAT (SCD)

Ph1 (n=86 HV) SAD/MAD

- ✓ safety/tolerability
- ✓ target engagement
- ✓ QD dosing

Q2 2019

Ph2 STRONG-SCD study in SCD

- safety, tolerability, PK
- fit-for-purpose patient-reported outcomes (ePRO) instrument
- pharmacodynamic effect: biomarkers (Hb, HbF, inflammation, adhesion) and daily symptoms

top line expected late Q3 2020

Ph 3 study: SCD

IW-6463 (CNS)

Ph1 (n=110 HV) SAD/MAD

- ✓ safety/tolerability
- ✓ target engagement
- ✓ QD dosing
- ✓ CNS penetration

December 2019

Ph1b translational pharmacology study

- safety/ tolerability in elderly subjects
- PK
- target and pathway engagement
- pharmacodynamic biomarkers: CBF, cGMP

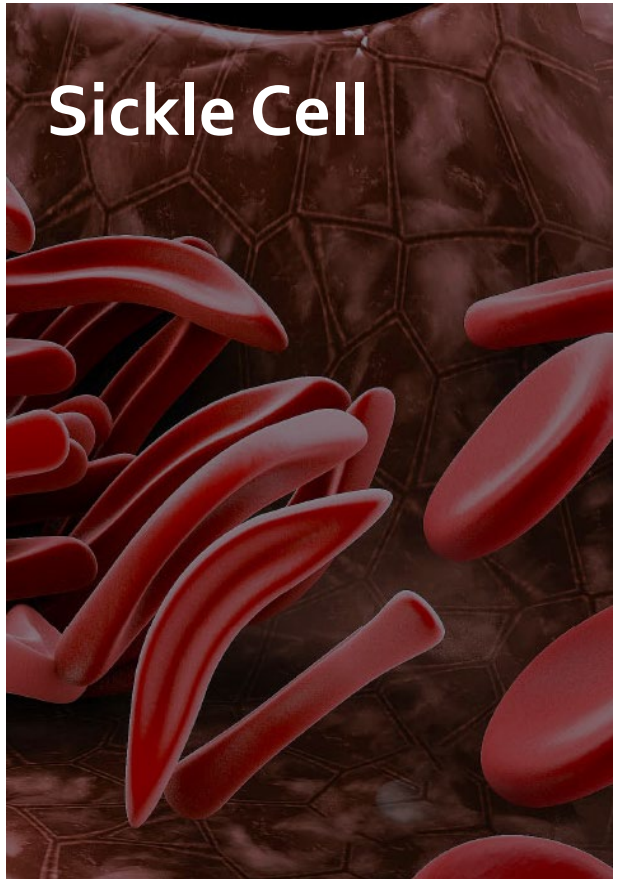
top line expected late summer 2020

Ph 2a study: MELAS

Ph 2a study: Alzheimer's disease with vascular pathology (ADv)

Lessons inform iterative development strategy

Olinciguat: potential to raise standard of care for sickle cell disease patients



- potential for broad clinical utility in SCD
- multi-dimensional mechanism that offers both upstream and downstream pharmacology
- 70 patients enrolled; dosing completed
- TL expected late Q3 2020
- Ph3 long-lead items underway: CMC, protocols, global ad board, regulatory plans
- plan to develop and commercialize ourselves, but partnerships will be considered

Potential for clinical utility broader than approved SCD therapies

Approved therapies target a single domain and benefit

REDUCE	REDUCE
Anemia	Painful Crises

Olinciguat targets four domains to potentially provide broader therapeutic benefit in an oral, once-daily formulation

REDUCE	REDUCE
Anemia	Painful Crises

AND…

IMPROVE	PRESERVE
Daily Symptoms	Organ Function

Potential to provide benefit alone or when used in combination with approved products

STRONG SCD

Olinciguat phase 2 trial designed to support rapid advancement

Topline results expected late Q3 2020

Structure

- 70 patients enrolled in all SCD genotypes, aged 16 – 70
- placebo controlled, double blind
- 4 dose levels
- 12-week treatment

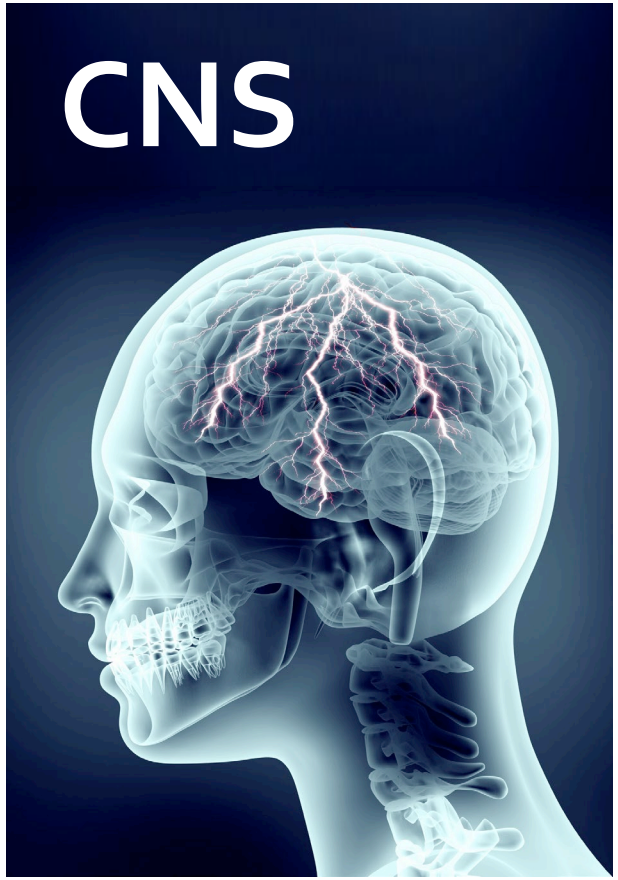
Objectives

- assess safety and tolerability
- confirm PK profile in SCD patients
- development of the CYCN fit-for-purpose patient-reported outcomes (ePRO) instrument
- signs of pharmacodynamic effect: biomarkers (Hb, HbF, inflammation, adheion) and daily symptom effects

Insights for Phase 3 design

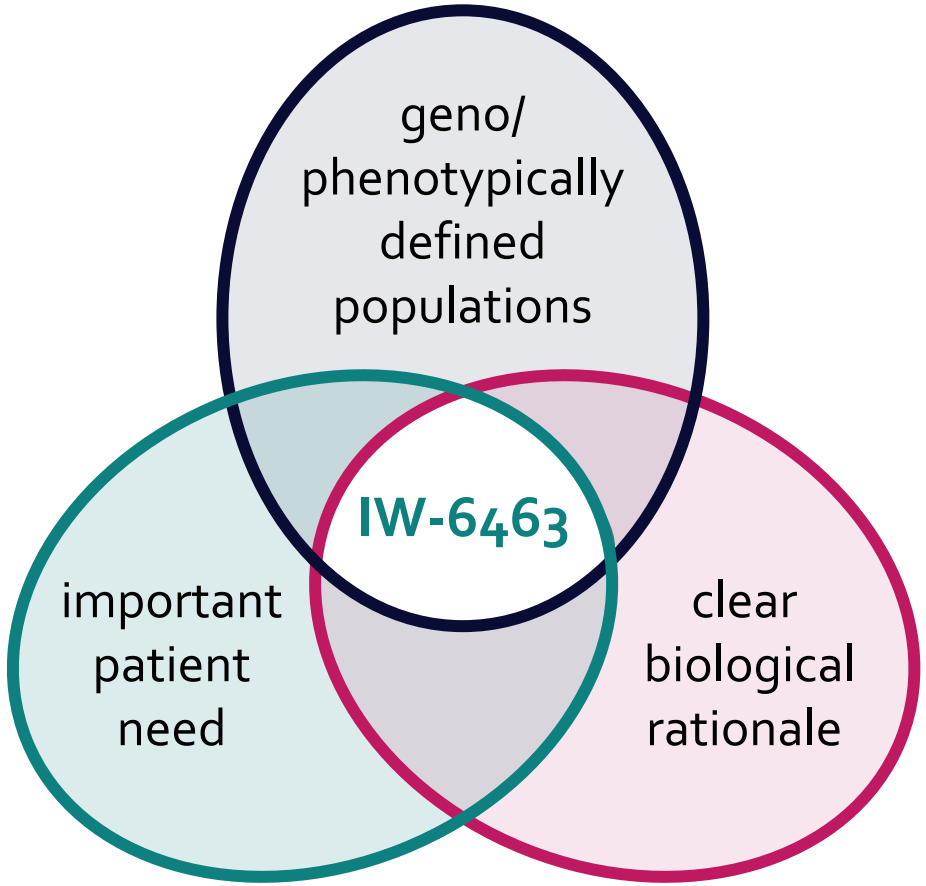
- endpoint selection based on results (biomarkers and ePRO)
- determine study sample size and dose(s)

Our strategy: target identifiable populations with important unmet needs



- targeting untapped NO neurotransmitter pathway by sGC stimulation
- our two initial indications characterized by
  - strong biological rationale
  - identifiable, targeted patient populations
  - large unmet patient need,
  - lack of approved therapies
- MELAS
  - genetically defined rare disease
  - most common mitochondrial disease, >90% have neurological symptoms (stroke-like episodes, dementia, epilepsy, vision loss)
- Alzheimer's disease with vascular pathology (ADv)
  - intersection of Alzheimer's and vascular dementias
  - well-defined subset of patients, ~2M patients in the US
- discovery research engine focused on expanding CNS platform
- exploring R&D collaboration to support pursuit of the best opportunities

Our approach: intersection of patients and biology



Raising the odds of success:

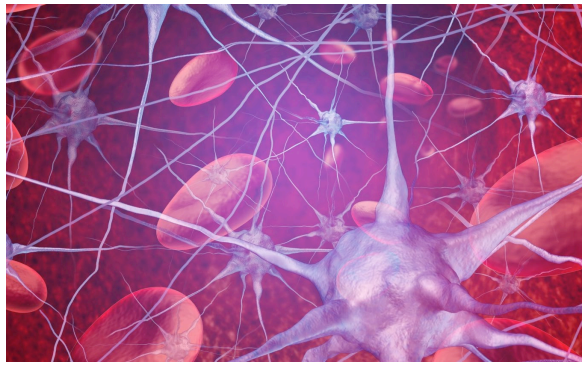
- pursue multiple indications in parallel
- leverage biomarkers to drive development
- implement nimble trials with leading edge investigators and imaging analytics
- investigate a strategic R&D partnership to explore full potential of sGC in the CNS

IW-6463 demonstrates in preclinical studies beneficial effects in four important domains of neurodegenerative diseases

IMPROVE

Cerebral Blood Flow

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



ENHANCE

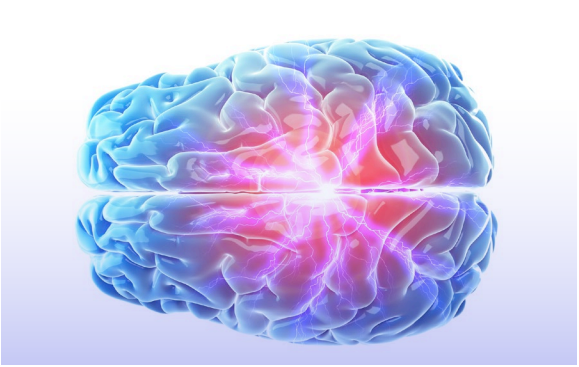
Cellular Bioenergetics

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

REDUCE

Neuro-inflammation

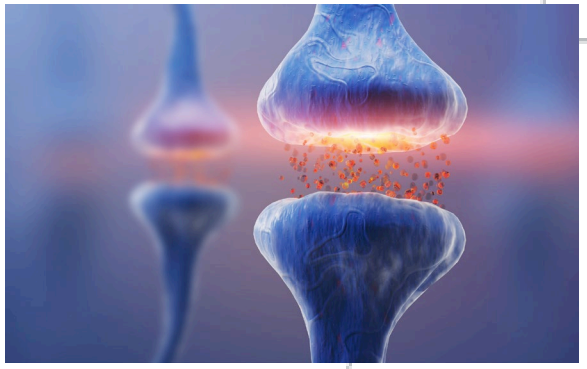
Decreased markers of LPS-induced neuroinflammation (ICAM1, VCAM1, IL6) *in vitro*



IMPROVE

Neuronal Function

Enhanced memory performance & spine density in aged animals; increased LTP in neurodegenerative disease models

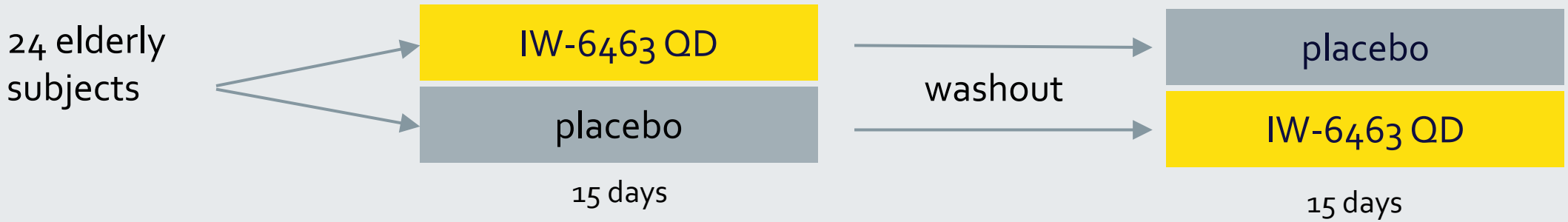


Biomarker-driven IW-6463 early clinical development strategy

top-line expected late summer 2020

CNS exposure ✓	***CNS activity***	***CNS disease biomarker***
Phase 1 (completed)	**Translational pharmacology study in elderly (ongoing)**	**Parallel exploratory Phase 2 studies**
• safety • pharmacokinetics • pharmacodynamics • target engagement • dose selection for next study	• safety • pharmacokinetics • target engagement • pharmacodynamic biomarkers	• focused patient subsets • translational biomarker data • safety • pharmacokinetics • pharmacodynamics • early impact on disease

Translational study design: pharmacodynamic biomarkers and safety



Assessing safety, PK and target engagement in CNS (cGMP)

Top line data expected late summer 2020

IMPROVE

Cerebral Blood Flow

- MRI arterial spin labeling (ASL)

ENHANCE

Cellular Bioenergetics

- brain metabolism via magnetic resonance spectroscopy (MRS)

REDUCE

Neuro-inflammation

- cytokines, adhesion molecules

IMPROVE

Neuronal Function

- qEEG
- measures of cognition and behavior (NeuroCart®)

MELAS: Strong supportive data for NO-sGC-cGMP pathway involvement

SCIENTIFIC RATIONALE FOR INDICATION AND PATIENT SELECTION

Clinical precedence for NO-sGC-cGMP pathway

- L-Arginine (NO precursor) recommended for acute and chronic treatment

Pathophysiology

- CNS metabolic dysfunction, elevated lactate, decreased NO
- CNS vascular pathology - impaired blood flow, inflammation, endothelial dysfunction, small vessel disease

IW-6463 pharmacology

- CYCN preclinical data suggest IW-6463 improves mitochondrial function and cerebral blood flow

AD with vascular pathology (ADv) – focused mixed dementia subset

Defined population well suited for treatment with IW-6463

DISEASE RATIONALE FOR PATIENT SELECTION

Pathophysiology

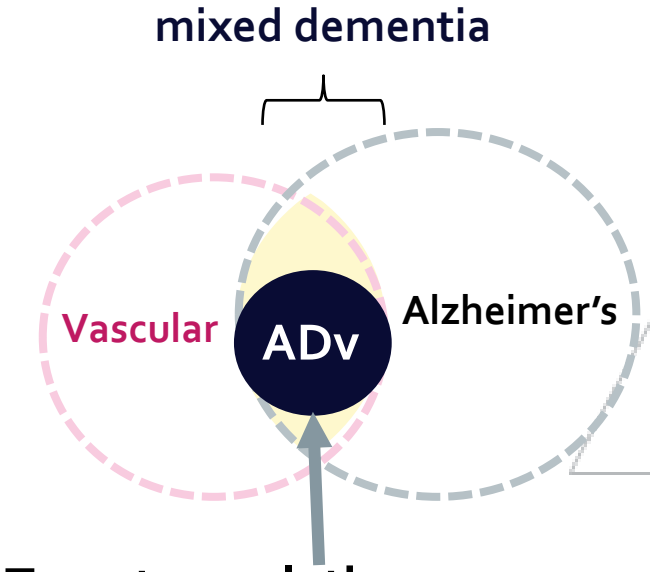
NO dysregulation, endothelial cell loss, impaired blood flow, vascular leakage, inflammation, neuronal dysfunction, and neuronal loss are major contributing factors to rapid disease progression

Standard of care

No approved therapies to treat vascular dementia.
AD therapies offer limited benefits; not disease modifying

Pharmacology

Our preclinical data suggests IW-6463 has potential to improve cerebral blood flow, endothelial health, neuroinflammation, and cellular energetics as well as prevent neurodegeneration



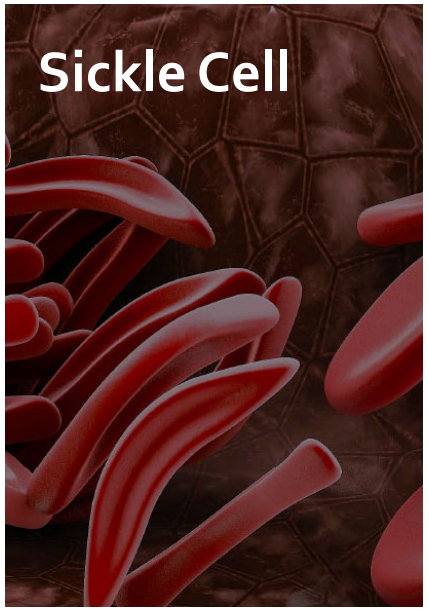
Target population

ADv: an identifiable subset of mixed dementia patients with:

- AD pathology **AND**
- sub-cortical vascular disease **AND**
- CV risk factors

Alzheimer's Association,, Rizzi et al., NCI Analysis

Cyclerion's value creation momentum



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