Delivering impact in CNS diseases

Investor webinar
July 9, 2020

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Applicable risks and uncertainties include those listed under the heading "Risk Factors" and elsewhere in our most recent Form 10-K filed with the SEC on March 12, 2020, and in our subsequent SEC filings, including our Quarterly Report on Form 10-Q filed with the SEC on May 4, 2020. These forward-looking statements speak only as of the date of this presentation, and we undertake no obligation and do not intend to update these forward-looking statements.

Welcome to Cyclerion's CNS discussion

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Pioneering therapeutics in SCD and CNS

Sickle Cell Disease (SCD)

- upstream + downstream pharmacology
- 70 patients enrolled; dosing completed
- top line expected end Q3 2020

Central Nervous System (CNS)

- potential to be next druggable neurotransmitter system
- IW-6463: oral, QD drug
- first CNS-penetrant sGC stimulator in development
- top line expected end of summer 2020

Cyclerion: delivering impact in CNS

1	Now is the time: value in CNS
2	sGC and CNS: scientific and clinical basis for CNS therapies
3	Translational pharmacology study: demonstrating CNS activity
4	Clinical direction in CNS: important indications that yield early answers

Objectives for today

1	Now is the time: value in CNS		**How Cyclerion can create value in CNS**
2	sGC and CNS: scientific and clinical basis for CNS therapies		**Discuss the broad therapeutic potential of sGC stimulators in CNS**
3	Translational pharmacology study: demonstrating CNS activity		**Describe the rich yield of data and its implications (data due late summer)**
4	Clinical direction in CNS: important indications that yield early answers		**Discuss our first indications: focused patient populations, biomarker-based development**

Cyclerion: delivering impact in CNS

1 **Now is the time: value in CNS**

2 sGC and CNS: scientific and clinical basis for CNS therapies

3 Translational pharmacology study: demonstrating CNS activity

4 Clinical direction in CNS: important indications that yield early answers

- growing patient populations and evolving science creates opportunity
- we believe our approach can raise the odds of success
- translational pharmacology data (due late summer) are expected to demonstrate CNS activity

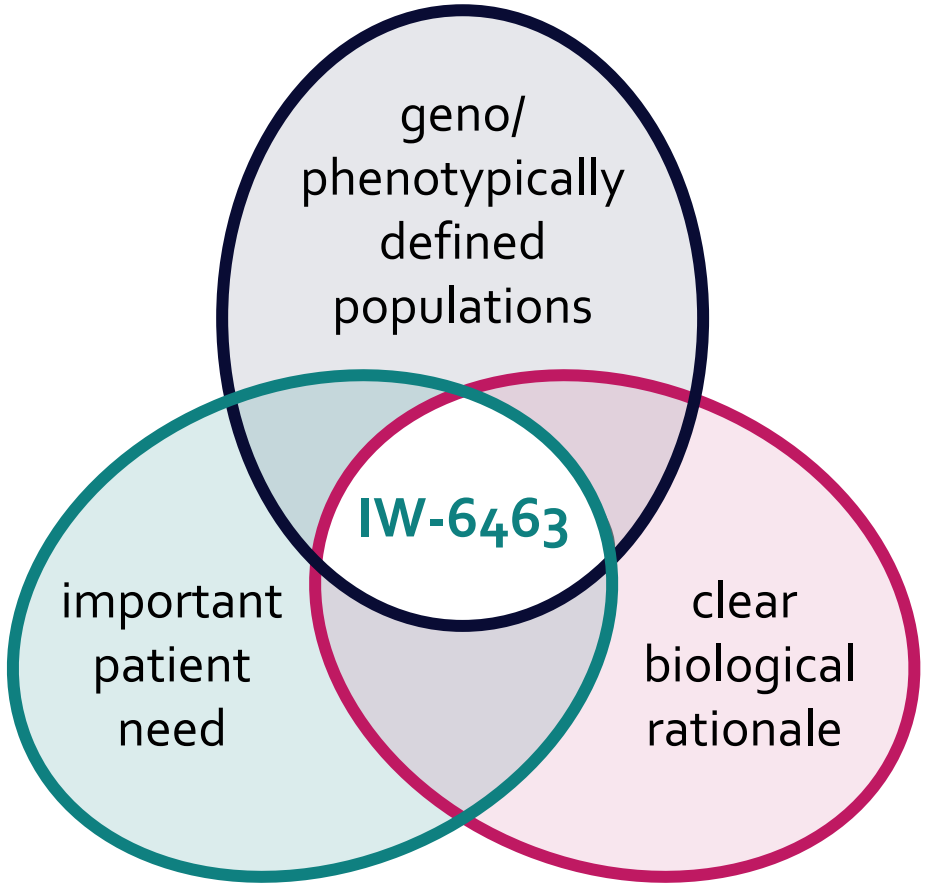
Capturing potential in a high reward therapeutic area

- rapidly growing patient population, lack of approved therapies, important unmet need
- quickly evolving science: genetic insights and technologies
- valued by investors and industry partners
- Cyclerion is the innovator of sGC in the CNS

We've learned from industry history

- understanding disease biology is critically important
- adequate CNS exposure is essential
- identifying translational CNS biomarkers is key

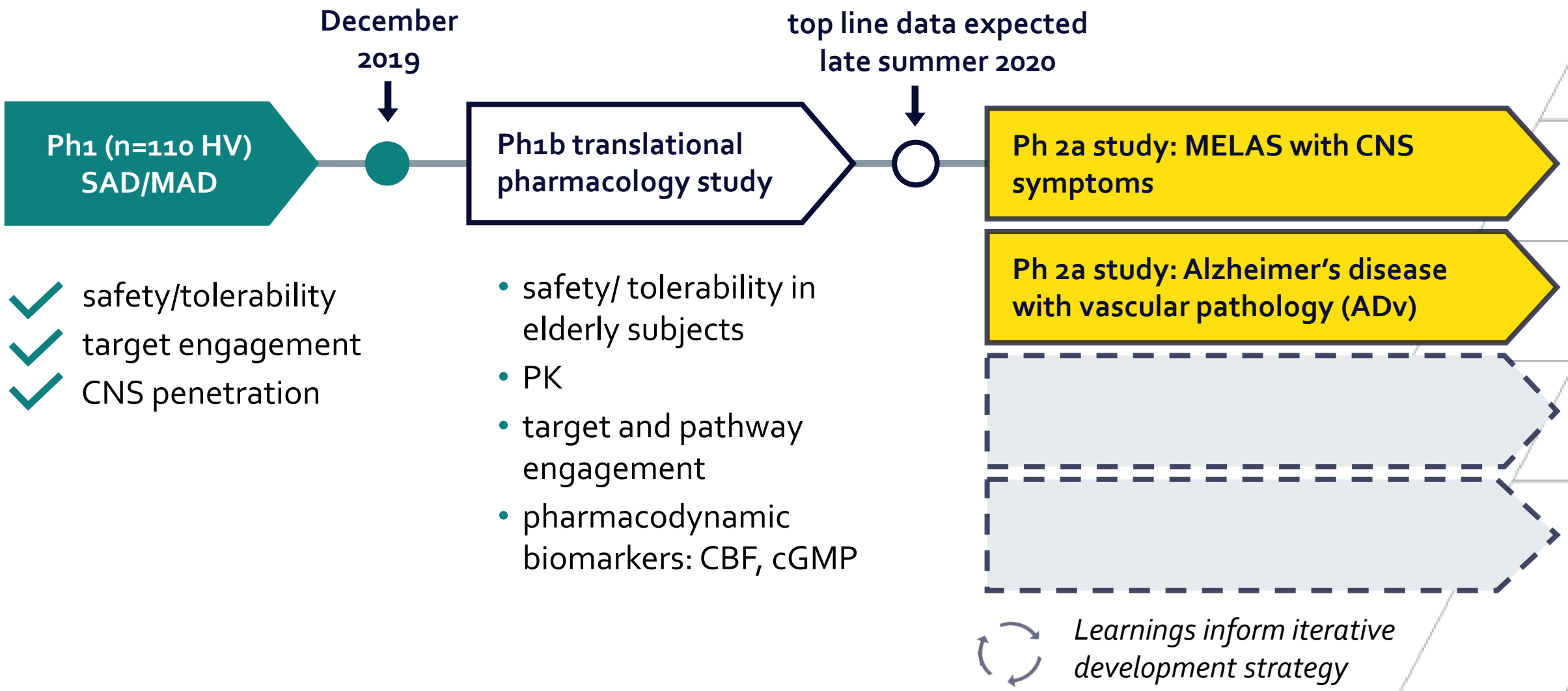
Our approach: intersection of patients and biology



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 biomarker-guided development in focused patient populations



sGC and CNS: scientific and clinical basis for CNS therapies

1 Now is the time: value in CNS

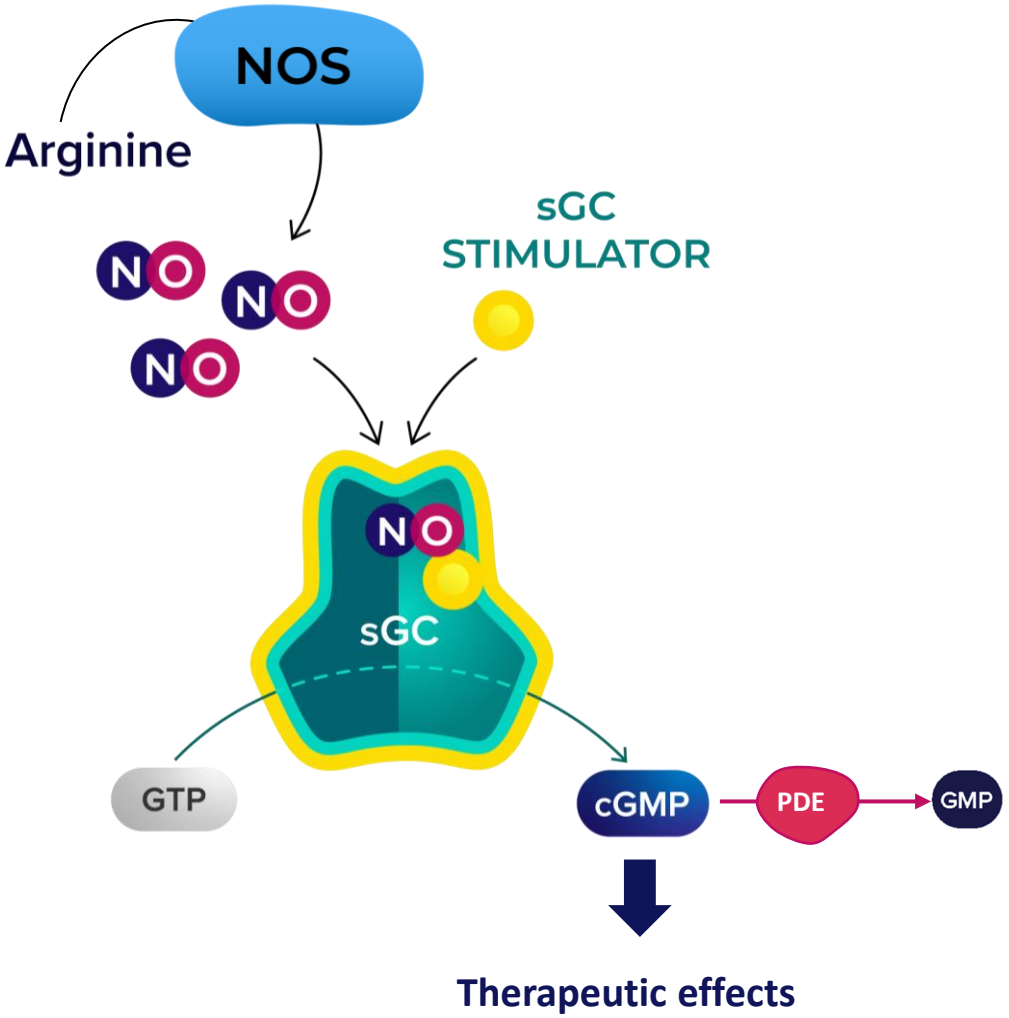
2 **sGC and CNS: scientific and clinical basis for CNS therapies**

3 Translational pharmacology study: demonstrating CNS activity

4 Clinical direction in CNS: important indications that yield early answers

- sGC stimulators are clinically validated in several diseases
- sGC/NO pathway identified as drug target for CNS diseases using systems biology approach
- IW-6463 active in four domains: cerebral blood flow, cellular bioenergetics, neuro-inflammation, neuronal function

sGC stimulators: ideal intervention in a genetically and clinically validated pathway



Multiple successful drugs target the NO-sGC-cGMP pathway for the treatment of CV diseases

NO donors, PDE5 inhibitors, sGC stimulators

NO-sGC-cGMP pathway plays central role in CNS diseases

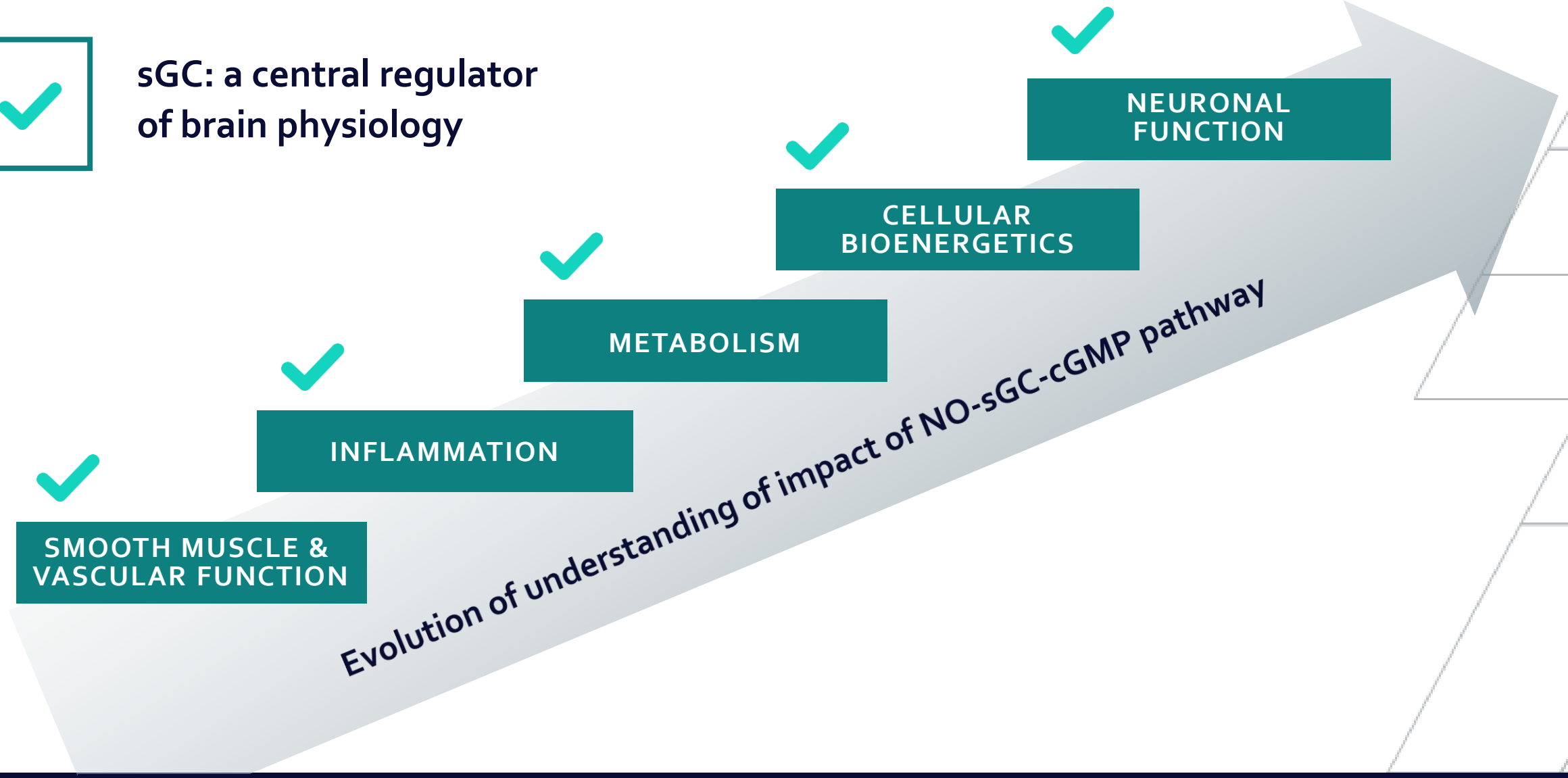
Network analysis delivers z-scores for CNS diseases similar to validated CV diseases

sGC: optimal target for pathway intervention

Broadly expressed in CNS, amplifies endogenous signaling, increases cGMP levels at the source with no attenuation of response

Growing appreciation of the role of NO-sGC-cGMP pathway in CNS disease

sGC: a central regulator of brain physiology



sGC stimulators: potential to be next druggable neurotransmitter system

Nitric oxide

- IW-6463

Successfully drugged neurotransmitter systems

GABAergic

- Valium® (1963)
- Ambien® (1992)

Dopaminergic

- Levodopa (1970)
- Risperdal® (1993)

Adrenergic/Serotonergic

- Amitriptyline (1961)
- Prozac® (1987)
- Paxil® (1992)

Cholinergic

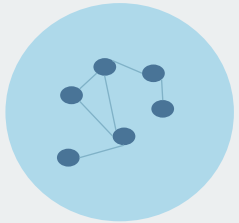
- Scopolamine (1979)
- Aricept® (1996)

Glutamatergic

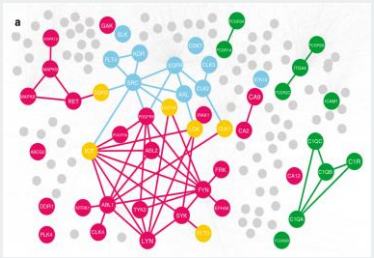
- Ketamine (1970)
- Namenda® (2003)

NO-sGC-cGMP pathway:
From validated cardiometabolic diseases to CNS disease validation

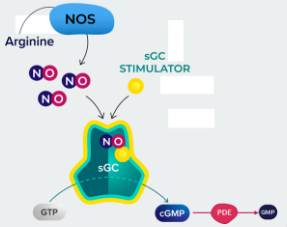
Disease genetics network



Human interactome



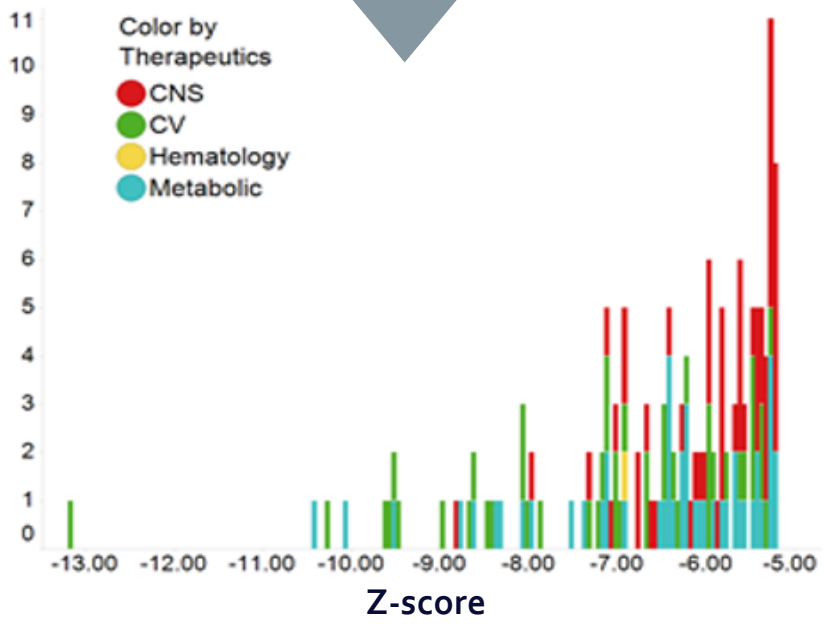
NO-sGC-cGMP pathway



Network analysis reveals disease linkage

Cardiometabolic Diseases

- hypertension*
- diabetic nephropathy*
- heart failure*
- arteriosclerosis
- diabetes*
- PAH*
- sickle cell anemia



CNS Diseases

- Alzheimer's disease
- cognitive impairment
- stroke
- bipolar disorder
- schizophrenia
- depression
- Huntington's disease

**sGC stimulator(s) with clinical effects*

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

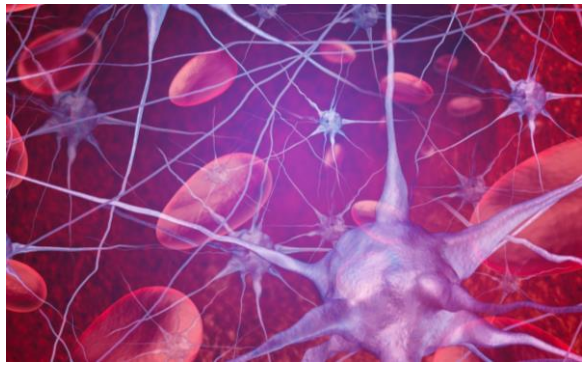
Neuro-inflammation

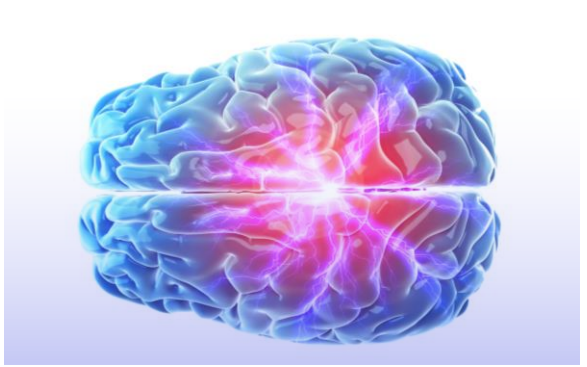
Decreased markers of LPS-induced neuroinflammation (ICAM1, VCAM1, IL6) *in vitro*

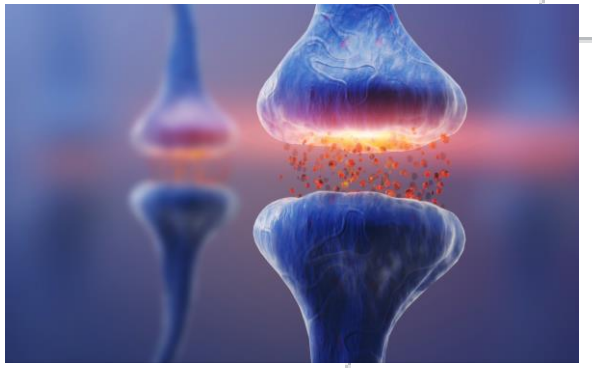
IMPROVE

Neuronal Function

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







Attractive nonclinical profile supports clinical development

- IW-6463 demonstrates pharmacological activity across four distinct domains in multiple preclinical models
- preclinical results support straightforward translation into the clinic
- CNS exposure and target engagement demonstrated in multiple species
- no evidence of CYP enzyme inhibition and IW-6463 not a P-gp substrate
- nonclinical toxicology profile consistent with other sGC stimulators in development

Translational pharmacology study: confirming CNS activity

1 Now is the time: value in CNS

2 sGC and CNS: scientific and clinical basis for CNS therapies

3 **Translational pharmacology study: demonstrating CNS activity**

4 Clinical direction in CNS: important indications that yield early answers

- rational indication selection approach for CNS diseases
- phase 1 GO – identified well-tolerated doses achieving the desired CNS exposure
- elderly translational pharmacology study focused on CNS target engagement (late summer)

Biomarker-driven IW-6463 early clinical development strategy

top line data 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

IW-6463 Phase 1: CNS exposure, target engagement, PK, and safety

PHASE 1 *(completed)*

Study design

- three stages:
  - SAD
  - MAD
  - food interaction
- 110 healthy volunteers
- age range 18-63
- standard safety
- PK (blood & CSF)
- wide dose range tested

GOALS ACHIEVED

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*

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®)

Translational approach from discovery to approval and beyond

Establish PD biomarkers preclinically

Effects across four domains of neurodegenerative disease

Validate PD biomarkers in the clinic

Translational pharmacology study in elderly

Top line data late summer 2020

Refine clinical strategy

- *indication selection*
- *patient selection*
- *biomarker enrichment*
- *endpoint selection*
- *trial design*
- *regulatory approach*

Smaller/shorter studies

Evaluate IW-6463 in focused patient populations

Initial approvals based on predictive surrogate and/or symptomatic and functional endpoints

Larger/longer studies

Evaluate IW-6463's full potential

Potential to expand label to broader populations and to demonstrate disease modification

Clinical direction in CNS: important indications that yield early answers

1 Now is the time: value in CNS

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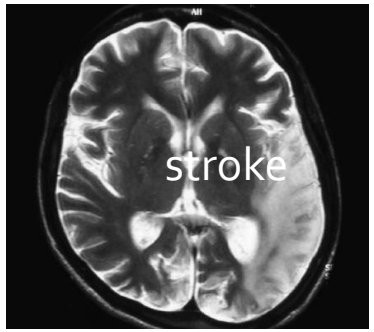
4 **Clinical direction in CNS: important indications that yield early answers**

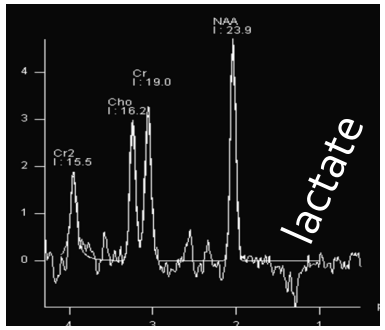
- MELAS and ADv trials designed to uncover meaningful CNS biomarker engagement
- approach efficiently de-risks & allows quick progression to the next development stages

Mitochondrial Encephalomyopathy, Lactic Acidosis,& Stroke-like Episodes (MELAS)

genetically defined orphan disease, serious CNS & multi-system problems, no approved treatments

SYMPTOM OVERVIEW



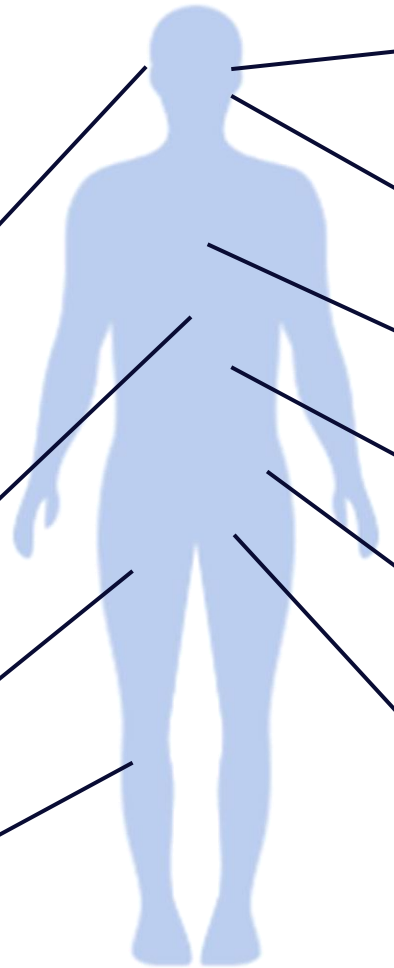


Central Nervous system
Strokes, Stroke-like Episodes (SLEs), Ataxia (Imbalance), Epilepsy (Seizures), Migraine, Headaches, Cognitive Impairment, Learning Disability, Dementia, Mood disorders

Autonomic Nervous System
Dysautonomia, Temperature Intolerance, Heart Rate Instability (POTS)

Peripheral Nervous System
Peripheral Neuropathy

Skeletal muscle
Muscle weakness, myopathy, exercise intolerance



Vision
Vision Loss, Cortical Blindness, Ptosis, Ophthalmoplegia, Retinal-Optic Nerve Disease

Hearing
Sensorineural Hearing Loss, Tinnitus

Cardiac
Sudden Death, Arrhythmias, Cardiomyopathy

Gastrointestinal
Vomiting, Pseudoobstruction

Endocrine/Metabolic
Diabetes Mellitus, Short Stature, Underweight, Fatigue, Lactic Acidosis

Renal
Nephropathy

Focused MELAS trial population for trials; potential for broader use

US prevalence of mitochondrial disease and CNS symptoms

Primary Mitochondrial Disease (PMD) prevalence is 1 in 4,300 individuals = US case estimate ~65K

MELAS	Kearns-Sayre Syndrome	Leigh Syndrome	Mitochondrial Depletion Syndromes	Other Presentations
≥ 90% who present with classical MELAS have stroke-like episodes, dementia, epilepsy, vision loss	**~80%** experience cerebellar ataxia, sensorineural hearing loss, ophthalmologic problems, neuropathies	**Almost all patients** present with neurologic symptoms such as stroke and developmental disabilities	**Almost all patients** exhibit neurological manifestations, including hypotonia, epilepsy, ataxia, etc.	**Prevalence of neurological symptoms ranges from 40% to 70%** for each and includes ataxia, epilepsy, vision loss, etc.

~50K PMD patients exhibit CNS symptoms

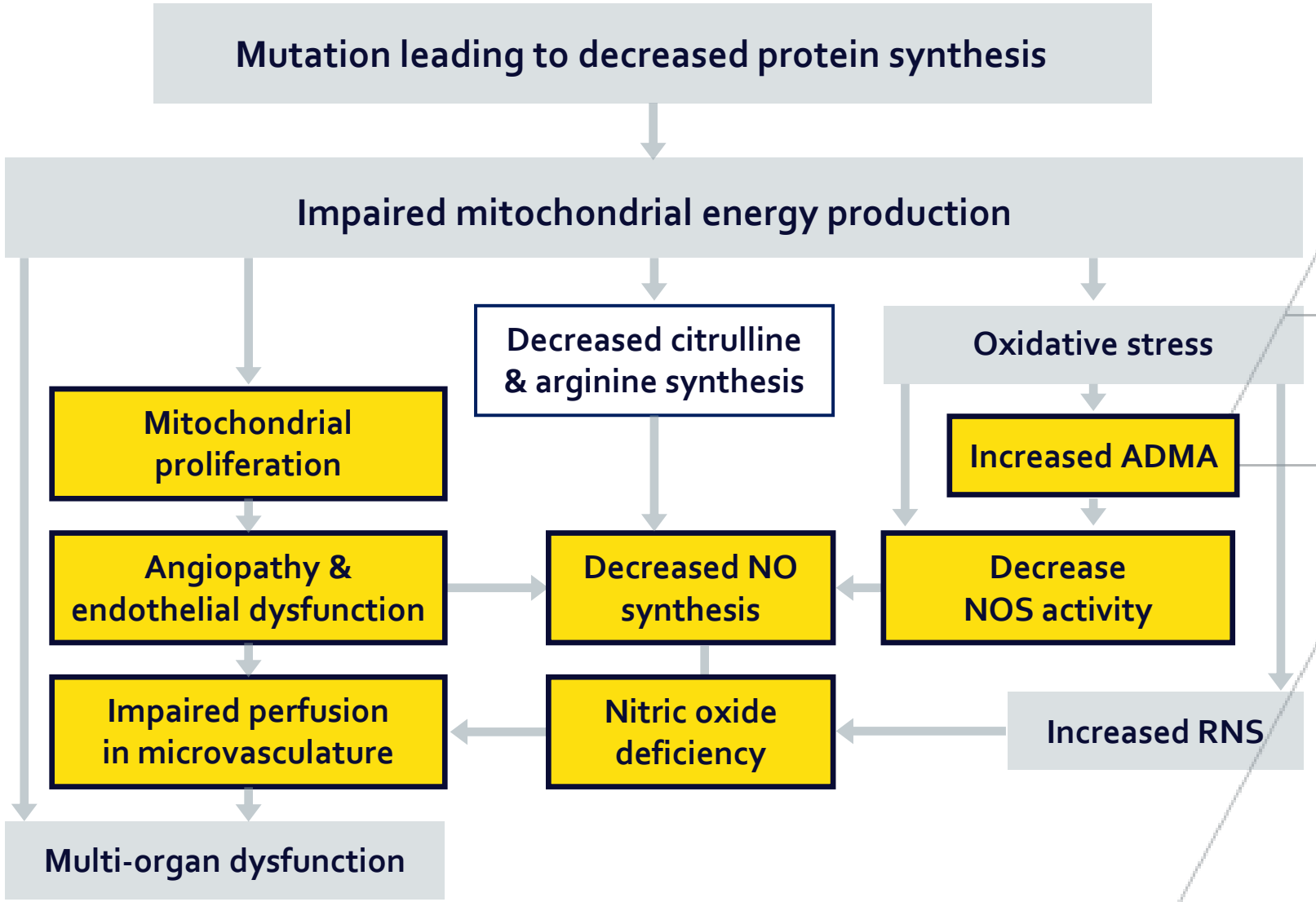
40-50% (~30K) of total PMD patients are 16 years or older
Of the 4 target diseases, 55-65% (~25K) fall into this age category due to both later diagnosis and longer life expectancy

See citations in the appendix

IW-6463: potentially impacts MELAS pathophysiology at multiple points

Impact of L-Arginine/citrulline treatment

Potential therapeutic benefit of IW-6463



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

Ph 2a: open-label study of IW-6463 in patients with MELAS

STUDY START 2H 2020

Enrichment strategy

- genetically defined MELAS with neurological features and elevated plasma lactate (disease biomarker)

Treatment

- once-daily IW-6463
- 29 days
- up to 20 adults (targeting 12 completers)

Sites

- centers of excellence for mitochondrial diseases: CHOP, MGH, Children's National, Columbia, Hopkins

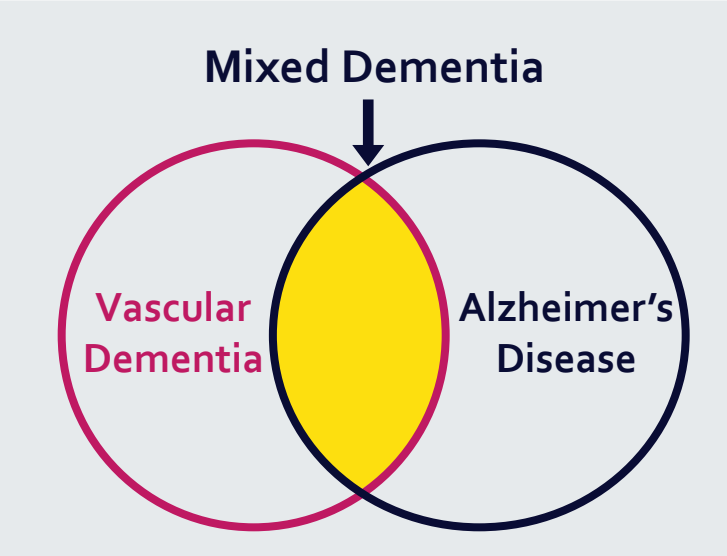
Objectives

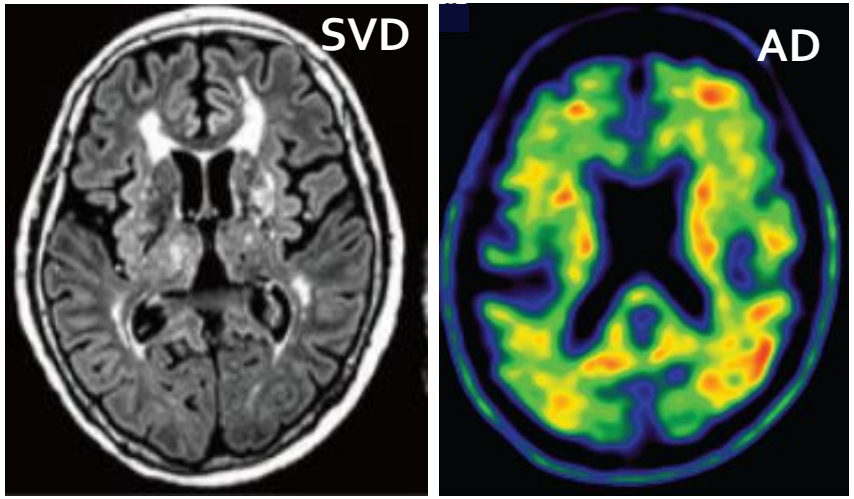
- evaluate safety, tolerability, and pharmacodynamics
- assess near-term impact on disease-specific biomarkers
- de-risk and accelerate future development

DISEASE DOMAIN	ASSESSMENT
Mitochondrial dysfunction	Lactate
Dysregulated brain perfusion	Cerebral Blood Flow (MRI ASL)
Neurodegeneration	NF-L
Cognitive impairment	Cognitive and behavior tests

Improved lactate and CBF would indicate an impact on the underlying disease mechanism and suggest potential for broad benefit for these patients.

Vascular pathology in dementia – clinical perspective





PATIENT PRESENTATION & CHARACTERISTICS

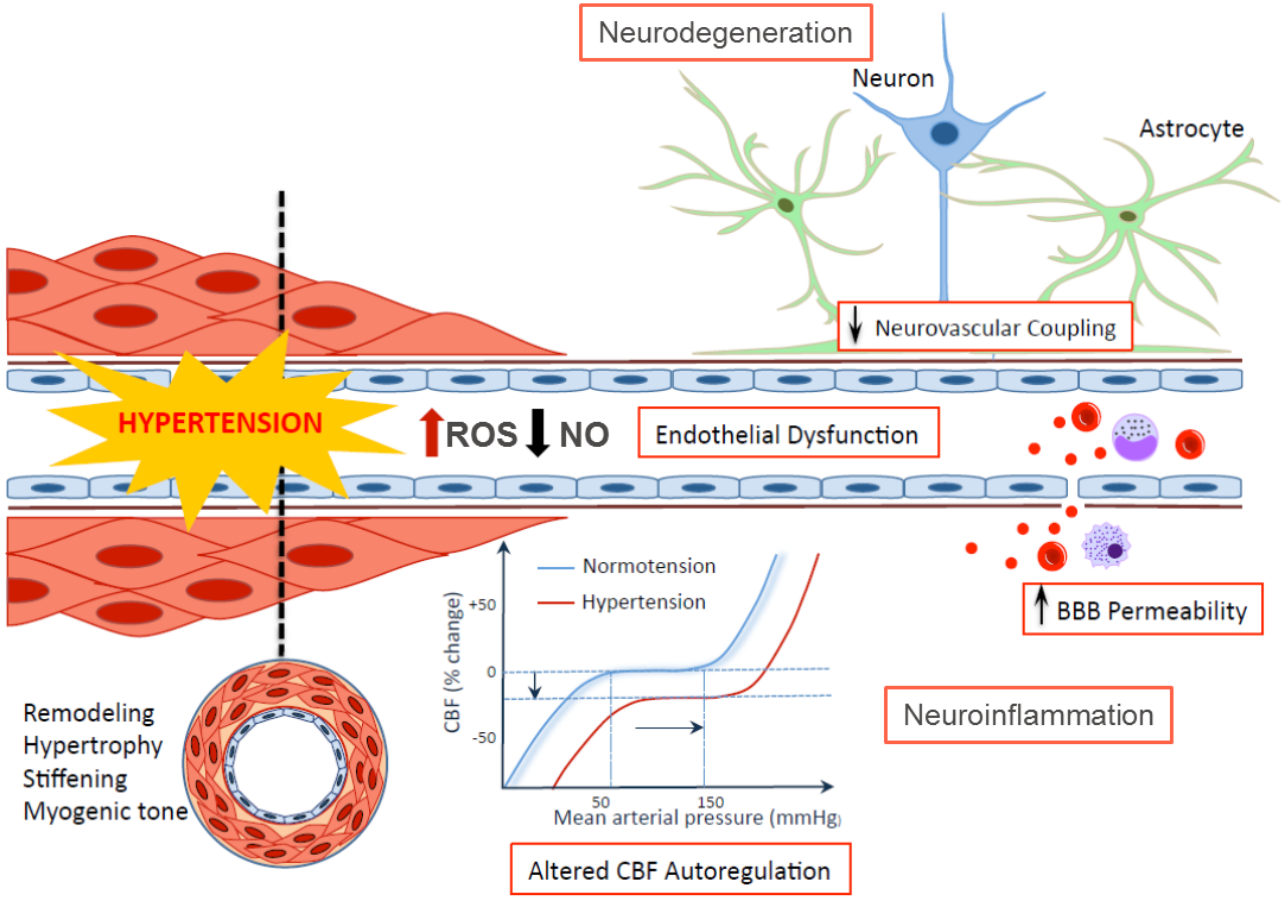
- AD & vascular dementia - two most common dementias
- pure forms exist, but vascular pathology widely prevalent in AD
- mixed dementia = broad area of overlap
- subcortical small vessel disease (SVD) in a significant portion
- mixed dementia patients more rapidly progressive disease, higher symptom severity

UNMET NEED

- ~2M US patients; incidence increasing with aging
- symptomatic treatment for AD – modest, brief benefit
- no disease-modifying therapies, none targeting the vasculature

Dementia type	Pathophysiology
Alzheimer's	• neurofibrillary tangles • amyloid plaques
Vascular	• impaired brain blood flow
Mixed Dementia	• combination of the above

Vascular pathology: a key contributor to dementia



SUPPORTIVE EVIDENCE

- risk factors and common comorbidities: DM, HTN, HL, Smoking, CAD
- ApoE risk partly mediated by endothelial dysfunction and BBB breakdown
- brain ischemic changes present in dementia, including AD; possibly independent disease progression risk factor
- vasculature implicated in a-beta brain clearance, a process that fails in AD

Adapted from Faraco and Iadecola (2013) Hypertension 62:810

See citations in the appendix

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

Defined population well suited for treatment with IW-6463

DISEASE RATIONALE FOR PATIENT SELECTION

Pathophysiology

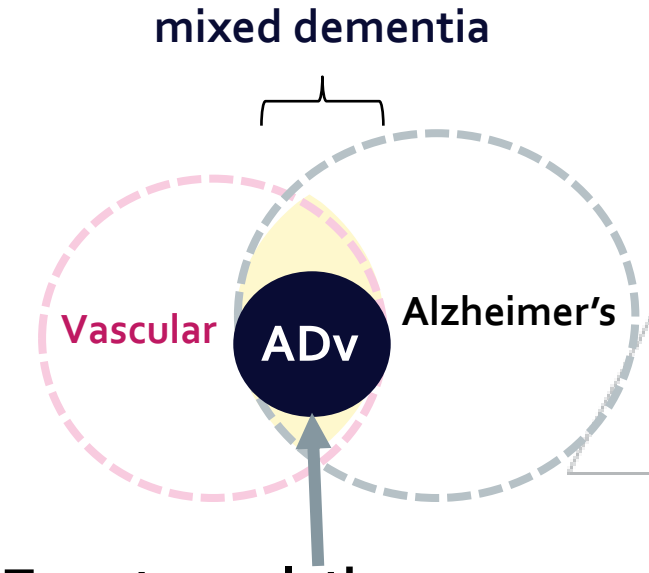
NO dysregulation, endothelial cell loss, impaired blood flow, vascular leakage, inflammation, neuronal dysfunction, and neuronal loss are major contributing factors to rapid disease progression

Standard of care

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

Pharmacology

Our preclinical data suggest 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

Ph 2a study of IW-6463 in ADv: emerging design

STUDY START 1H 2021

Treatment

- once-daily IW-6463

Enrichment strategy

- confirmed AD pathology (PET, CSF)
- 3+ cardiovascular risk factors
- mild-moderate subcortical small-vessel disease on MRI
- mini Mental State Exam score (16-26)

Objectives

- establish safety and pharmacodynamic effects of IW-6463 in a short-term study
- de-risk progression to larger, longer symptomatic and disease modification trials

DISEASE DOMAIN	ASSESSMENT
Vascular dysfunction	ASL (CBF)
Neurodegeneration	neurofilament light chain
Neuroinflammation	vascular cell adhesion molecule
Mitochondrial dysfunction	N-acetyl aspartate (MRS)
Cognitive impairment	cognitive and behavior tests

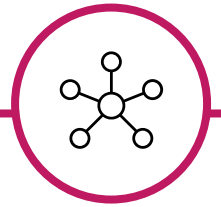
Improved CBF, particularly in the context of memory improvements, would indicate an impact on the underlying disease mechanism and enable a targeted design for the next development stage.

Committed to building CNS as a core therapeutic area

Immediate Execution

- pioneer understanding of powerful pharmacology
- IW-6463 MELAS study
- IW-6463 ADv study
- explore partnership

Current



Portfolio Advancement

- IW-6463 late stage dev
- IW-6463 additional POCs
- expanded CNS sGC portfolio
- explore additional targets/assets
- partnership(s)

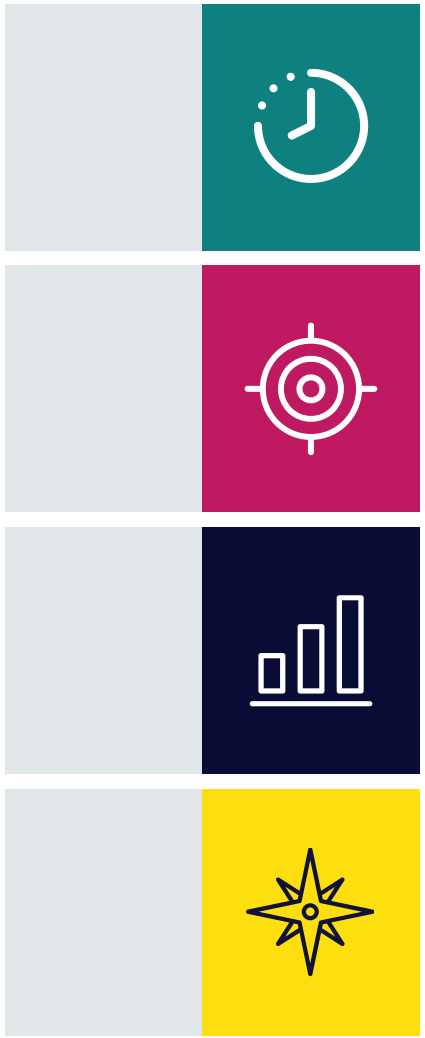
Mid-term

Portfolio Growth

- commercialization
- diversified portfolio
- robust series of clinical catalysts
- partnership(s)

Long-term

Thank you for joining



- powerful platform for potential CNS therapies
- adaptive, risk-reducing, development approach
- seasoned drug development leaders with specialized scientific advisors
- multiple ways to win: SCD and CNS
- ownership base of long-term investors and employees

Questions

Delivering impact in CNS diseases

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Citations

Page	Topic	Citation
25	MELAS epidemiolgy	Sources: 1. J Neurol. 2016; 263: 179–191; US population estimated at 327.2 million;2. Brain. 2003; 126(5): 1231–1240; 3. NIH Genetics Home Reference; 4. NCBI GeneReviews; 5. Neurotherapeutics. 2013 Apr; 10(2): 186–198
26	MELAS MOA	El-Hattab, AW et al, 2016
30	Vascular pathology	• Smith and Markus. New Treatment Approaches to Modify the Course of Cerebral Small Vessel Diseases (Stroke. 2020;51). • Bakker, Erik NTP et al. Lymphatic clearance of the brain; perivascular, paravascular and significance for neurodegenerative diseases. Cell Molec Neurobiol 36.2 (2016): 181-194. • Venturelli, Ben Aisa et al, (Cur Med Chem, 2016, 23, 2770-2788. Targeting NO/cGMP Signaling in the CNS for Neurodegeneration and Alzheimer's Disease). • Montagne et al, (Nature, 581, 7 May 2020. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline). • Iadecola C et al. (Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019;73(25):3326-44.). • Coutu JP, et al. (Two distinct classes of degenerative change are independently linked to clinical progression in mild cognitive impairment. Neurobiol Aging. 2017; 54:1-9.).