A Phase 2a pilot study evaluating IW-6463, a CNS-penetrant sGC stimulator, in individuals with MELAS

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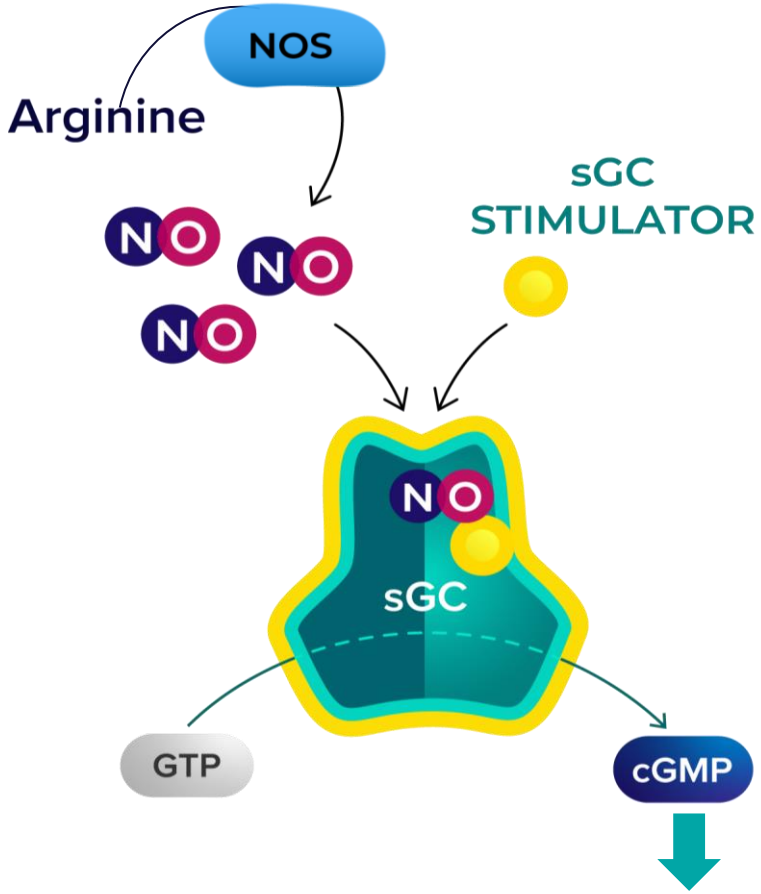
Rationale for the evaluation of IW-6463, a CNS-penetrant sGC stimulator, in mitochondrial disease



Potential Therapeutic Effects

- NO-sGC-cGMP signaling plays a central role in mitochondrial biogenesis and function, neuroprotection, and vascular homeostasis
- ~80% of individuals with mitochondrial disease have CNS symptoms
- Nitric oxide deficiency and impaired NO-sGC-cGMP signaling are well documented in mitochondrial disease and associated with CNS manifestations
  - Use of precursors of NO (L-arginine or L-citrulline) in MELAS is recommended by MMS
- IW-6463 binds to sGC, the central enzyme in the pathway, and amplifies endogenous NO signaling

Graphic adapted from Buys et al. 2018.. Nitric Oxide 78:72-80

MMS=Mitochondrial Medicine Society

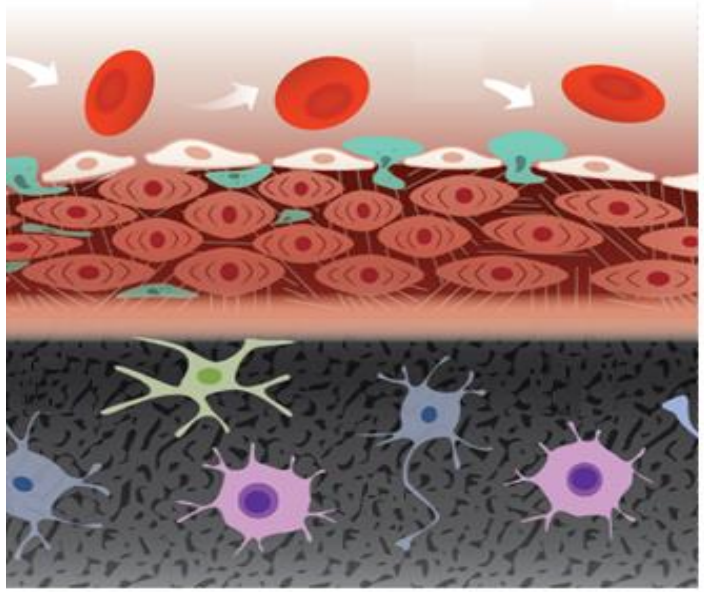
In preclinical studies, IW-6463 demonstrates positive effects across four key domains of neurodegenerative disease

Cerebral Blood Flow	**Improved** cerebral blood flow in areas associated with memory and arousal by fMRI BOLD imaging
Cellular Bioenergetics	**Increased** ATP and restored an already depressed gene expression in cells from individuals with mitochondrial diseases
Neuroinflammation	**Decreased** markers of LPS-induced neuroinflammation in vitro
Neuronal Function	**Restored** hippocampal long-term potentiation in a mouse neurodegenerative model and **prevented** decline in hippocampal spine density in aged animals **Improved** cognitive performance in rodent models with cognitive deficits

IW-6463 has the potential to restore NO signaling in individuals with mitochondrial disease

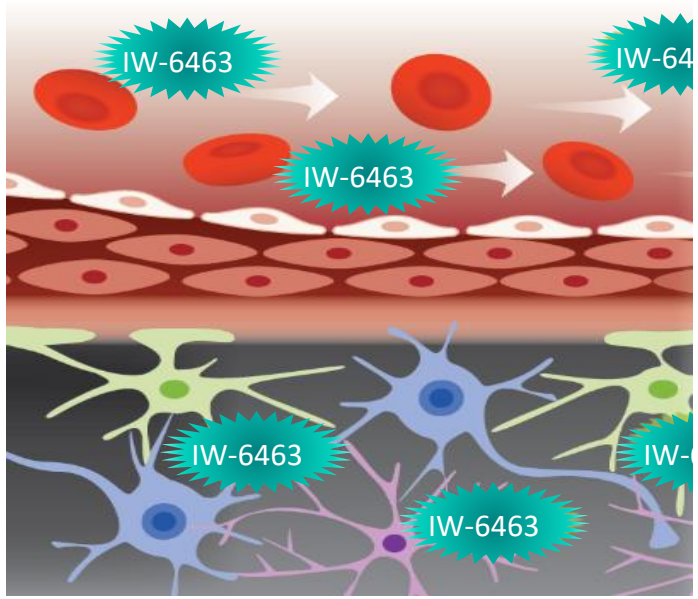
Deficient NO signaling

- Impaired neurovascular blood flow
- Mitochondrial dysfunction
- Neuroinflammation
- Neurodegeneration



Restore NO signaling

- Increase blood flow
- Improve bioenergetics
- Decrease inflammation
- Enhance neuronal function



Adapted from Tobin, Zimmer et al. J Pharmacol Exp Ther 2018;365:664-675. Copyright © 2018 The Author(s).

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

A three-part, randomized, placebo-controlled study in 110 healthy volunteers

Phase 1 (completed)

Overview of results

- Well tolerated at all single and multi-dose levels
  - No discontinuations due to AEs, no SAEs
  - All AEs reported were mild
- Linear, predictable PK; consistent with QD dosing
- May be taken with or without food
- CNS exposure confirmed
- Evidence of target engagement

Dose Selected

Identified safe and well-tolerated dose level with steady-state CNS exposure in therapeutic target range*

*Based on positive CNS pharmacology in multiple preclinical models

MELAS: rare neurometabolic mitochondrial disease of high unmet need

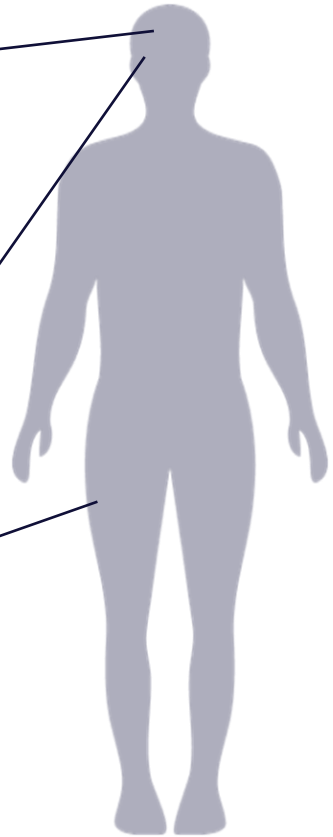
Genetically/phenotypically defined, nitric oxide deficiency, no approved treatments

MELAS Symptom Overview

Nervous system
Seizures, SLEs, ataxia, dementia, headaches, altered consciousness, hearing loss, learning disability, peripheral neuropathy

Eyes
Vision abnormalities

Skeletal muscle
Muscle weakness, myopathy, exercise intolerance



Rationale for selection of MELAS

Clinical precedence for NO-sGC-cGMP pathway

L-Arginine (NO precursor) for acute and prophylactic treatment for stroke-like episodes

Pathophysiology

Impaired blood flow, inflammation, angiopathy, and endothelial dysfunction with severe impacts on small vessels in the brain

Pharmacology

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

MELAS=mitochondrial myopathy, encephalomyopathy, lactic acidosis, and stroke-like episode

Phase 2a multicenter, open-label, pilot study in individuals with MELAS

Objectives

Evaluate safety, tolerability, and pharmacodynamics; assess near-term impact on disease-specific biomarkers

Enrichment strategy

Neurological features of MELAS and elevated plasma lactate

Treatment

Once-daily IW-6463 for 29 days

- *Note: Participants may continue taking concomitant arginine/citrulline*

Enrolling ~20 participants

Disease domain	Assessment
Mitochondrial dysfunction	Lactate*, GDF-15, pyruvate, alanine, IL1-β, L-arginine
Dysregulated brain perfusion	ASL (CBF), fMRI BOLD, asymmetric dimethylarginine
Neurodegeneration	NF-L
Cognitive impairment	Tests of cognitive function & mental fatigue

*Lactate assessment includes in the brain via Magnetic Resonance Spectroscopy

- GDF-15=growth differentiation factor-15
- IL-1β =interleukin- 1beta
- ASL=arterial spin labeling
- CBF=cerebral blood flow
- NF-L=neurofilament light chain