A pilot study of IW-6463*, a CNS-penetrant sGC stimulator, in individuals with MELAS

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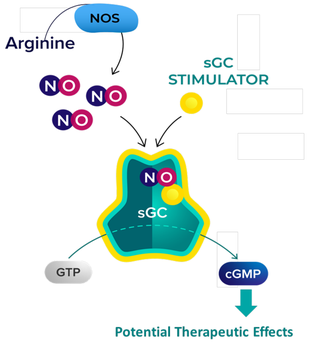
*Also known as CY6463

Mechanism of Action

IW-6463 is an orally administered central nervous system (CNS)-penetrant stimulator of soluble guanylate cyclase (sGC), a signaling enzyme that catalyzes the formation of cyclic guanosine 3',5'-monophosphate (cGMP) from guanosine triphosphate (GTP) in response to nitric oxide (NO) binding.



The NO signaling pathway plays a role in cognitive processes and neuroprotection and is critical for the regulation of mitochondrial function and biogenesis.

Preclinical Evidence

Data from nonclinical studies evaluating IW-6463 support the hypothesis that sGC stimulation may have beneficial effects on several key aspects of mitochondrial disease pathologies

- IW-6463 **increased ATP** and **normalized gene expression** in cells from patients with mitochondrial diseases (*see Mito Medicine 2020 poster by Liu et al. for more details*)
- IW-6463 **increased brain activity** in areas associated with memory and arousal as measured by fMRI BOLD imaging in rats

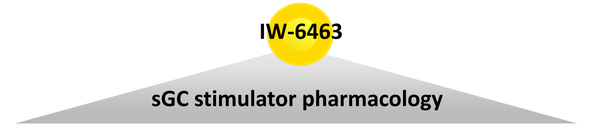
MELAS Pathophysiology

MELAS patients have metabolic dysfunction, elevated lactate, decreased NO, as well as CNS vascular pathology (e.g., impaired blood flow, inflammation, endothelial dysfunction, and small vessel disease).

The inclusion of L-Arginine (an NO precursor) in treatment guidelines for the acute management of stroke-like episodes suggests that modulation of this pathway is a promising pharmacological approach to treating MELAS.

MELAS Pathophysiology

Mitochondrial dysfunction and the energy deficiency that results, gives rise to a range of downstream pathophysiological findings that the multidimensional pharmacology of IW-6463 has the potential to address.



Vasculopathy
Angiopathy, dysregulated perfusion, poor endothelial health and function

NO Deficiency
Decreased arginine, citrulline and NO synthesis

Oxidative stress
Increased reactive oxygen/nitrogen species

El-Hattab et al 2015

Arginine may have the potential to enhance IW-6463 pharmacology

MELAS Clinical Phenotype

MELAS is a serious, multi-system disease with no approved treatments and significant CNS involvement

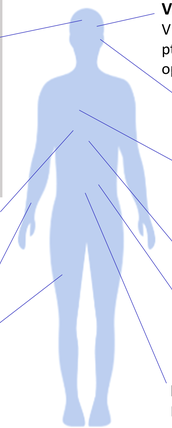
IW-6463 current treatment focus

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, pseudo-obstruction

Endocrine/Metabolic
Diabetes mellitus, short stature, underweight, fatigue, lactic acidosis

Renal
Nephropathy

Phase 1 First-in-Human Study Design

A three-part, randomized, placebo-controlled study

KEY GOAL Identify a safe, well-tolerated dose with steady-state CNS exposure in therapeutic target range established by preclinical pharmacology

Single ascending dose	Multiple ascending dose	Food interaction
• 7 cohorts of 8 subjects (6:2) • PK in plasma	• 4 cohorts of 10 subjects (8:2) • 14 days of repeat daily dosing • PK in plasma and CSF	• 14 subjects • 2 treatment, 2 sequence

Total of 110 healthy volunteers age 18-64
Standard and neurological safety assessments
Blood and CSF sampling for pharmacokinetics

Phase 1 First-in-Human Study Findings

- Linear, predictable PK; consistent with once-daily 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

Goal Achieved
Identified safe and well-tolerated dose level with steady-state CNS exposures in the targeted range

MELAS Pilot Study Design

Objective: Evaluate safety, tolerability, pharmacodynamics and effects on disease-specific biomarkers

Treatment
- Once-daily IW-6463, open-label, for 29 days
- Up to 20 adults (targeting 12 completers)

MELAS Pilot Study Design

Enrichment strategy
- Genetically confirmed mitochondrial disease
- Neurological features consistent with MELAS phenotype
- Elevated plasma lactate concentrations

Exploratory pharmacodynamic assessments

Disease domain	Assessment
Mitochondrial dysfunction	Brain/plasma lactate
Dysregulated brain perfusion	Cerebral blood flow
Neurodegeneration	NF-L
Cognitive impairment	Cognitive, behavior tests

Conclusions

- IW-6463 is the first CNS-targeted sGC stimulator in clinical development
- Preclinical data suggest IW-6463 has the potential to impact multiple MELAS pathophysiologies and support clinical evaluation of IW-6463 in these patients
- In healthy subjects, single and multiple once-daily doses of IW-6463 were well-tolerated with no safety concerns, and pharmacokinetics were linear, predictable, and not impacted by food
- This Phase 2a pilot study (NCT04475549) in participants with MELAS will evaluate IW-6463's safety/PK profile, pharmacodynamic effects, and impact on disease-specific biomarkers
- Data to inform further development in Phase 2/Phase 3 are expected mid-2021

References

- Liu G, Jung J, Yan S, Hadcock J, Germano P, Jones J, Iyengar R, Winrow C, Correia S. CY6463, a CNS-penetrant sGC stimulator, increases cellular ATP levels and mitochondrial gene expression in mitochondrial disease patient cells. Mitochondrial Medicine Conference 2020.
- 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.
- Bates MG, Bourke JP, Giordano C, d'Amati G, Turnbull DM, Taylor RW. Cardiac involvement in mitochondrial DNA disease: clinical spectrum, diagnosis, and management. Eur Heart J. 2012 Dec;33(24):3023-33