There are thousands of children with mitochondrial diseases and zero cures.

We're working to change that.

At Akron Children's Mitochondrial Center, our world-renowned pediatric neurologists are helping lead the industry in mitochondrial research, treatment and the search for a cure. Using an integrative approach, we tailor our care to specifically meet the needs of each child and are dedicated to helping them thrive.

Visit us at: **akronchildrens.org/MitochondrialCenter**

Mitochondrial Center | Akron Children's Hospital

Primary Mitochondrial Myopathy Study

Stride Study

What is this study about?

Reneo is conducting a study with REN001, an investigational drug that could help decrease fatigue, improve physical activity, and improve other symptoms in patients with primary mitochondrial myopathies (PMM). The study will help Reneo learn if REN001 is safe and well tolerated and if it improves symptoms in patients with PMM.

Who can take part?

The STRIDE Study will include adult (18 years and over), male and female patients with a confirmed PMM diagnosis due to a known genetic mutation of the mitochondrial DNA.

As with all clinical studies, before you take part in this study, your doctor will need to conduct some tests to make sure it is safe for you to participate.

What is REN001?

The study drug used in this study is called REN001.

REN001 was tested previously in 4 clinical studies, including more than 100 people, including healthy volunteers and patients with PMM.

In all these studies, REN001 was generally well tolerated. Laboratory tests and exercise tests indicate that REN001 may improve energy production within muscle cells, improve muscle function and reduce fatigue and other symptoms associated with PMM.

Will there be any costs to me associated with my participation in the study?

There are no costs to you associated with taking part in this study. All the costs related to your participation in the study will be covered. If you need to travel to the study site, a concierge service will help book, organize and pay for your travel and hotels and will also make sure you are promptly reimbursed for any other study expenses such as refreshments.

Patients taking part in the study will be supported with the option of home nursing visits for some study visits if they would prefer not to travel to the study location.

What is involved in taking part in the STRIDE study?

If you agree to participate in this study, you will be asked to take the study drug (two capsules) once a day with food for 24 weeks. You have a 50/50 chance of being given REN001 or a Placebo (inactive medication). You, your doctor, and Reneo will not know which treatment you received (REN001 or Placebo) until the end of the study. The study will have 8 visits however, only 4 of these will need to be at the study center; the other 4 visits may take part at your home if you prefer.

Visit 1: Screening visit
(approximately 6 hours at study center)

Visit 2: Baseline visit
(approximately 8 hours at study center). If appropriate, this visit may be conducted over 2 days due to the number of tests.

Visit 3: Week 2
(approximately 1 hour at study center or at home)

Visit 4: Week 4
(approximately 1.5 hours at study center or at home)

Visit 5: Week 2
(approximately 8 hours at study center)

Visit 6: Week 18
(approximately 1.5 hours at study center or at home)

Visit 7: Week 24 visit
(approximately 8 hours at study center)

Visit 8: Follow Up visit
(approximately 1 hour at study center or at home)

Most visits will include blood tests, questionnaires, and short exercise tests. These tests will be done to determine whether REN001 is safe and effective.

Where is the study taking place?

The study is being run in many study centers in the United States and globally in United Kingdom, New Zealand, Australia, and Europe.

How do I find out more about the Stride study?

If you are interested in taking part in the study and would like more information, **click here.**

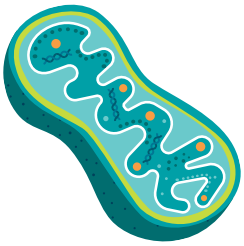
Reneo® Pharmaceuticals

Understanding TK2d

A Rare, Under-Recognized Genetic Mitochondrial Disorder

THYMIDINE KINASE 2 DEFICIENCY

Thymidine kinase 2 deficiency (TK2d) is a debilitating and life-threatening genetic disorder that causes progressive and severe muscle weakness.[1,2,3,4] Many patients lose the ability to walk, eat, and breathe independently.[1,2,3,4]



What causes TK2d?

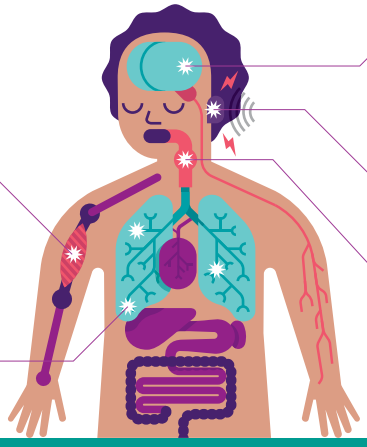
TK2d is caused by a genetic mutation in the TK2 gene.[1,4] This mutation leads to a decrease in mitochondrial DNA production.[1,4] Mitochondria generate most of the energy that powers our cells. Errors in mitochondrial DNA can lead to insufficient energy, and as a result, muscles and organs can't function properly.[4,5,6]

How many people have TK2d?

1 in 5,000 people have some form of genetic mitochondrial disease.[7] Prevalence of TK2d itself is still being researched.

PROGRESSIVELY WORSENING SYMPTOMS

TK2d can manifest in different ways and affect different parts of the body[1,2,3]



Nervous System
Fatigue
Developmental delays/ missed milestones (younger patients)

Ears
Progressive hearing loss

Gastrointestinal
Difficulty swallowing

Muscles
Muscle weakness
Low muscle tone
Difficulty walking, talking
Droopy eyelids (ie, ptosis)

Lungs
Difficulty breathing

IMPACTS ALL AGES: Age of onset predicts disease severity[1,2]

EARLY ONSET: MORE SEVERE — LATER ONSET: LESS SEVERE

Normal Development — **Infant/Child Onset** — **Adolescent Onset** — **Adult Onset**

TK2D TREATMENT TODAY: No FDA-approved therapies currently available[8]

Patients require medical equipment and therapies[1,3,8]

- Respiratory support
- Feeding tubes
- Wheelchairs
- Respiratory physiotherapy
- Physical therapy

Patients may take nutraceuticals ("mito-cocktail") to manage disease symptoms[8]

Patients rely on supportive care provided by many specialists[7]

- Neurologists
- Pulmonologists
- Metabolic specialists
- Gastroenterologists
- Physical therapists
- Speech therapists
- Clinical geneticists
- Genetic counselors

Genetic Testing Is Necessary

Earlier accurate diagnosis helps to identify patients sooner and get them on supportive care and into clinical trials faster.[1,2,3]

Because TK2d can present like other diseases (muscular dystrophy, Pompe, SMA, mtDNA depletion syndrome, and others), genetic testing is needed to confirm a diagnosis.[1]

If you or your family member has TK2d:

Learn more at www.tk2d.com

Our Commitment

At Zogenix, we are proud to partner with physicians and patient communities in our work.

Together we can bring hope and support to patients and families impacted by rare diseases.

1 Garone C, Taylor RW, Nascimento A, et al. Retrospective natural history of thymidine kinase 2 deficiency. J Med Genet. 2018;55(8):515-21. **2** Wang J, Kim E, Dai H, et al. Clinical and molecular spectrum of thymidine kinase 2-related mtDNA maintenance defect. Mol Genet Metab. 2018;124:124-30. **3** Domínguez-González C, Hernández-Laín A, Rivas E, et al. Late-onset thymidine kinase 2 deficiency: a review of 18 cases. Orphanet J Rare Dis. 2019;14(1):100. **4** National Institute of Health. TK2-related mitochondrial DNA depletion syndrome, myopathic form. https://medlineplus.gov/genetics/condition/tk2-related-mitochondrial-dna-depletion-syndrome-myopathic-form/#genes. Accessed April 27, 2021. **5** United Mitochondrial Disease Foundation. Understanding & Navigating Mitochondrial Disease. https://www.umdf.org/what-is-mitochondrial-disease-2/. Accessed April 27, 2021. **6** Hirano M, Marti R, Ferreiro-Barros C, et al. Defects of intergenomic communication: autosomal disorders that cause multiple deletions and depletion of mitochondrial DNA. Semin Cell Dev Biol. 2001;12:417-27. **7** Parikh S, Goldstein A, Karaa A, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2017;19(12):10.1038/gim.2017.107. **8** El-Hattab AW and Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013;10:186-98.

ZOGENIX
Rare Disease Therapies

ASP0367 Development Program and 0367-CL-1201 Study Update

About ASP0367

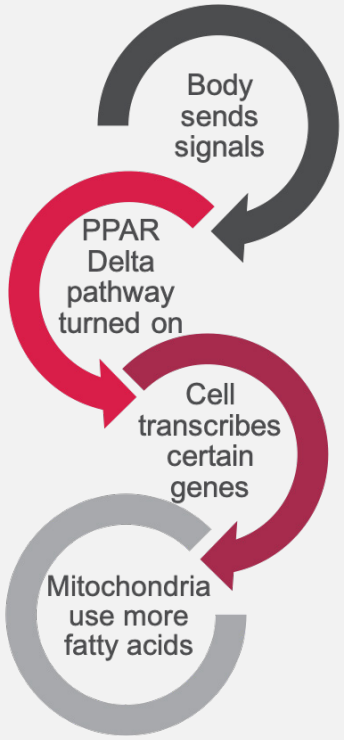
ASP0367 is an oral 1 x daily tablet being investigated for the treatment of **exercise intolerance, endurance, and fatigue** in patients with **mitochondrial myopathies.**

Primary Mitochondrial Myopathies (PMM) are genetically defined disorders leading to defects in mitochondrial function affecting mainly skeletal muscle.

ASP0367 is being investigated to determine whether it can turn on the PPAR δ pathway.*

*The safety and efficacy of the ASP0367 has not been established. There is no guarantee that ASP0367 will receive regulatory approval or become commercially available for uses being investigated . ASP0367 is not authorized for sale in any jurisdiction.

- The PPAR δ pathway regulates mitochondria by turning on different genes in the cell.
- When the pathway is on, the mitochondria use fatty acids more often and more mitochondria are made.
- Using more fatty acids for energy results in increased energy production.



Wang et al., Regulation of muscle fiber type and running endurance by PPAR delta. PLoS Biol. 2004

Barish et al., PPARδ: a dagger in the heart of the metabolic syndrome. J Clin Invest. 2006

Phase 2/3 Clinical Trial

Study design & population

- Phase 2/3, randomized, double-blind, placebo-controlled clinical trial
- A total of 139 adult participants (ages 18 to 80) with PMM

Primary purpose

- To assess the effect of ASP0367 on functional improvement relative to placebo
- To assess the safety and tolerability of ASP0367

Site locations

- Approx 15 sites across the United States
- To find a participating site near you, visit www.clinicaltrials.gov and search NCT04641962

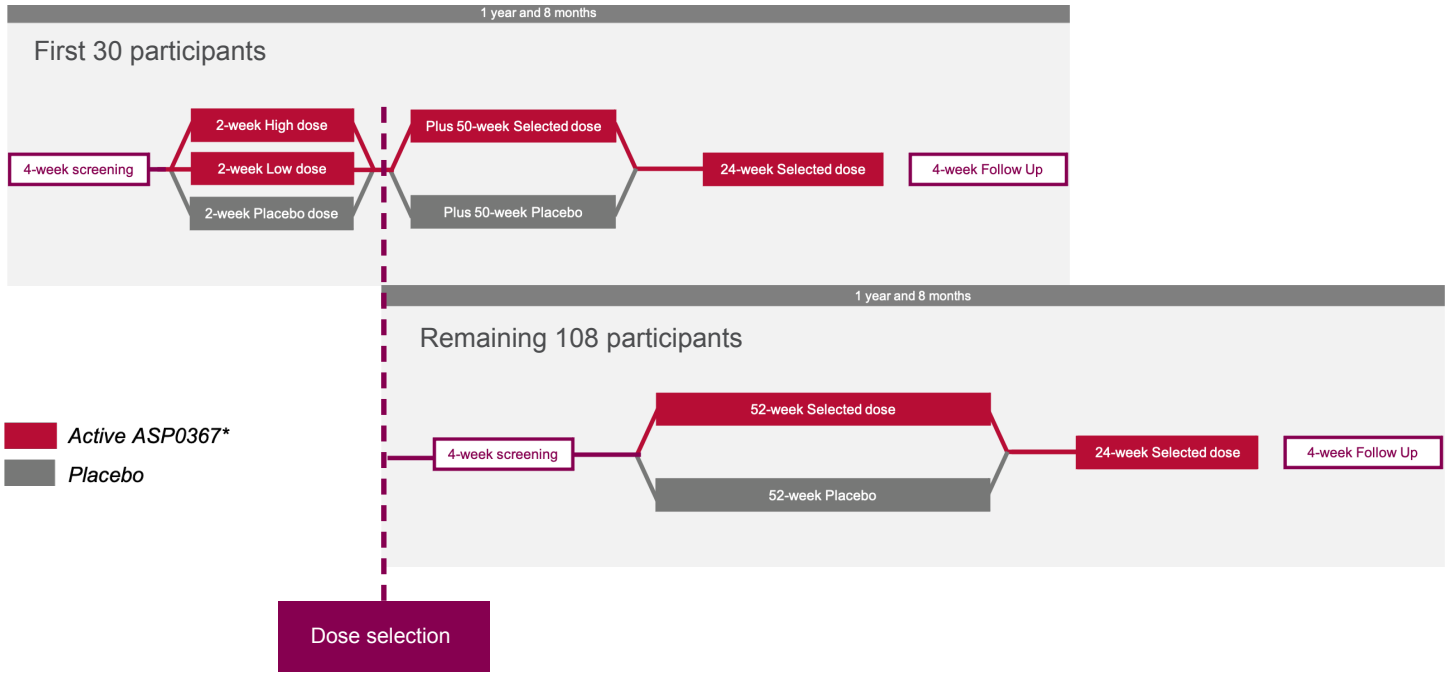
astellas

Community Newsletter

Do you have questions? Astellas Pharma Global Development can help.

Email: astellas.registration@astellas.com Call: (800) 888-7704

Study Schedule



What Happens at Study Visits

Your general health

Exams by your study doctor at visits, blood and urine tests

Heart tests

ECG

Muscle function tests with imaging markers (at a specific clinical center only)

Muscle and heart imaging assessments

How your body uses the drug

Blood and urine tests

How you move your body

Tests in clinic: 6-minute walk test and 5 times sit to stand

Test at home: video recordings using mobile app

How you feel and think

Tests in clinic: Quality of Life surveys, fatigue scales and other surveys

Tests at home: remote interviews and surveys on the impact of your condition as well as any changes in your daily activities

Inclusion Criteria

- Adult (ages 18 to 80 years old)
- Has a diagnosis of PMM confirmed by genetic testing with reported symptoms of myopathy
- Can adhere to the study requirements such as performing 6 minutes walking test (6MWT), the use of digital applications and video recordings

More Information

- Visit www.clinicaltrials.gov and search for NCT04641962 for more details about this study.
- Email to Astellas Pharma Global Development Astellas.registration@astellas.com, or call at 800-888-7704.

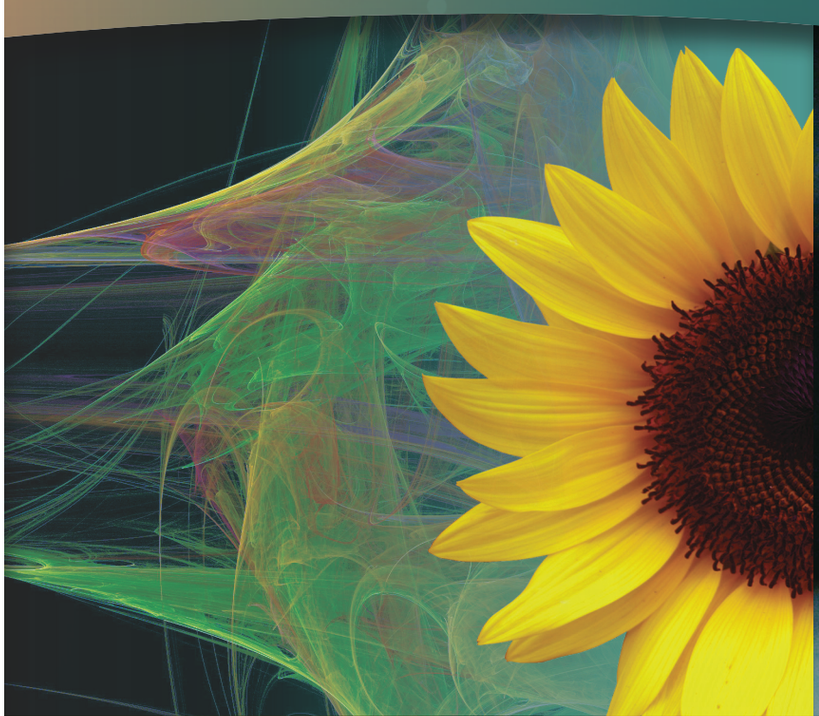
astellas

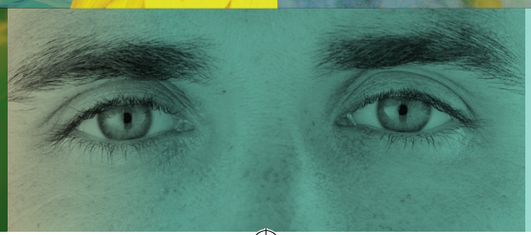
GenSight BIOLOGICS

GENE THERAPY PIONEER TARGETING BLINDNESS

GenSight Biologics is developing ground-breaking gene therapies against inherited degenerative diseases of the eye and central nervous system.

GenSight-Biologics.com





The MIT-E Study

A clinical research study for children and teenagers who have mitochondrial disease with associated epilepsy.

Find out more at
www.themit-estudy.com

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UNITED MITOCHONDRIAL DISEASE FOUNDATION®

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Vincent Canzanese, RPh, Owner, CEO

CONTACT

3400 Edgmont Avenue
Brookhaven, PA 19015

Phone: 610-872-5418
Toll free: 866-872-5430 (toll free)
Fax: 610-872-969 (fax)
Web: www.summithealthrx.com

HOURS OF OPERATION

Monday-Friday
8:30am-7:00pm

Saturday
9:00am-3:00pm

Sunday
Closed

AFTER HOURS

A Pharmacist is available to answer your urgent concerns **24/7**. Just follow the telephone prompts and leave a message. A pharmacist will return your call.

CURRENTLY SERVING:

PA, DE, MD, NJ, OH, CT, IN, IA, IL, and FL

We are currently pursuing licenses in additional states, so please contact us for additional service areas.

SUMMIT HEALTH PHARMACY

ELEVATE YOUR HEALTHCARE

Compounding Specialists

ABOUT US

Summit Health Pharmacy is an independent community pharmacy. We are here to help meet all your medication needs: whether you need standard medications, medication compounding, or individualized medications, we have you covered. We have made investments in education, research, technology and a state-of-the-art facility to become experts in the field of mitochondrial medication.

MITOCHONDRIAL MEDICATION COMPOUNDING:

Summit Health Pharmacy has been involved in mitochondrial disease support for over 10 years. We continue to participate and follow closely the science, studies, independent testing and cutting-edge advancement of mitochondrial research. We view all aspects of mitochondrial medication with a critical eye including the highest quality medication ingredients in the industry. The distinguished chemicals we use have been tested and have met the highest standards of excellence. Beyond that, the complexity of the mitochondrial preparation warrants only the skill of a pharmacist with expertise in mitochondrial medication compounding. Specifically, we take every measure to ensure a custom, pure, workable end product for our patients.

SERVICE

Here at Summit Health Pharmacy, we develop a personal connection to our "Mito" patients and their families. We work closely with providers and caregivers to handle every delicate and specific issue that arises to ensure our patients take their medication comfortably and maximize the health benefits.

ADVOCACY

We handle any insurance and payment issues within our ability and deflect these issues away from the patients and their families. At your request, we are pleased to advocate for your mitochondrial patient in the appeals process to insurance boards. We have had much success in the past, and we are willing to help you too!

ABLIVA

Abliva - Delivering Mitochondrial Health

Abliva is a biopharmaceutical company developing medicines for the treatment of primary mitochondrial diseases.

Innovative strategies to restore mitochondrial energy

The portfolio includes two advanced projects and several early opportunities.

- **KL1333** restores the balance of NAD^+/NADH, creating new mitochondria. KL1333 will start enrolling patients in a global, Phase 2/3 study later this year.
- **NV354**, an energy replacement therapy, is in preclinical development with the goal of entering clinical Phase 1 in 2022.

Find out more in our videos

Patients

Strategy

Mitochondria Day 2020

info@abliva.com

www.abliva.com

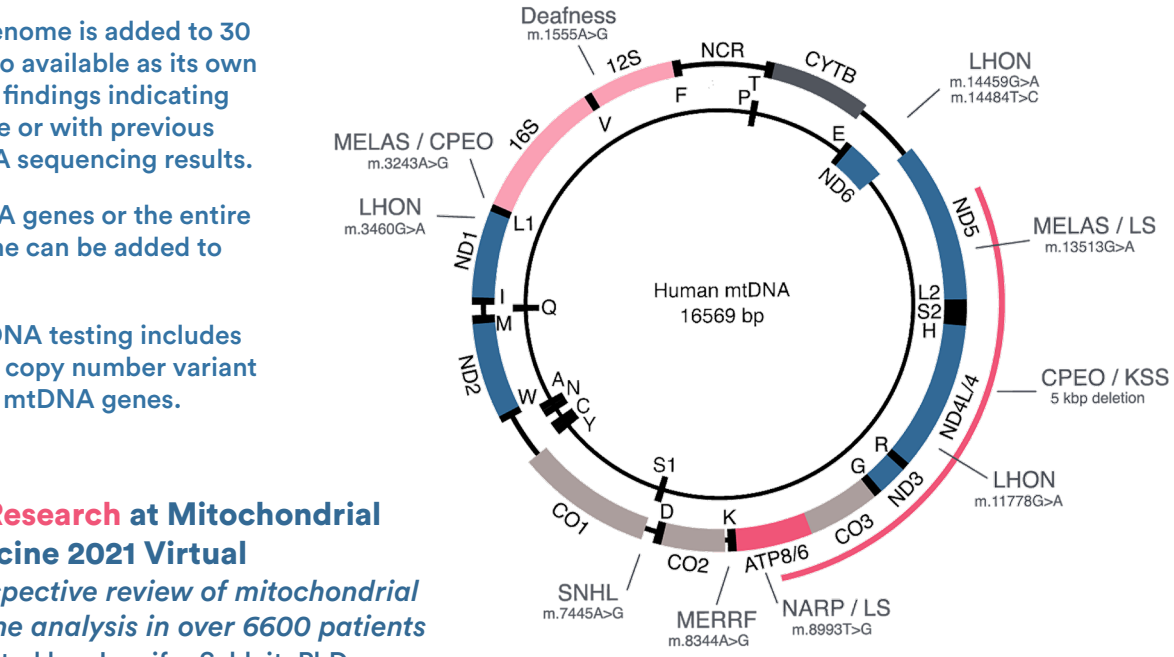
LinkedIn

YouTube

Mitochondrial genome analysis in panel-based testing: A powerful diagnostic tool

A high-quality mitochondrial DNA analysis combines deep, uniform coverage across the whole mitochondrial genome, exceptional testing performance, and high resolution detection for mitochondrial deletions.

- The mitochondrial genome is added to 30 of our panels. It is also available as its own test for patients with findings indicating mitochondrial disease or with previous negative nuclear DNA sequencing results.
- Any individual mtDNA genes or the entire mitochondrial genome can be added to any panel.
- Our high-quality mtDNA testing includes both sequencing and copy number variant analysis for all the 37 mtDNA genes.



Our Research at Mitochondrial Medicine 2021 Virtual

Retrospective review of mitochondrial genome analysis in over 6600 patients

Presented by: Jennifer Schleit, PhD

Heteroplasmy detection capabilities:	
SNVs	92.3% sensitivity at 5% heteroplasmy
INDELs	>94% sensitivity at 5% heteroplasmy
Large 500bp – 5,000kb deletions	down to 10% (at 99% sensitivity)
Coverage:	
Mean sequencing depth	18,224x
100% of base pairs covered	1,000x

Visit: blueprintgenetics.com/mitochondrial-disorders

Blueprint Genetics

IW-6463 for MELAS

Cyclerion Therapeutics has initiated a Phase 2a multi-center, open-label study (ClinicalTrials.gov Identifier: NCT04475549) in participants with Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS). The study will assess safety and the impact of short-term IW-6463 treatment on biomarkers of mitochondrial dysfunction, brain perfusion, neurodegeneration, and cognition.

IW-6463 IS THE FIRST CNS-PENETRANT SGC STIMULATOR DESIGNED AND IN DEVELOPMENT FOR NEURODEGENERATIVE DISEASES.

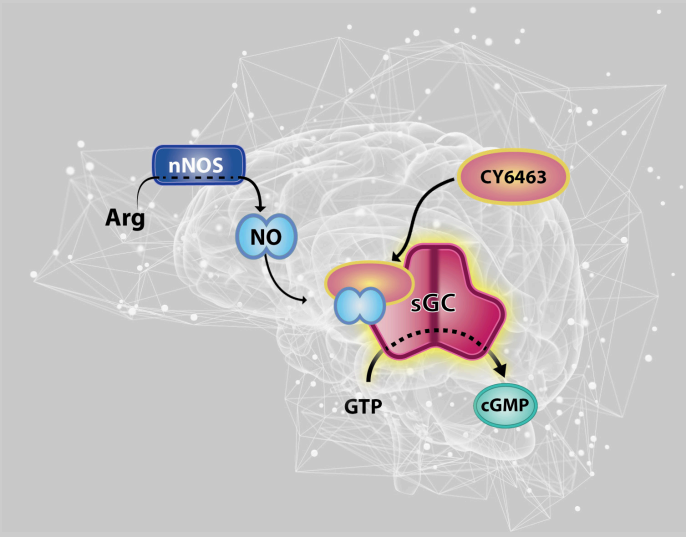
IW-6463 acts on the nitric oxide signaling pathway in your brain and central nervous system. This pathway is critical for the regulation of mitochondrial function and synthesis, and in people with mitochondrial disease, dysregulation of this pathway contributes to impaired blood flow in the brain, oxidative stress, inflammation, metabolic crises (i.e., stroke-like episodes), and cognitive impairment.

In preclinical studies, IW-6463 showed benefits in multiple animal models and across four domains of human neurodegenerative diseases:

- Improves Neuronal Function
- Improves Cerebral Blood Flow
- Enhances Cellular Bioenergetics
- Reduces Neuro-inflammation

So how is IW-6463 different from arginine and citrulline which are also related to the nitric oxide pathway and used in people with MELAS?

Citrulline and arginine have no direct action on this pathway and are simply converted into nitric oxide. In contrast, IW-6463 acts together with nitric oxide to stimulate soluble guanylate cyclase (sGC), the key component of this pathway, to amplify the body's natural NO signaling. Stimulation by IW-6463 with nitric oxide increases concentrations of a molecule called cyclic guanosine monophosphate (cGMP) beyond concentrations that can be achieved following arginine or citrulline administration. cGMP is the molecule responsible for the beneficial effects of this pathway.



ELIGIBILITY

To be considered for this ongoing Phase 2a clinical trial, you must be at least 18 years of age, have prior genetic confirmation of mitochondrial disease, clinical features of MELAS, and elevated blood lactate concentrations during screening. Please visit Cyclerion's virtual booth for more details.

IW-6463 is an investigational therapy and not approved for the treatment of people with MELAS.

bringing energy to life

KHONDRION

Khondrion is a clinical-stage biopharmaceutical company discovering and developing therapies targeting primary mitochondrial disease.

The company is advancing its proprietary science through a wholly-owned clinical and preclinical small molecule pipeline with the potential to deliver transformative medicines and treatments for patients living with primary mitochondrial disease.

Khondrion was founded by Professor Dr. Jan Smeitink who has devoted his entire career to the care of primary mitochondrial disease patients and the study of mitochondrial medicine, to better understand the complexity of this disease. His life mission is to develop a disease-modifying mitochondrial treatment for this high impact, often early, fatal group of ultra-rare disorders.

Fully operational since 2012 and located in Nijmegen, The Netherlands, Khondrion focuses primarily on the development of innovative therapies for inherited mitochondrial diseases, including Leigh disease, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), maternally inherited diabetes and deafness (MIDD) and other respiratory chain / oxidative phosphorylation (OXPHOS) disorders.

The Company's lead pipeline asset, *sonlicromanol*, is a potential first-in-class medicine and one of the most advanced disease-modifying drug candidates for mitochondrial disease in clinical development. A novel redox modulator with anti-inflammatory properties, it targets key underlying mechanisms of mitochondrial disease based on a unique triple mode of action. A Phase IIb study is ongoing in adult patients with MELAS spectrum disorders, to evaluate the dose-effect of this compound on cognitive function, and earlier this year the Company commenced a paediatric Phase II study to evaluate its effect on motor function among children.

The investigational medicine has Orphan Drug Designations for the treatment of MELAS, Leigh disease and patients with MIDD in Europe and for all inherited mitochondrial respiratory chain disorders in the USA. It has also been granted a Rare Pediatric Disease designation by the US Food and Drug Administration for the treatment of MELAS.

Prof. Dr. Jan Smeitink, Chief Executive Officer at Khondrion, said: "Mitochondrial diseases are complex rare diseases, often overlooked or misdiagnosed because of the wide range and varying severity of symptoms. Their impact on everyday life can be significant, for patients, their families and carers. Despite advances in the understanding of mitochondrial disorders, treatment options remain extremely limited. At Khondrion our goal is to discover and develop new treatments that can halt disease progression and restore normal cellular function, to make a substantial impact on the lives of mitochondrial disease patients.

"We don't want to leave any mitochondrial disease patient behind. Research to discover new treatment approaches is vital. New treatment approaches are long overdue."

Despite the unprecedented challenges faced globally over the past year, we applaud the commitment and agility of organisations like the United Mitochondrial Disease Foundation in providing invaluable support for patients. They highlight the strength of this patient community and we congratulate UMDF on their 25th anniversary.

For more information visit www.khondrion.com

minovia | mitochondrial cell therapy

UNITED MITOCHONDRIAL DISEASE FOUNDATION.

Our mission is to deliver life-changing therapies by treating the root cause of mitochondrial diseases. Working hand in hand with patient's advocacy groups, from our beginning, was much more then an aspiration. This is the place where our science transforms into meaningful therapies.

Visit our site for more info:

www.minoviatx.com

Contact us with any question:

info@minoviatx.com

Mitochondrial Augmentation Therapy (MAT):

*MAT is an investigational drug, currently undergoing a clinical trial for Pearson Syndrome.

If you don't have a genetic confirmation for your Leigh's Syndrome (LS) diagnosis you could have Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In one study of people with PDCD, 50 of 186 patients (27%) had Leigh's Syndrome based on neuroimaging studies. LS and PDCD share other similarities as well. The table below lists symptoms that are common to both diagnoses:

LS and PDCD Share Similar Phenotypes

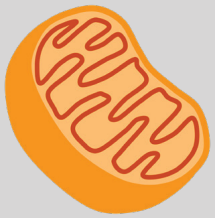
Symptom/Sign	LS[1]	PDCD[2]
Develop. delay	X	X
Hypertonia/hypotonia	X	X
Seizures	X	X
Ataxia	X	X
Lactate (blood, CSF, brain)	X	X
MRI findings (esp. basal gang.)	X	X

1. Gerards M et al. Mol Gen Metal 117:300, 2016
2. Patel K et al. Mol Gen Metab 106:385, 2012

There is a Phase 3 Trial of Dichloroacetate (DCA) in Pyruvate Dehydrogenase Complex (PDC) Deficiency that is currently recruiting.

NOW RECRUITING

Clinical Trial:
DCA in PDC Deficiency



WHO?

Patients with genetically confirmed pyruvate dehydrogenase complex (PDC) deficiency ages 6 months through 17 years.

WHERE?

9 academic health centers throughout the US. Visit http://tinyurl.com/DCA-trial to find a study site near you. Travel assistance is provided if needed.

WHY?

This is a study of an investigational drug called sodium dichloroacetate (DCA). Investigational means that the study drug has not been approved by the US Food and Drug Administration (FDA) and that its use in this study is experimental. The purpose of this research study is to see if DCA improves health and function for patients with PDCD.

HOW?

For more information contact
Peter W. Stacpoole, PhD, MD, pws@ufl.edu

solace

NUTRITION

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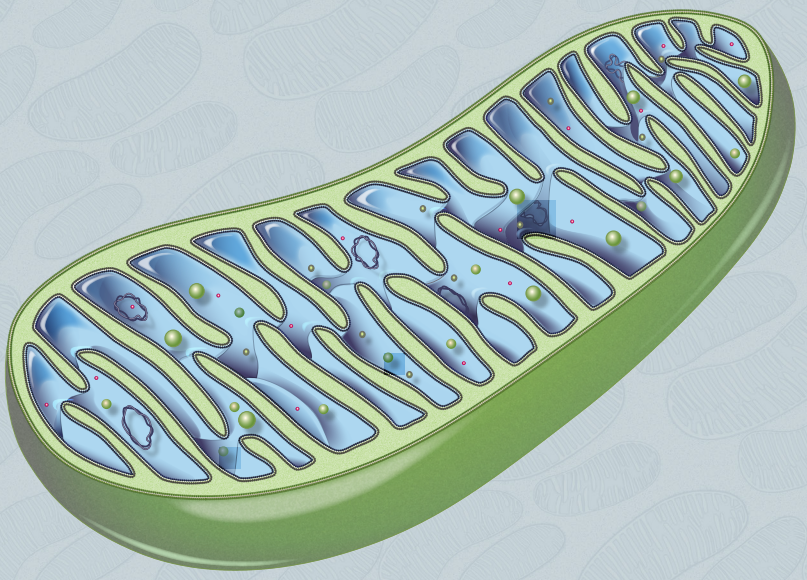

Stealth BioTherapeutics is committed to the development of therapies for mitochondrial disease and is a proud supporter of UMDF's Mitochondrial Medicine Symposium.

To learn more about our work, please visit StealthBT.com

variantyx

Variantyx offers comprehensive testing for Mitochondrial disorders

Variantyx utilizes the Genomic Unity® single platform method allowing for full analysis of both the nuclear and mitochondrial genes. This provides two options for full phenotypic analysis of clinical symptoms consistent with mitochondrial disorders.

Genomic Unity® Mitochondrial Genome Analysis

✔ Complete Mitochondrial genome analysis

Genomic Unity® Mitochondrial Disorders Analysis

✔ Complete Mitochondrial genome analysis plus sequencing and duplications/deletions analysis of nuclear mitochondrial genes

Proprietary algorithms optimized for each variant type are used to perform discrete *in-silico* analyses of the data. These are brought together for collective interpretation, providing a complete genetic picture.

For more information, visit us on line https://www.variantyx.com.

Variantyx, Inc.
1671 Worcester Rd. Suite 300
Framingham, MA 01701

Delta Gamma
1873

The Delta Gamma Foundation is proud to support the United Mitochondrial Disease Foundation.

Learn about the Delta Gamma Foundation at
www.deltagamma.org/foundation