AMYLYX

Phase 2 HELIOS Interim Data in Wolfram Syndrome

April 10, 2024

Raquel, living with Wolfram syndrome.

Our mission is to one day end the suffering caused by neurodegenerative diseases.

Every day, we strive for better therapies.

On Today's Call

Welcome
Lindsey Allen
Head, Investor Relations and Communications, Amylyx

Opening Remarks
Josh Cohen and Justin Klee
Co-CEOs, Amylyx

Wolfram Syndrome Treatment Landscape
Dr. Fumihiko "Fumi" Urano
Samuel E. Schechter Professor of Medicine, and Professor of Medicine and Pathology & Immunology, Division of Endocrinology, Metabolism and Lipid Research, Washington University in St. Louis
Principal Investigator for Phase 2 HELIOS Clinical Trial of AMX0035 in Wolfram Syndrome

AMX0035 Wolfram Syndrome Program & Phase 2 HELIOS Interim Data
Dr. Camille L. Bedrosian
Chief Medical Officer, Amylyx

Closing Remarks
Josh Cohen and Justin Klee
Co-CEOs, Amylyx

Q&A Session

Disclaimer

Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding the potential of AMX0035 as a treatment for neurodegenerative diseases, including Wolfram syndrome (WS) and expectations around the timing of full results for the HELIOS trial of AMX0035 in WS; expectations about the market size for WS; expectations around interactions with regulatory authorities on potential development plans for AMX0035 in WS; and expectations regarding our longer-term strategy. Any forward-looking statements in this presentation are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include: the success, cost, and timing of Amylyx’ program development activities, including ongoing and planned clinical trials, Amylyx’ ability to execute on its research, development, and regulatory strategy, regulatory developments, Amylyx’ ability to fund operations, and the impact that the COVID-19 pandemic may have on Amylyx’ operations, as well as the risks and uncertainties set forth in Amylyx’ United States Securities and Exchange Commission (SEC) filings, including Amylyx’ Annual Report on Form 10-K for the year ended December 31, 2023, and subsequent filings with the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Amylyx undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

Opening Remarks

Josh Cohen and Justin Klee
Co-CEOs, Amylyx

AMYLYX

Wolfram Syndrome Treatment Landscape

Dr. Fumihiko “Fumi” Urano, MD, PhD

Samuel E. Schechter Professor of Medicine
Washington University, St. Louis, USA
Primary Investigator for Phase 2 HELIOS Trial

Disclosures: Fumihiko Urano, MD, PhD

Patents licensed:

- Amarantus Bioscience
- Opris Biotechnologies

Technologies licensed:

- Novus Biologicals
- Sana Biotechnology

Patents:

- US 9,891,231

SOLUBLE MANF IN PANCREATIC BETA CELL DISORDERS

- US 10,441,574
- US 10,695,324

TREATMENT FOR WOLFRAM SYNDROME AND OTHER ER STRESS DISORDERS

Research support:

- NIH
- Prilenia
- Amylyx Pharmaceuticals

Board Member:

- Healthbeat

Founder and President:

- CURE4WOLFRAM, INC

Scientific Advisory Board:

- Emerald Biotherapeutics, INC
- Opris Biotechnologies, INC

Off-label use:

- Dantrolene sodium
- Liraglutide
- Valproic acid

WashU-Urano lab
Cris Brown
Stacy Hurst
Mary Jane Clifton
Joshua Chen
Shrini Bimal
Caroline Raso
Brianna Carman
Juan Gallardo Pinera
Nila Palaniappan
Saumel Ahmadi
Devynn Hummel
Venu Gurram
Jessica Roberts
Rachel Reiss
Rohan Krishnamoorthi

WashU-Genetics and Genomics
Julie Neidich
Molly Schroeder
Yang Cao
Meagan Corliss
Chris Sawyer
Mike Heinz
Patricia Dickson
Marwan Shinawi
Kathy Grange
Linda Manwaring

BJC-Wolfram Clinic
Christine Manning, RN
Stacy Hurst, CDE, RN
Bess Marshall
Amy Viehoever
Rober Bucelli
Greg Van Stavern
Margaret Reynolds
Saumel Ahmadi

WashU-Longitudinal Study
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Bess Marshall
Neil White
Samantha Ranck
Olga Neyman
Linda Manwaring
Toni Pearson
Amy Viehoever
Amy Licis
James Hoekel
Lawrence Tychsen
Angela Reiersen
Yanina Pepino
Wolfram Study Group

WashU-Wolfram Trial
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Teresa Arb
Megan Arb
Ashley Simpson
Yi Zhang
Phyllis Klein
Tamera Roussey
Robert Bucceli
Toni Pearson
James Hoekel
Laurence Tychsen
Greg Van Stavern
Bess Marshall
Neil White
Tamara Hershey
Stephen Stone
Alexis McKee
Amy Viehoever
Hongjie Gu
Janet McGill
Ken Schechtman
Christina Gurnett

WashU-Wolfram iPSC
Xiaoxia Cui
Amber Neilson
GESC
Jeff Millman
Kristina Maxwell
Punn Augsornworawat

WashU-Optic Nerve Atrophy
Rithwick Rajagopal
Raj Apte

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Mario Plaas
Anton Terasmaa
Sulev Koks

KU Leuven
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Mart Saarma
Maria Lindahl
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Boston University
Samagya Banskota

U Birmingham
Timothy Barrett

AEIASW- Spain
Gema Esteban Bueno

Hadassah Medical Center
Gil Leibowitz
Avivit Cahn

Sheba Medical Center
Noga Minsky

Schneider Children Med Ctr
Yael Goldberg
Nurit Assia Batzir

Dor Yeshorim
Rabbi Joseph Ekstein
Yoel Hirsch
Martin M Johansson
Tzvi Weiden

U Exter
Andrew Hattersley

NIH/NCATS
Francis Collins
Anton Simeonov
Mark Henderson

U-Chicago
Louis Philipson
Lisa Letourneau-Freiberg
Siri Greeley

Patients and Families
Snow Foundation
Silberman Fund
Ellie White Foundation
Unravel Wolfram Syndrome Fund
Stowe Fund
Eye Hope Foundation
Feiock Fund
Cachia Fund
Gildenhorn Fund
Godat Fund
Associazione Gentian - Sindrome di Wolfram Italia
Alianza de Familias Afectadas por el Sindrome Wolfram Spain
Wolfram syndrome UK
Association Syndrome de Wolfram France
Wolfram Saudi Arabia

NORD
Multisite WG

RareCap
Jannifer Micham
Marshall Summers

Industry Partners
Opris Biotechnologies
Emerald Biotherapeutics
Prilenia
Amylyx

Objectives

1. Summarize **two types of Wolfram syndrome** and related disorders.
2. Share lessons and stories from past and current Wolfram Syndrome clinical studies, including both achievements and obstacles.
3. Emphasize the need for cooperation with patient organizations and industry partners to support the development of new therapies.

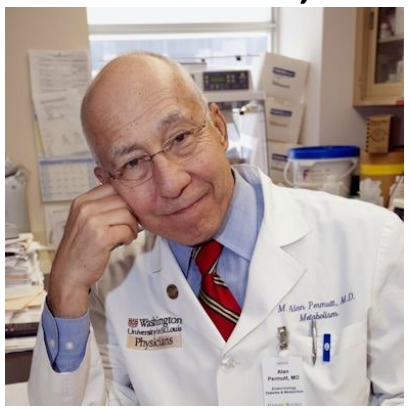
Wolfram Syndrome

- Diabetes Mellitus (median age 6) – Insulin, GLP-1R agonists, metformin
- Optic nerve atrophy (median age 11)
- Deafness (median age 14) – Hearing aids, cochlear implants
- Diabetes Insipidus (median age 13) - DDAVP
- Neurodegeneration (begin to appear during the later years of adolescence)
- *Causative Genes: WFS1 and CISD2 (autosomal Recessive)*

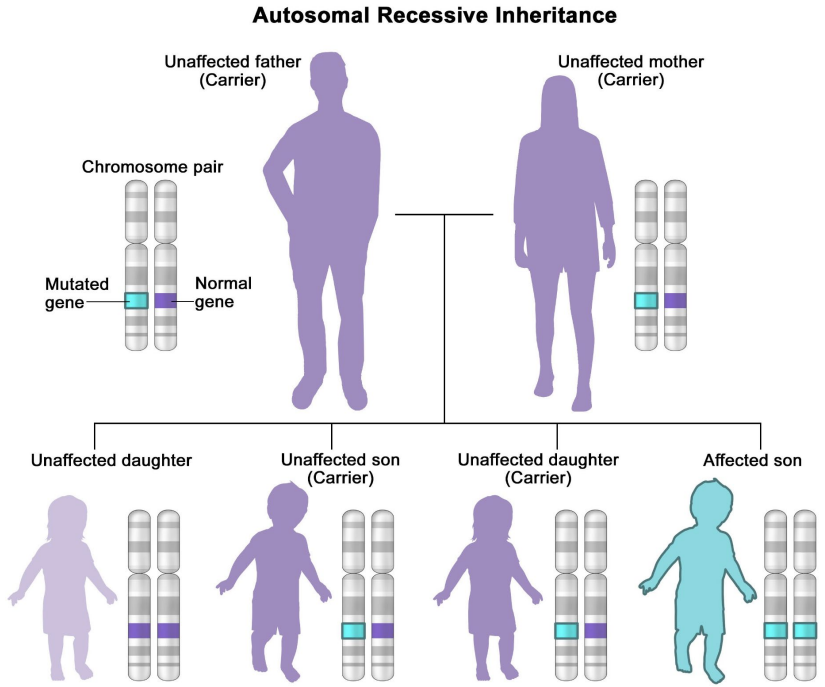
Two Types of Wolfram Syndrome

Type	Gene	Inheritance
WFS Type 1	*WFS1*	**Autosomal Recessive**
WFS Type 2	*CISD2*	Autosomal Recessive

Alan Permutt, MD



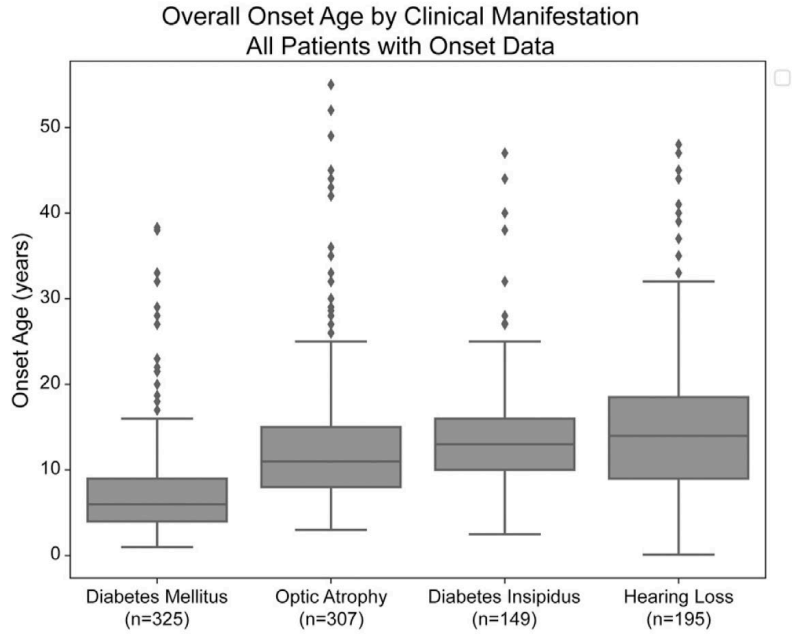
- **Most patients have Wolfram Type 1**
- **Prevalence: 1 in 250,000-700,000**
- **Patients have two mutated copies of WFS1 or CISD2 gene (autosomal recessive)**



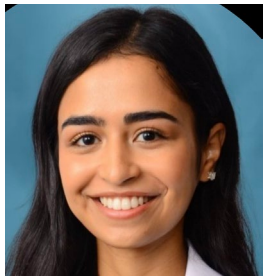
Wolfram Syndrome Type 1: A spectrum disorder

Genotype and clinical characteristics of patients with Wolfram syndrome and WFS1-related disorders

Evan M. Lee[1,2,3], Megha Verma[1,4], Nila Palaniappan[1,5], Emiko M. Pope[1], Sammie Lee[1], Lindsey Blacher[1], Pooja Neerumalla[1], William An[1], Toko Campbell[1], Cris Brown[1], Stacy Hurst[1], Bess Marshall[6], Tamara Hershey[7], Virginia Nunes[8,9], Miguel López de Heredia[10] and Fumihiko Urano[1,2]*



Evan Lee, WUSTL MSTP

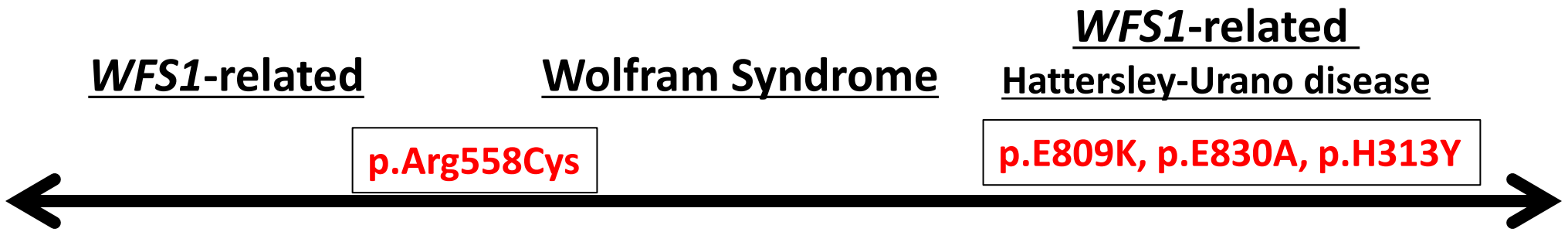


Megha Verma SLU Med

Nila Palaniappan UMKC Med

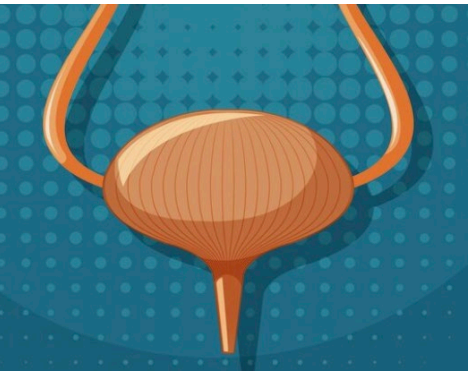
- Females: Milder symptoms than males
- Two or one missense WFS1 variants: Milder symptoms (**60% of our cohort**)
- Two frameshift/nonsense WFS1 variants: More severe symptoms (**40%: a classic form**)
- WFS1 c.1672C>T (p.Arg558Cys), a common variant in Ashkenazi-Jewish population associated with mild manifestations
- **Prevalence could be 1:70,000 (5000 pts in the US)**

Wolfram syndrome and *WFS1*-related disorders



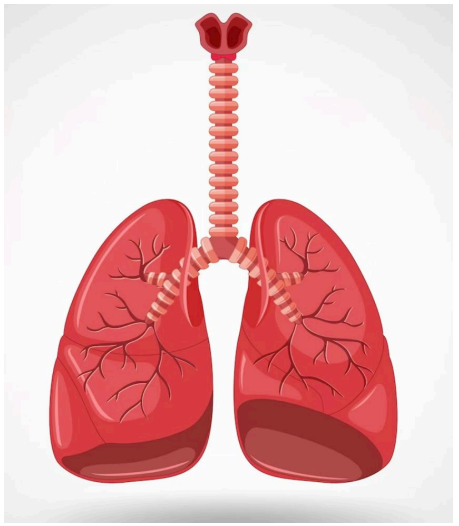
1 pathogenic dominant *WFS1*	2 pathogenic *WFS1* or *CISD2*	1 pathogenic dominant *WFS1*
Diabetes	**Wolfram Syndrome** • Diabetes Mellitus • Diabetes Insipidus • Optic Nerve Atrophy • Hearing loss • Neurodegeneration	(Hattersley & Urano, 2017) • Neonatal diabetes • Congenital cataracts/glaucoma • Sensorineural deafness • Hypotonia • Developmental delay/Intellectual disability
Hearing loss		
Optic Nerve Atrophy & Hearing loss		
Cataract		

https://wolframsyndrome.wustl.edu/



Neurogenic Bladder

- Urodynamic testing
- Anti-cholinergic medications
- Botox injections
- Antibiotics
- Neural stimulator
- Catheterization



Respiratory failure

- Sleep test
- Positive pressure

Choking

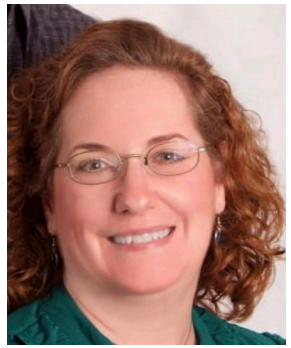
- Swallow test
- Speech pathologist

https://wolframsyndrome.wustl.edu/

Wolfram Clinic Contact:
WolframSyndrome@wustl.edu
Phone: 314-747-7055

Christine Manning
BSN, RN

Stacy Hurst
BSN, RN, CDE



Cris Brown, BA

Caroline Raso

Consensus Clinical Guidelines

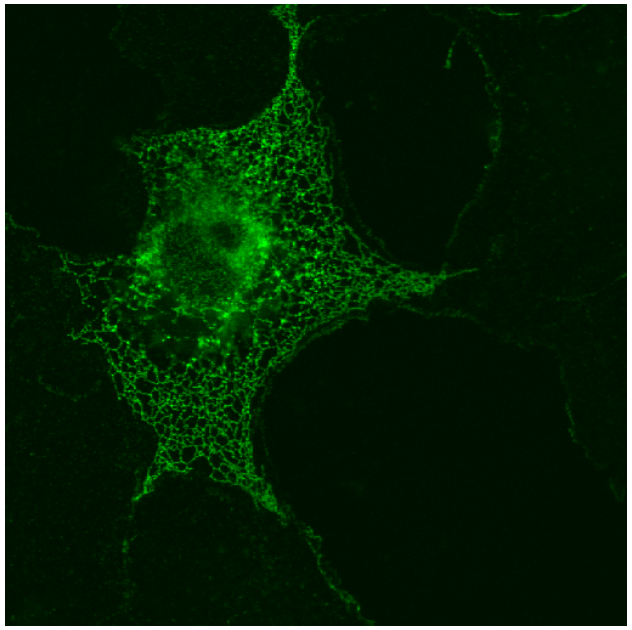
RareCAP

Rare Disease Clinical Activity Protocol Program

Jennifer Micham, PhD, RN
Rare Disease Clinical Protocol Curator

Marshall Summar, MD
Board Member

- Genetics/Diagnosis
- Endocrinology
- Neurology
- Psychiatry
- Urology
- Ophthalmology



Wolfram Syndrome: Prototype Endoplasmic Reticulum (ER) Disorder

Loss of Function of WFS1

1. **High levels of ER stress, Mitochondrial dysfunction**
2. **Lower levels of ER calcium, higher levels of cytoplasmic calcium**

The Spectrum of ER dysfunction

COMMON
MILD

RARE
SEVERE

Aging

Type 2 Diabetes

WFS1-related disorders (Wolfram-like)

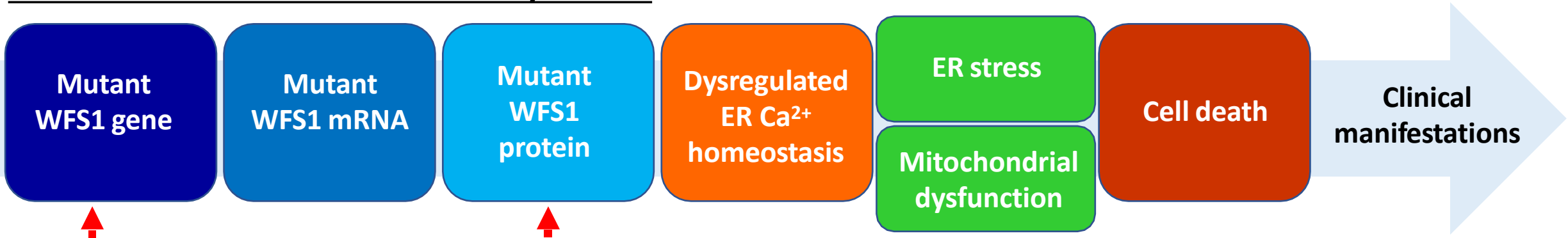
- **Congenital Nephrotic syndrome**
- **Achromatopsia (ATF6)**

Wolfram syndrome (WFS1)

- **Pelizaeus-Merzbacher Disease (PLP1)**
- **Marinesco-Sjögren Syndrome (SIL1)**
- **FENIB (SERPIN1)**
- **Walcott-Rallison Syndrome (PERK)**

Therapeutic Development Pipelines and Timeline

Molecular Mechanisms of Wolfram Syndrome



Enhancement of residual functions (Ongoing)

AMX0035 (Amylyx)

Washington University in St. Louis

Institute of Clinical and Translational Sciences

Gene therapy / Regenerative therapy (3-10 years)

- Transfer normal *WFS1* gene by AAV
- Correct pathogenic *WFS1* variants (Drs. Lu, Verfaiile, Moon)
- Transfer a regenerative factor MANF (Opris Bio)
- Transplant iPSC-derived tissues

Pharmacological compensation (Ongoing)

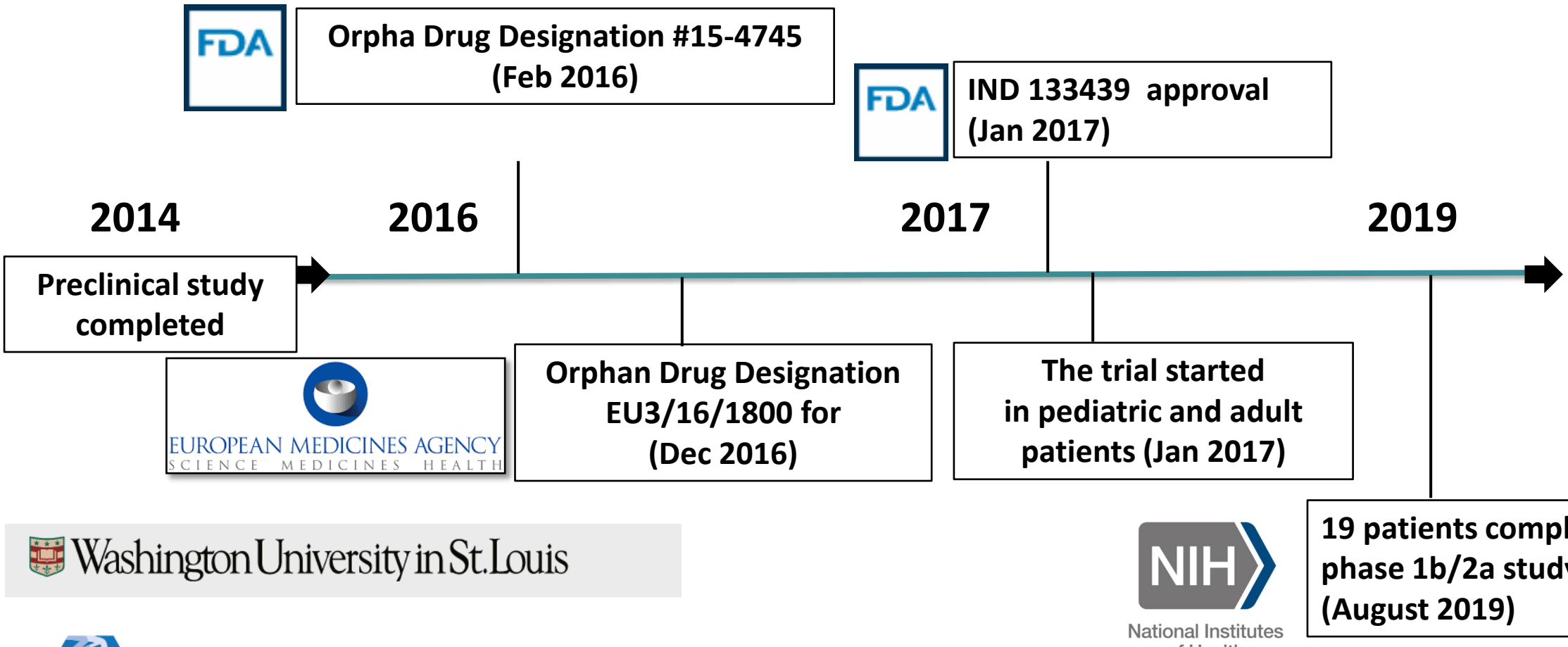
- Dantrolene sodium
- ER calcium stabilizers
- GLP-1 R agonists
- Sigma 1 R agonist - Pridopidine (Prilenia)
- Valproic Acid (Prof Barrett, U-Birmingham)
- Ibudilast (Prof Ehrlich, Yale)

NIH NCATS

Marked in Red: URANO team at Washington U

ER: Endoplasmic Reticulum

Wolfram syndrome - Dantrolene Sodium Clinical Trial Progress



Washington University in St. Louis

NIH
National Institutes of Health

Institute of Clinical and Translational Sciences

IDDRC
Washington University in St. Louis

Ellie White FOUNDATION
For Rare Genetic Disorders

SNOW FOUNDATION
FOR WOLFRAM SYNDROME RESEARCH
A GLOBAL VOICE FOR RARE DISEASE

JCI insight

CLINICAL MEDICINE

Damien Abreu, MD, PhD
(Current: Resident Derm PSTP)

Stephen Stone, MD
(Current: Asst Professor)

A phase Ib/IIa clinical trial of dantrolene sodium in patients with Wolfram syndrome

Damien Abreu,[1,2] Stephen I. Stone,[3] Toni S. Pearson,[4] Robert C. Bucelli,[4] Ashley N. Simpson,[5] Stacy Hurst,[1] Cris M. Brown,[1] Kelly Kries,[1] Chinyere Onwumere,[1] Hongjie Gu,[6] James Hoekel,[7] Lawrence Tychsen,[7] Gregory P. Van Stavern,[7] Neil H. White,[3] Bess A. Marshall,[3] Tamara Hershey,[8] and Fumihiko Urano[1,9]

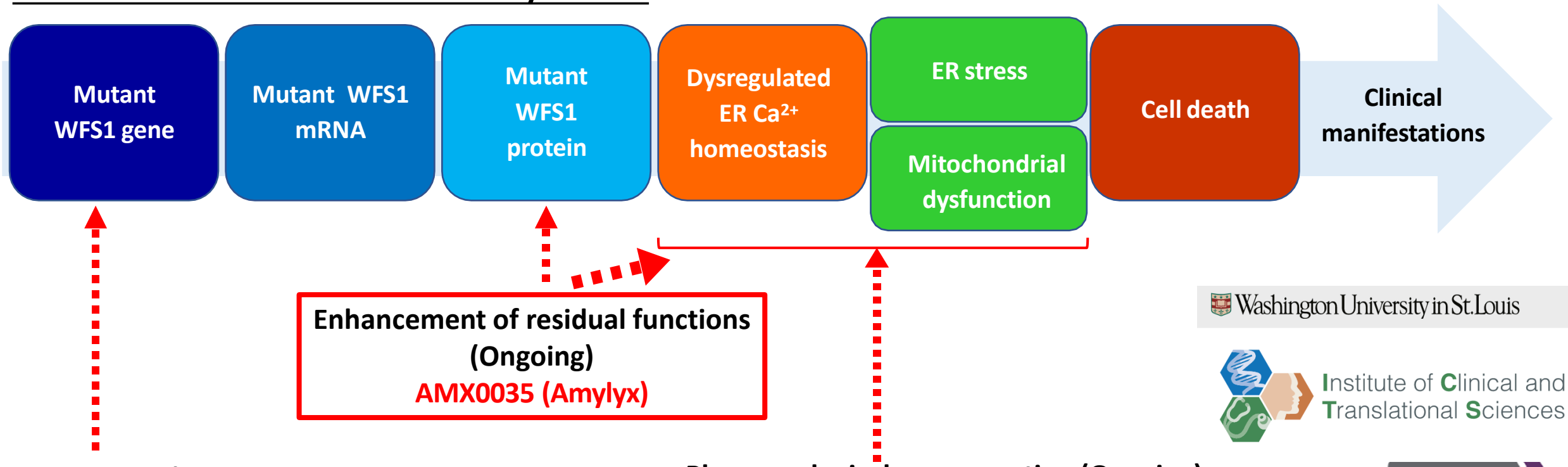
[1]Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, [2]Medical Scientist Training Program, [3]Division of Endocrinology and Diabetes, Department of Pediatrics, [4]Department of Neurology, [5]Center for Clinical Studies, [6]Division of Biostatistics, [7]Department of Ophthalmology & Visual Sciences, [8]Departments of Psychiatry and Radiology, and [9]Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, Missouri, USA.

Lessons Learned from the Dantrolene Repurposing Trial

- **Cost-effective:** Less expensive than developing new drugs
- **Faster development:** Can speed up the drug development process since the drug has already undergone clinical trials for other indications and has been tested for safety.
- **Outcome measures**: 30-min MMTT is not sufficient, MMTT could improve, Visual acuity could improve.
- **Challenge: Not designed for Wolfram**
- **Challenge: Limited patent protection:** Limited patent protection, which can limit financial incentives for pharmaceutical companies to invest in repurposing efforts.

Therapeutic Development Pipelines and Timeline

Molecular Mechanisms of Wolfram Syndrome



Washington University in St. Louis

Institute of Clinical and Translational Sciences

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- Ibudilast (Prof Ehrlich, Yale)

NIH NCATS

Marked in Red: URANO team at Washington U

ER: Endoplasmic Reticulum

Clinical Trial of AMX0035 in adult patients with Wolfram syndrome

1. Started a collaboration with Amylyx (2017)
2. The U.S. FDA granted an orphan drug designation to AMX0035 for the treatment of Wolfram syndrome (October 2020).
3. IND (September 2022)
4. Washington University IRB Approval (February 2023)
5. Started a trial (April 2023) – First patient was dosed on April 12, 2023

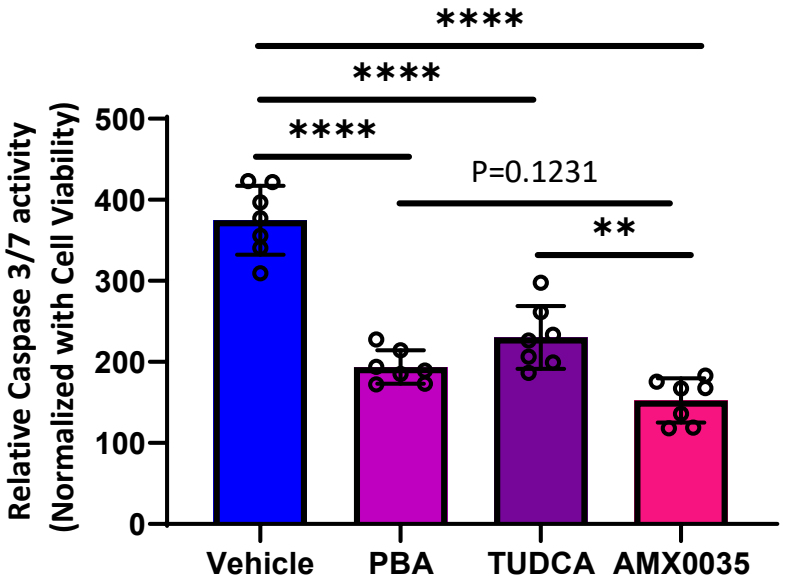
Amylyx Pharmaceuticals Announces First Participant Dosed in Phase 2 Study of AMX0035 for the Treatment of Wolfram Syndrome

- Recently published preclinical data demonstrate initial proof-of-concept for the therapeutic development of AMX0035 (sodium phenylbutyrate and taurursodiol) in Wolfram syndrome

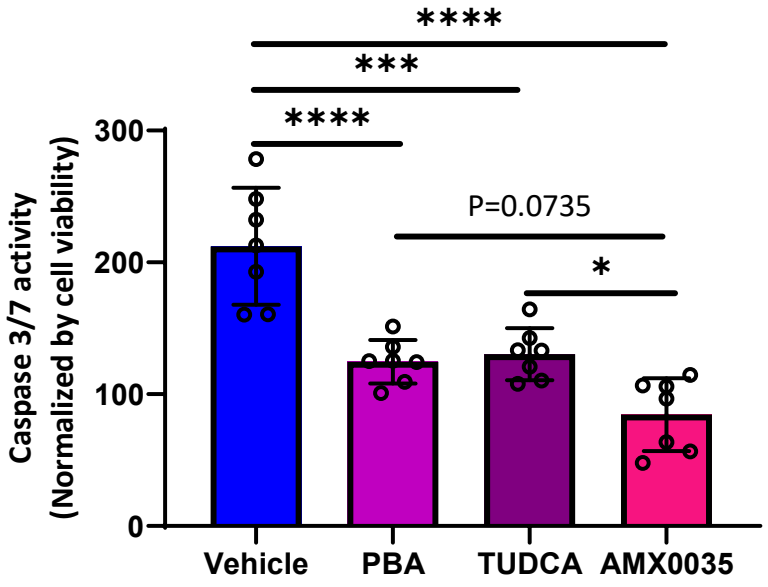
April 13, 2023 09:00 AM Eastern Daylight Time

Pre-clinical Efficacy: AMX0035 suppresses cell death in Wolfram iPSC-derived Neuronal Progenitor Cells

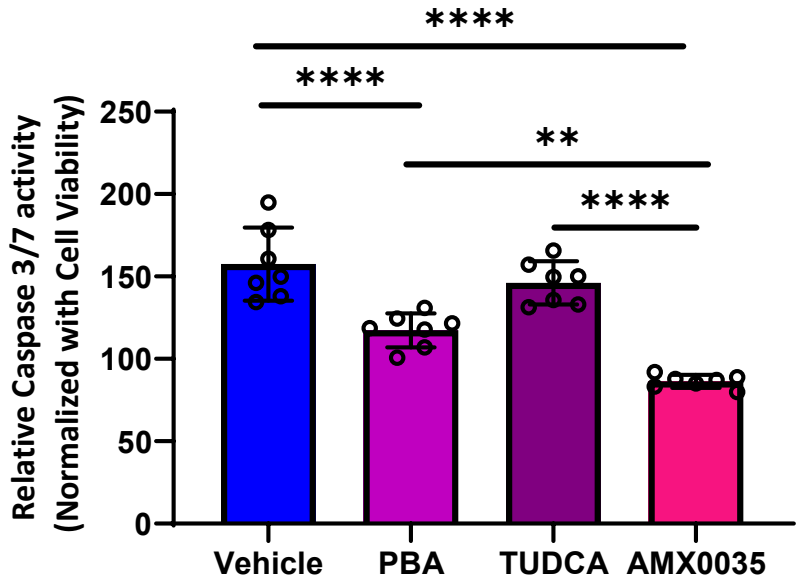
W024



W392

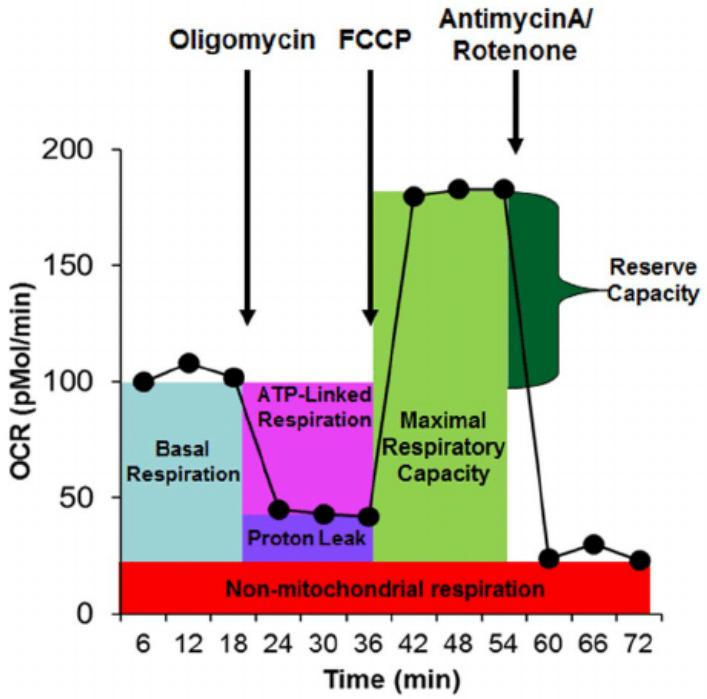


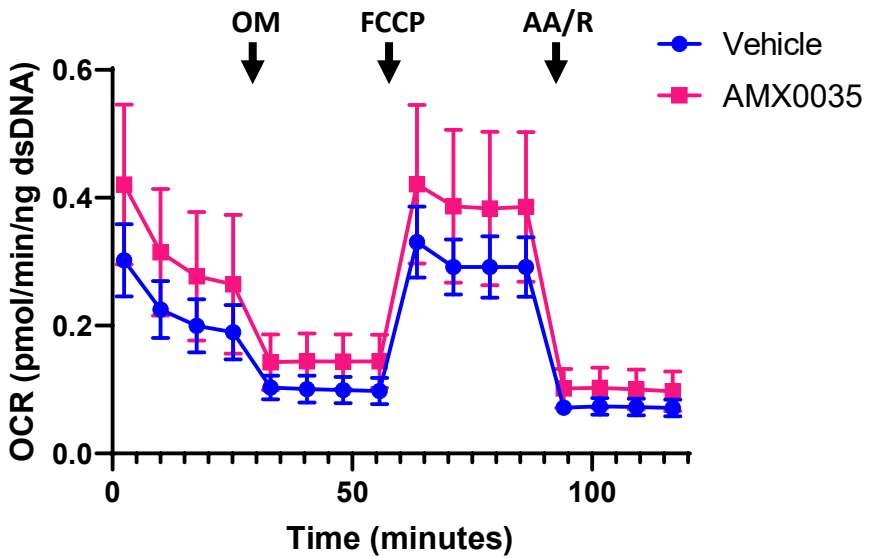
W121



Pre-Clinical Efficacy: AMX0035 restores mitochondrial function in Wolfram iPSC-derived NPCs

Mito stress test (Seahorse machine) W024 NPCs

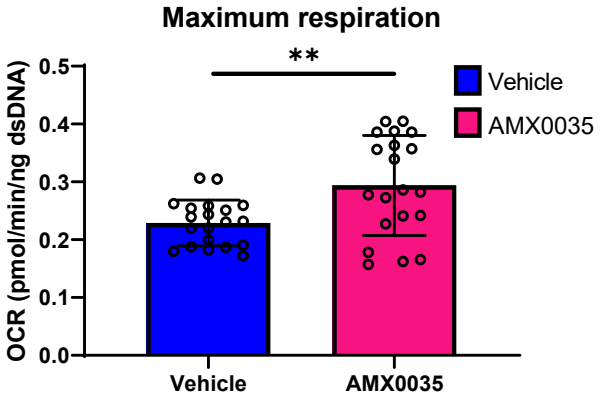


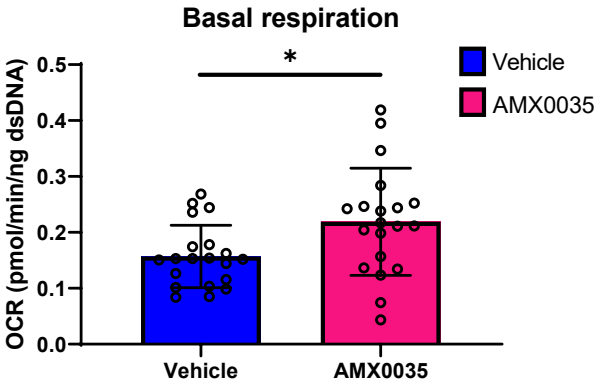


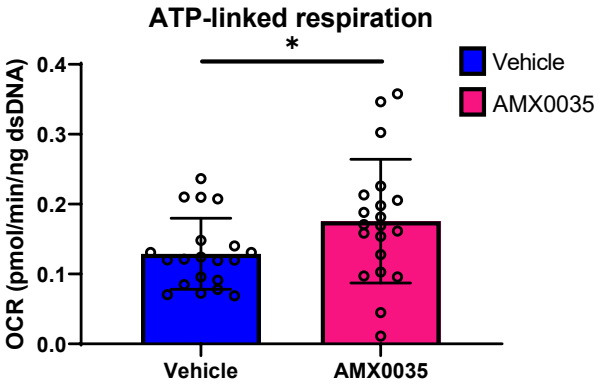
OCR is increased

↓

Mitochondrial function is improved



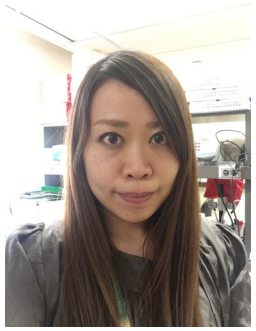




JCI insight

RESEARCH ARTICLE

Multidimensional analysis and therapeutic development using patient iPSC–derived disease models of Wolfram syndrome



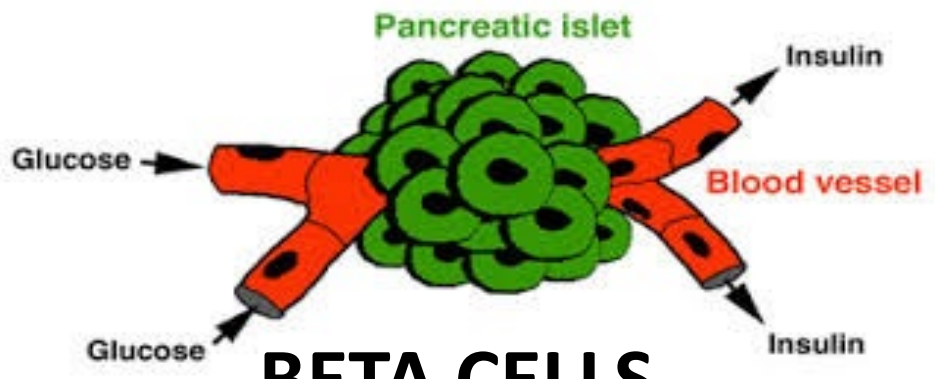
Rie Asada Kitamura,[1] Kristina G. Maxwell,[1,2] Wenjuan Ye,[3] Kelly Kries,[1] Cris M. Brown,[1] Punn Augsornworawat,[1,2] Yoel Hirsch,[4] Martin M. Johansson,[4] Tzvi Weiden,[5] Joseph Ekstein,[4] Joshua Cohen,[6] Justin Klee,[6] Kent Leslie,[6] Anton Simeonov,[3] Mark J. Henderson,[3] Jeffrey R. Millman,[1,2] and Fumihiko Urano[1,7]

[1]Department of Medicine, Division of Endocrinology, Metabolism, and Lipid Research, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA. [2]Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, Missouri, USA. [3]National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), Rockville, Maryland, USA. [4]Dor Yeshorim, Committee for Prevention of Jewish Genetic Diseases, Brooklyn, New York, USA. [5]Dor Yeshorim, Committee for Prevention of Jewish Genetic Diseases, Jerusalem, Israel. [6]Amylyx Pharmaceuticals Inc., Cambridge, Massachusetts, USA. [7]Department of Pathology and Immunology, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA.

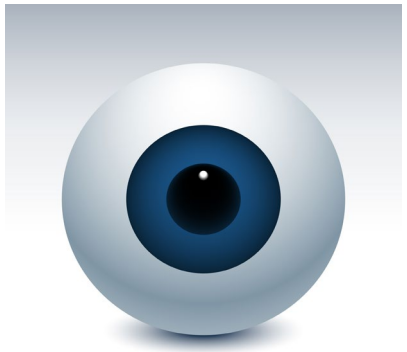
Authorship note: RAK and KGM contributed equally to this work. JRM and FU are co–corresponding authors.

Conflict of interest: FU is an inventor of 3 patents related to Wolfram syndrome treatment, US 9,891,231 "Soluble MANF in pancreatic beta-cell disorders," and US 10,441,574 and US 10,695,324 "Treatment for Wolfram syndrome and other endoplasmic

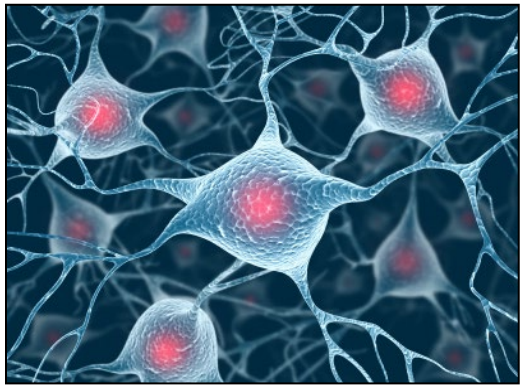
Measure Efficacy and Safety



BETA CELLS
(Diabetes)

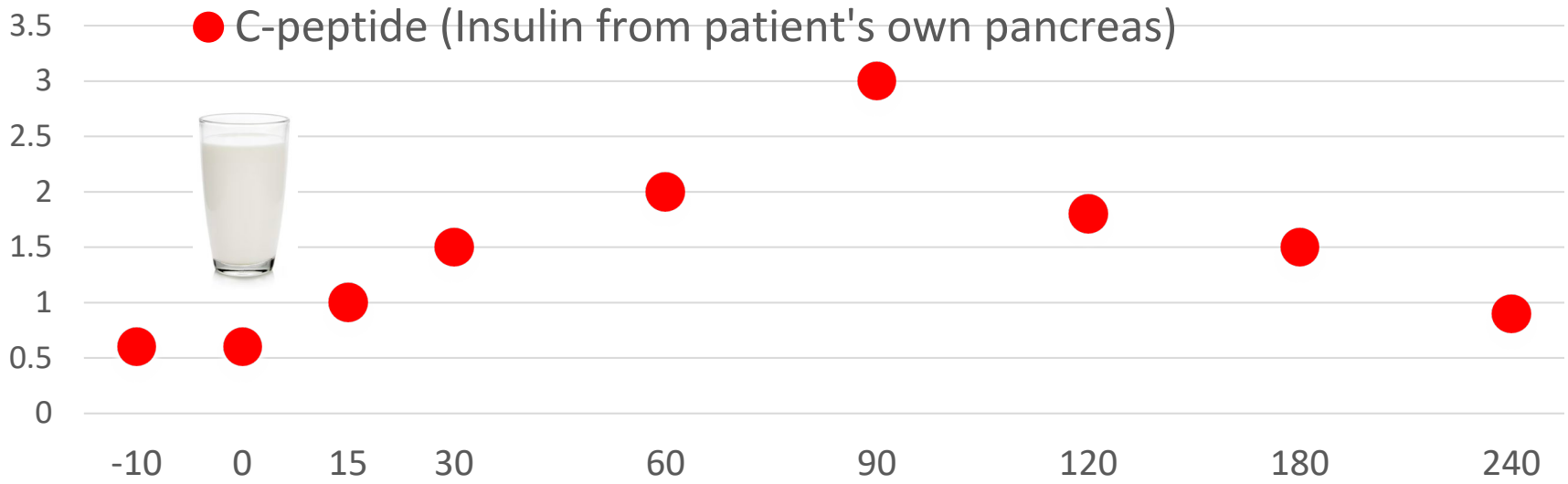


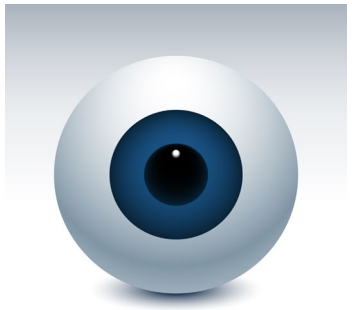
EYE
(Visual Acuity)



Neurological Functions

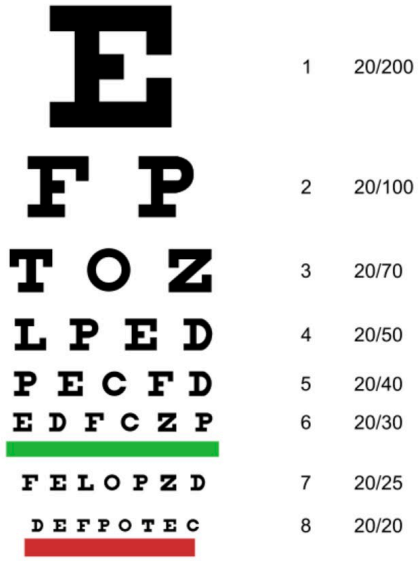
BETA CELLS





EYE

Snellen

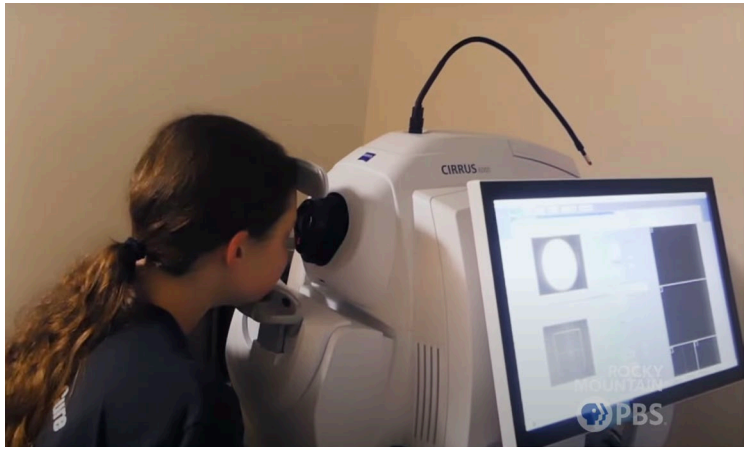


LogMar

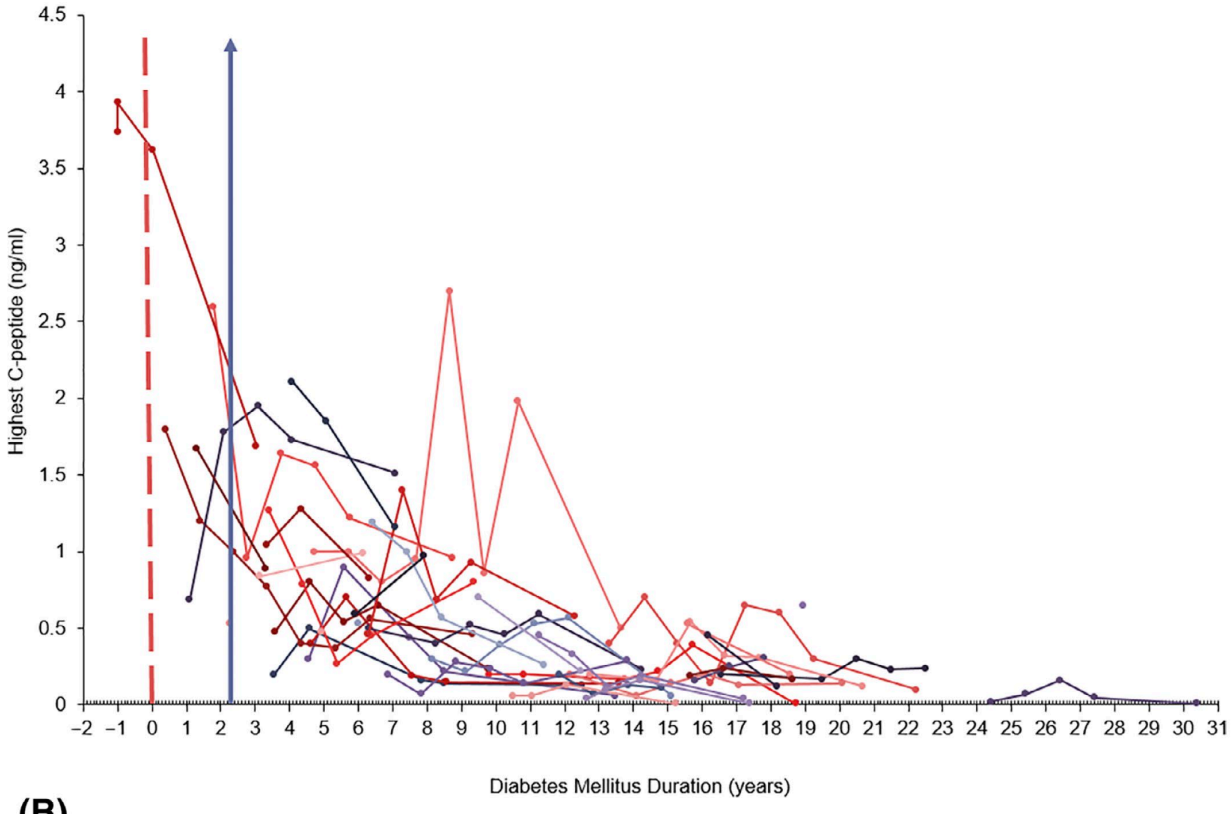
1.0

0

OCT



C-peptide in Wolfram syndrome



C-peptide in Monogenic Diabetes

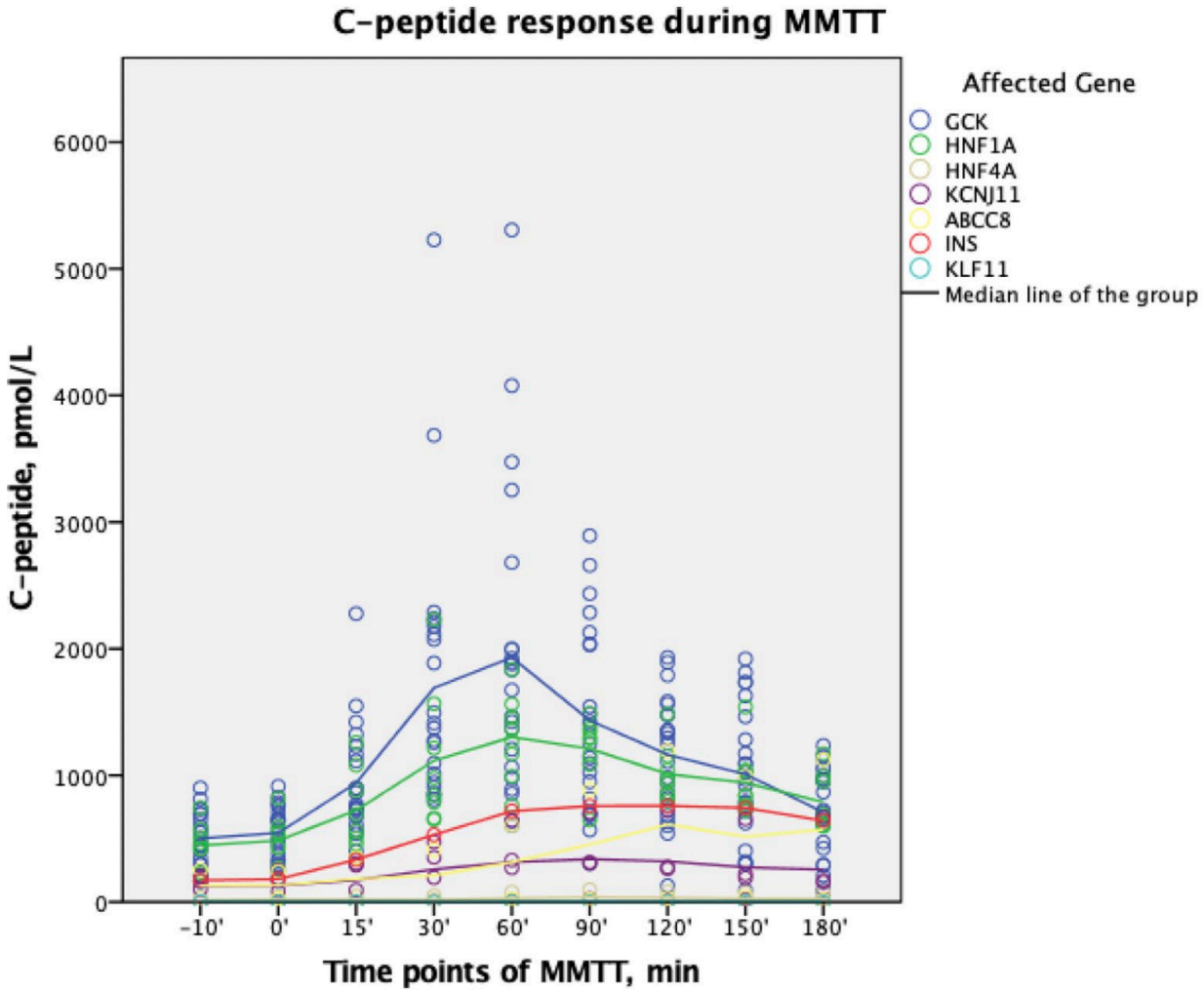
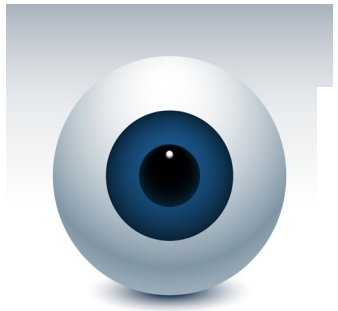


Fig. 1 – C-peptide response during MMTT (mixed meal tolerance test) according affected gene.

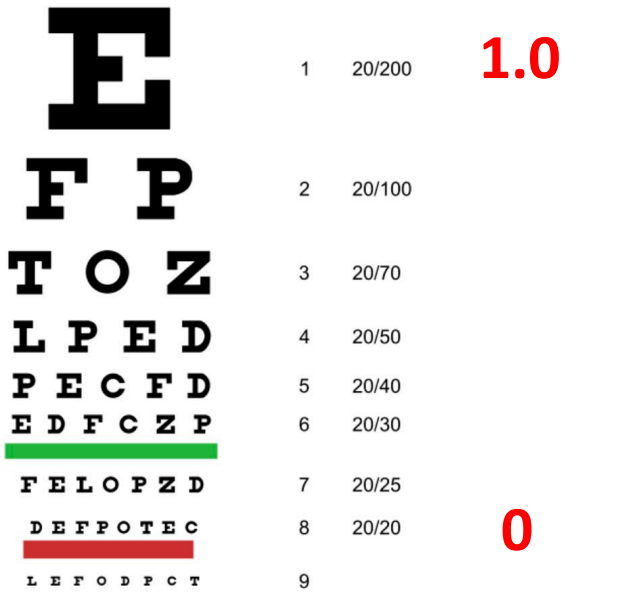
Stankute et al. 2021

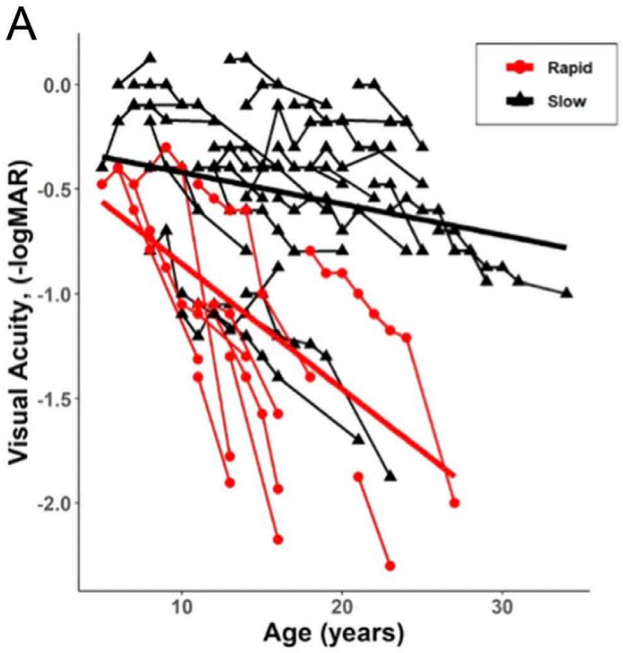
1000 pmol/L = 3.02 ng/ml

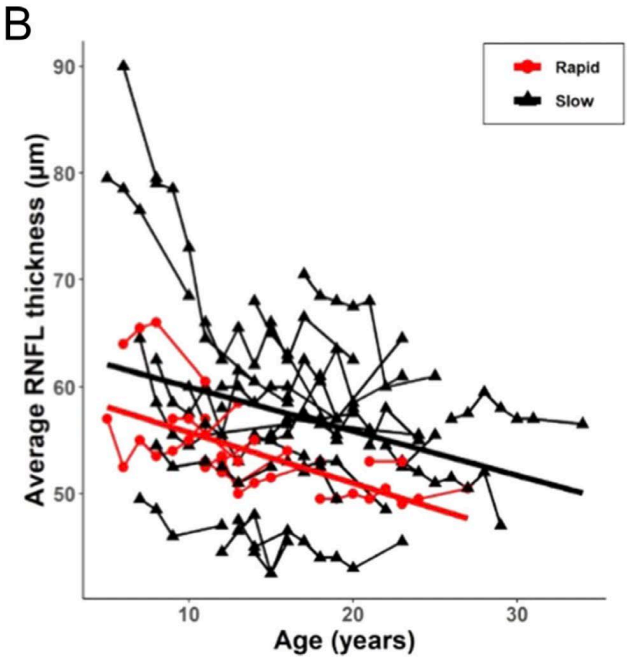


EYE

James Hoekel OD &
Larry Tychsen MD







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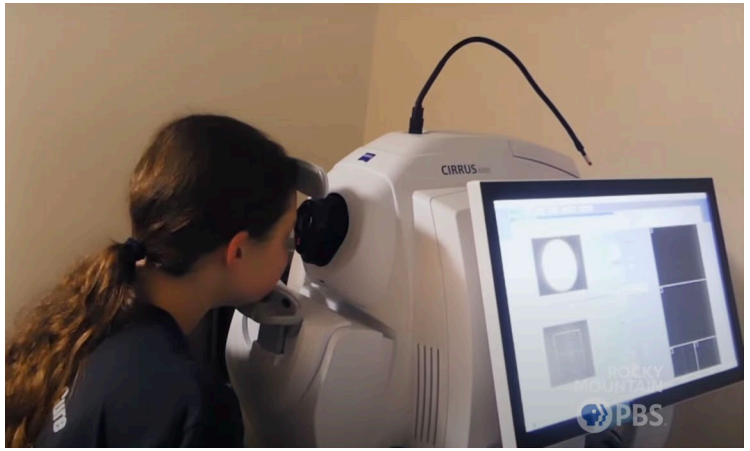
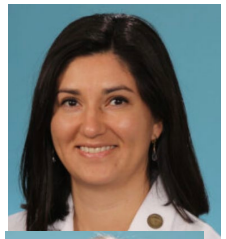


Greg Van Stavern MD

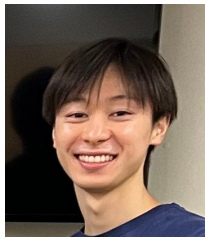
Trial Team

Bess Marshall, MD (Endocrinology, Medical Director)
Stacy Hurst, RN, CDE (Lead Nurse Coordinator)
Paulina Cruz Bravo, MD (Endocrinology)
Alexis McKee, MD (Endocrinology)
Amy Viehoever, MD, PhD (Neurology)
Saumel Ahmadi, MD, PhD (Neurology)
Greg Van Stavern, MD (Ophthalmology)
Tamara Hershey, PhD (Neuropsychiatry)
Jennifer Powers Carson, PhD (Core Lab)
Cris Brown (Research Lab)
Gabriel Skinner (Research Lab)
Caroline Raso (Coordinator)
Joshua Chen (Coordinator)
Nila Palaniappan (Coordinator)
Mary Jane Clifton (Coordinator)
Kathryn Bohnert (Coordinator)
Fumihiko Urano, MD, PhD (PI, Medical Genetics)
Amylyx Pharmaceuticals (Sponsor)



Bess Marshall MD

Cris Brown



Josh Chen

Tamara Hershey PhD

Significance of Working with Patient Organizations

- Raising awareness for Wolfram syndrome.
- Patient Organizations facilitate collaboration between academic researchers and industry.
- Collaborative research between researchers, clinicians, and patients is necessary to ensure patient-centered outcomes.

WOLFRAM SYNDROME UK
Inform, Support, CURE

SNOW FOUNDATION™
FOR WOLFRAM SYNDROME RESEARCH
A GLOBAL VOICE FOR RARE DISEASE

The Snow Foundation
February 13 ·

What a great day today meeting Dr. Fumihiko Urano's Lab! The Snow Foundation presented a check for a research project and Raquel and I had lunch with his team. We learned about all the great research projects that are currently taking place. Extremely informative and very inspiring! Keep up the good work Urano Lab!

Ellie White FOUNDATION
For Rare Genetic Disorders

Rocky Mountain PBS @rmpbs · Feb 23
We're honored to have hosted such an important conversation!

> **Fumi Urano MD PhD** @FumihikoUrano · Feb 23
> I had an amazing interview session with Beth and Ellie White at PBS in Denver! Together, we discussed Wolfram syndrome and our shared mission to raise awareness and work towards finding a cure! @rmpbs @JeremyDanMoore @DanaKnowles123 @littleelliebean @EllieWhiteFound @PBS

Improve Clinical Care

CURE4WOLFRAM

Raise Awareness

Wolfram Syndrome Clinic

PATIENT ORGANIZATIONS

Entrepreneurship
CURE4WOLFRAM
Emerald Biotherapeutics
Amylyx Pharmaceuticals
Prilenia

Philanthropies /Grants (i.e. $)

Rachel Hartmann
WashU

Therapeutic and Diagnostic Development

SNOW FOUNDATION FOR WOLFRAM SYNDROME RESEARCH
A GLOBAL VOICE FOR RARE DISEASE

WOLFRAM SYNDROME UK
Inform, Support, CURE

Association Syndrome Wolfram

Ellie White FOUNDATION
For Rare Genetic Disorders

IT TAKES A VILLAGE TO ACHIEVE A CURE FOR WOLFRAM SYNDROME

Mentors

Jane Workman
Edward Berk
Marjorie Feinstein
Junichi Hata, MD, PhD
Akihiro Umezawa, MD, PhD
David Ron, MD
Michael Green, MD, PhD
Julie Neidich, MD
Aldo Rossini, MD

https://wolframsyndrome.wustl.edu/

Junko Urano, MD
1936-2024

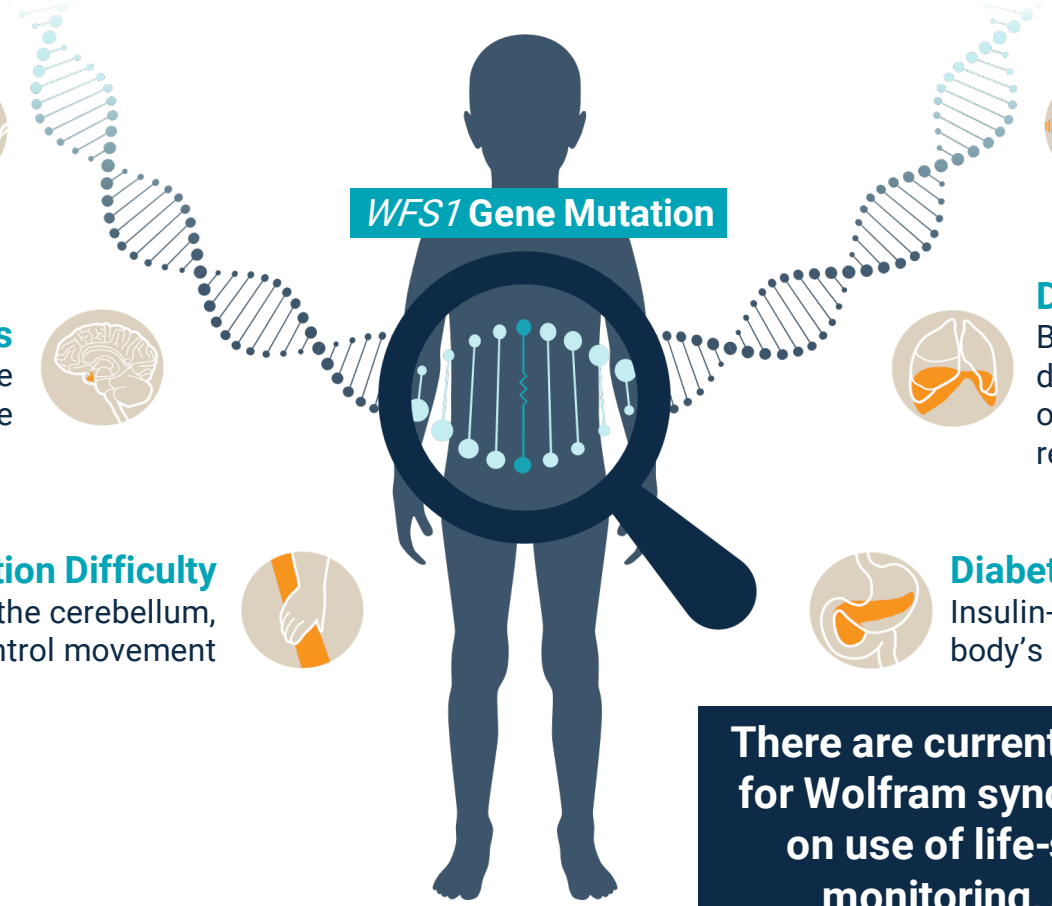
Urano J, Kamimura K, Nakamura K, Matsui J, Nakagome Y, Tanae A. **Le syndrome du cri du chat. Paediatr Univ Tokyo.** 1965 Aug;11:63-8. PMID: 5862318.

AMX0035 Wolfram Syndrome Program & Phase 2 HELIOS Interim Data

Dr. Camille L. Bedrosian
Chief Medical Officer, Amylyx

Wolfram Syndrome Is a Rare and Fatal Genetic Disorder[1,5]

Characterized by childhood-onset diabetes mellitus, optic nerve atrophy, deafness, diabetes insipidus, and neurodegeneration, eventually resulting in premature death[1-5]



Loss of Vision
As cells in the optic nerve die, individuals gradually go blind

Diabetes Insipidus
Because of a faulty pituitary gland, the kidneys produce too much urine

Balance and Coordination Difficulty
The disease attacks the cerebellum, hampering the ability to control movement

Deafness
People with Wolfram syndrome usually begin to lose their hearing in their teens

Difficulty Breathing
By damaging the brain stem, the disease can disrupt respiration; death occurs at a mean age of 30 years (range 25-49 years), mainly from respiratory failure

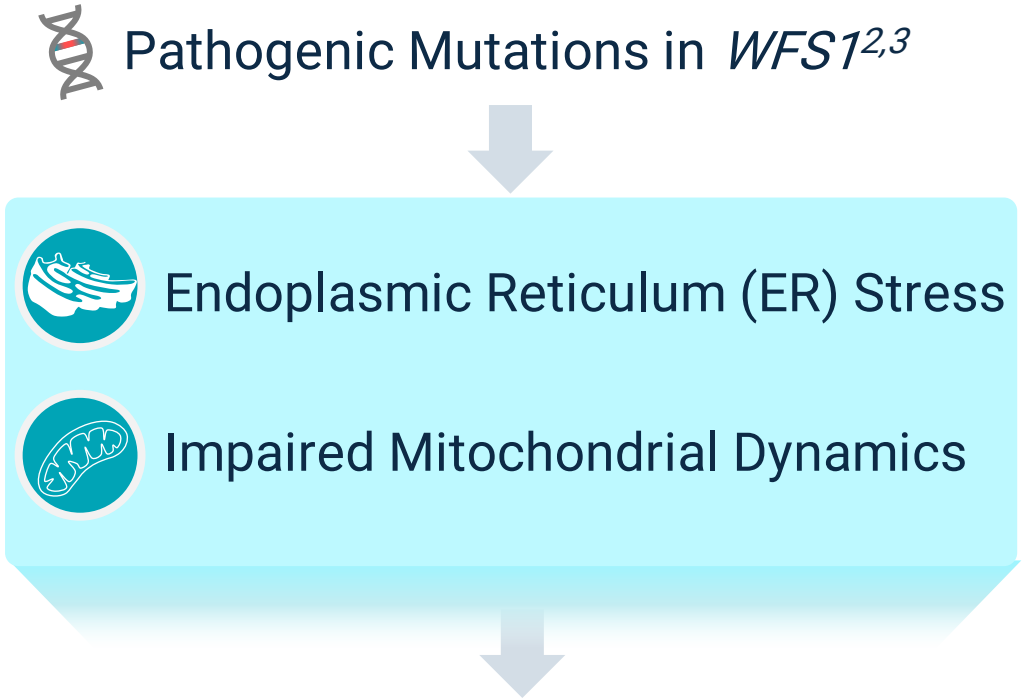
Diabetes Mellitus
Insulin-producing beta cells die, hindering the body's use of sugar as energy

There are currently no disease-modifying therapies for Wolfram syndrome; treatment strategies focus on use of life-sustaining medications, clinical monitoring, and symptom management[6,7]

Image adapted from Leslie M. Science. 2021;371(6530):663-665.

1. Urano F. Diabetes. 2014;63(3):844-846. **2.** Pallotta MT, et al. J Transl Med. 2019;17:238. **3.** Lee E, et al. Front Genet. 2023;14:1198171. **4.** Leslie M. Science. 2021;371(6530): 663-665. **5.** Matsunage et al. Plos One. 2014;9(9):106906. **6.** Urano F. Curr Diab Rep. 2016;16(1):6. **7.** Silvestri F, et al. AACE Clinical Case Rep. 2022;8(3):128-130.

Wolfram Syndrome is a Prototypical Endoplasmic Reticulum Stress Disorder[1]



1. Urano F. Diabetes. 2014;63(3):844-846. **2.** Mishra R, et al. Ther Adv Rare Dis. 2021:2:26330040211039518. **3.** Sarmara A, et al. Orphanet J Rare Dis. 2019; 14(1):279.

Recent Studies Suggest Wolfram Syndrome May be More Common than Previously Estimated[1]

Older literature estimates anywhere between ~500 to ~3,400 people living with Wolfram syndrome in the U.S.[2,3]

Studies Pre-Dating Molecular Genetic Testing	Prevalence Estimate	Extrapolated U.S. Prevalence Estimate[a]
1977 Publication Extrapolating Wolfram Prevalence Based on Frequency in Juvenile Diabetes in North America[2]	1:100,000 Individuals	**~3,400 cases**
1995 Prevalence Study in the U.K.[3]	1:770,000 Individuals	**~500 cases**

Studies Evaluating Genetic Causes of Diabetes	Prevalence Estimate	Extrapolated US Prevalence Estimate[a]
2023 *Diabetes* Study Evaluating Monogenic Diabetes in France[1]	*WFS1* mutations found in 3% of monogenic diabetes cases (monogenic diabetes = ~1% of diabetes cases in U.S.)	**~11,000 cases[b]**

[a]All U.S. prevalence extrapolations assume a U.S. population of 341,814,420.
[b]Extrapolations to U.S. prevalence from diabetes population are illustrative only to show potential trends in higher prevalence and should not be considered exact numbers. Extrapolation for monogenic diabetes assumes 38.4 million cases of diabetes in U.S.[4]; 1% of those cases are monogenic[5] = 384,000 people with monogenic diabetes in U.S.

1. Saint-Martin C, et al. *Diabetes*. 2022;71(3): 578-584. **2.** Fraser FC and T Gunn. *J Med Genet*.1977;14(3): 190-193. **3.** Barrett TG, et al. *Lancet*. 1995;346(8988): 1458-1463. **4.**National Diabetes Statistics Report. Centers for Disease Control and Prevention. Updated November 29, 2023. Accessed April 4, 2024. https://www.cdc.gov/diabetes/data/statistics-report/index.html. **5.** Riddle MC, et al. *Diabetes Care*. 2020;43(12): 3117-3128.

Enhanced Awareness and Testing Will Likely Result in Increased Prevalence Estimates as Has Been Observed in Other Rare Diseases

- As seen in other rare diseases, the prevalence of Wolfram syndrome may be underestimated due to underdiagnosis or misdiagnosis; several examples in rare disease highlight that prevalence estimates increase with improvements in disease awareness and diagnostic methods[1-5]
  - > In HELIOS participants:
    - Median age of diabetes onset (range)
      - 9 years old (3-32)
    - Median age at diagnosis (range)
      - 20 years old (8-35)

Example	Prevalence Trends
Paroxysmal Nocturnal Hemoglobinuria (PNH)	PNH prevalence increased with introduction of high sensitivity diagnostic test, increased awareness, and effective treatments **PNH Prevalence Over Time** 1991-2006: **1.59:100,000** (U.K.)[1] 2004-2018: **3.81:100 000** (U.K.)[2] 2016-2017: **12-13:100,000** (U.S.)[3]
Hypophosphatasia (HPP)	In a study from Spain, prevalence doubled when a new diagnostic algorithm introduced[4]
Huntington's Disease	Increase in Huntington's disease global prevalence attributed to enhanced availability of molecular testing, earlier diagnosis, increased life expectancy, and de novo mutations[5] **Huntington's Disease Prevalence Over Time**[5] 1985-2010: **2.71:100,000** 2010-2022: **4.88:100,000**

1. Hill A et al. *Blood*. 2006;108(11): 985. **2.** Richards SJ, et al. *Eur J Haematol*. 2021 Aug;107(2):211-218. **3.** Jalbert J, et al. *Blood*. 2019;134(supplement_1): 3407. **4.** González-Cejudo T, et al. *Clin Chem Lab Med*. 2023 Jul 14;62(1):128-137. **5.** Medina A, et al. *Mov Disord*. 2022 Dec;37(12):2327-2335.

AMX0035 Targets ER Stress and Mitochondrial Dysfunction, Critical Pathways in Wolfram Syndrome Pathophysiology[1-6]

Pathogenic Mutations in *WFS1*[2,3]

Endoplasmic Reticulum Stress

Impaired Mitochondrial Dynamics

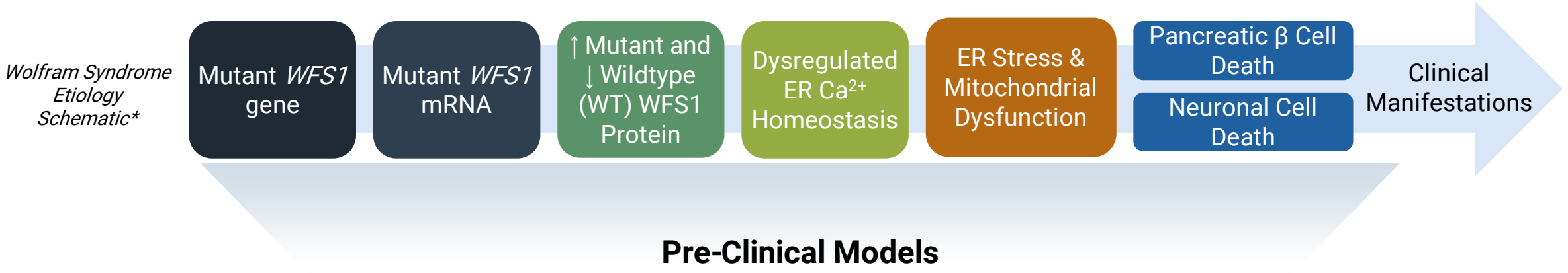
Dysfunction and apoptosis of cells, including pancreatic beta cells and neurons[2,3]

Sodium phenylbutyrate is a chemical chaperone shown to stabilize protein conformation during folding, decrease trafficking of mutant proteins, and restore normal insulin secretion in Wolfram mutant cells[3,4]

Taurursodiol stabilizes the mitochondrial membrane by reducing the translocation of cell death regulator Bax, improving mitochondrial function and energy production and increasing cell apoptotic threshold[5,6]

1. Mishra R, et al. Ther Adv Rare Dis. 2021:2:26330040211039518. **2.** Sarmara A, et al. Orphanet J Rare Dis. 2019; 14(1):279. **3.** Pallotta MT, et al. J Transl Med. 2019;7(1):238-249. **4.** Shang L, et al. Diabetes. 2014;63(3):923-933. **5.** Zhou W. J Biol Chem. 2011;286(17):14941-14951. **6.** Rodrigues CM, Steer CJ. Expert Opin Investig Drugs. 2001;10(7):1243-1253.

Wolfram Syndrome Pathophysiology is Well Characterized with Pre-Clinical Models that Allow Us to Evaluate Different Etiological Aspects



Patient iPSC-Derived Disease Models

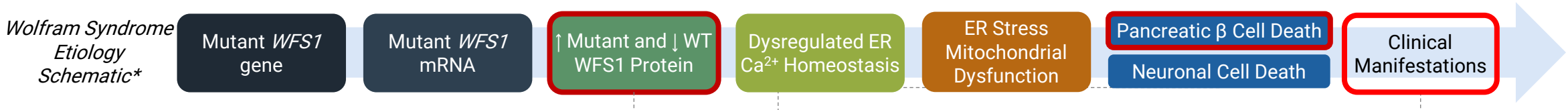
- Patient-derived induced pluripotent stem cells (iPSCs) with homozygous mutations of the *WFS1* gene, can be used to generate pancreatic islet (beta) and neural progenitor cells
- Cells exhibit hallmark features of Wolfram syndrome (e.g., decreased WFS1 expression, organelle function, viability, and insulin section)

Mouse Models

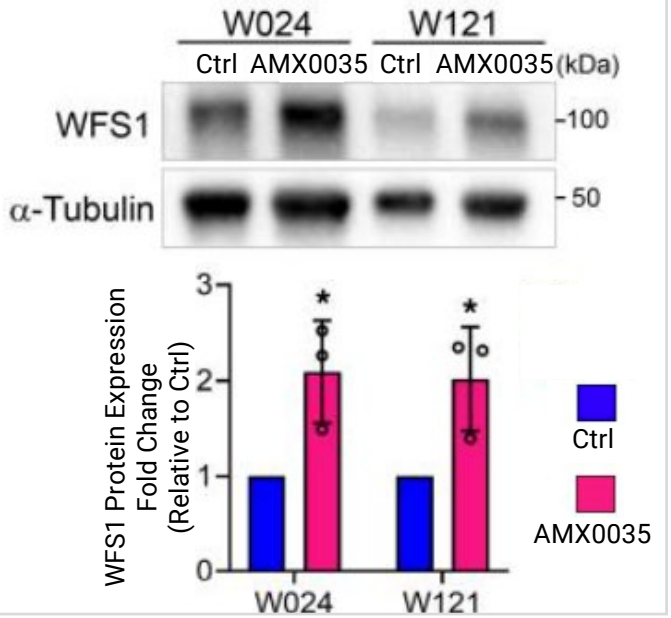
- *Wfs-1*-knockout mice develop progressive glucose intolerance during adolescence and do not exhibit increases in serum insulin in response to glucose stimulation
- Considered a valid mouse model of Wolfram syndrome

Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549. *Schematic adapted from paper.

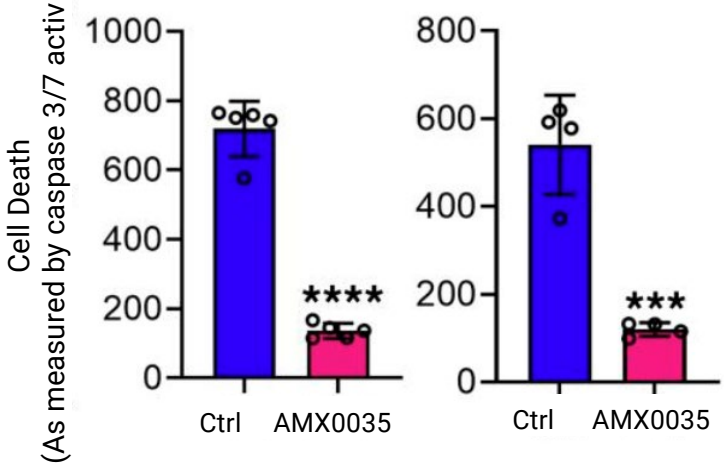
AMX0035 Rescues Wolfram Syndrome Phenotype In Patient-Derived Beta Cell Models



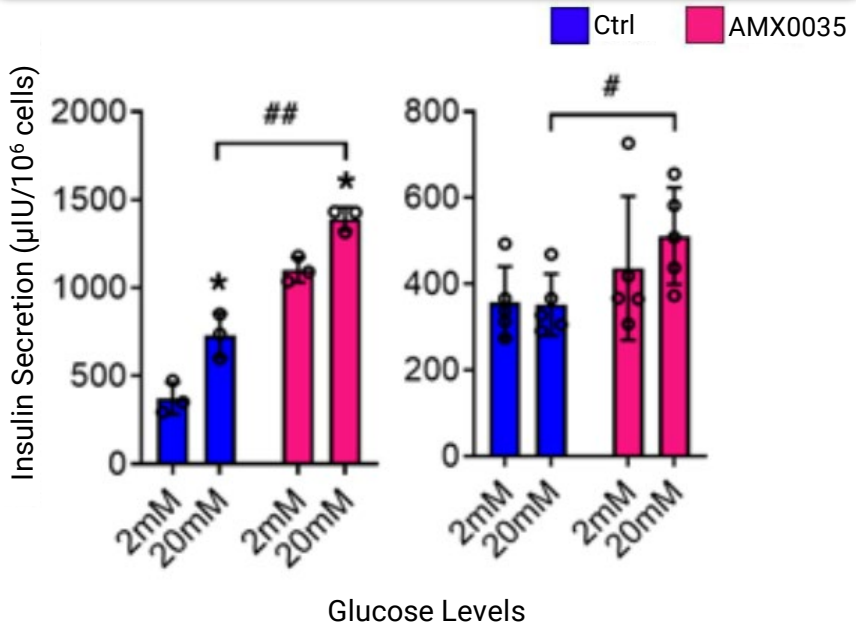
Increased WFS-1 Protein Levels in Patient-Derived Beta Cells (P<0.05)



Rescued WFS1-Mutant Islet Cell Viability in Patient-Derived Beta Cells (P<0.001)



Improved WFS1 Mutant Insulin Secretion in Two Patient-Derived Cell Lines (P<0.05)

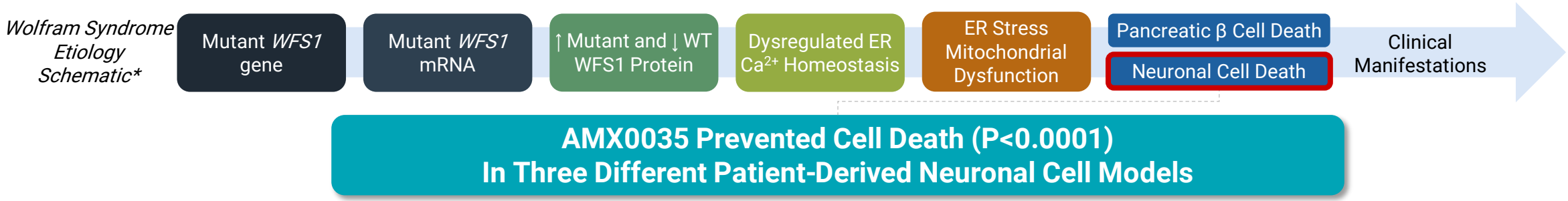


W024 and W121 indicate cell lines from specific patients

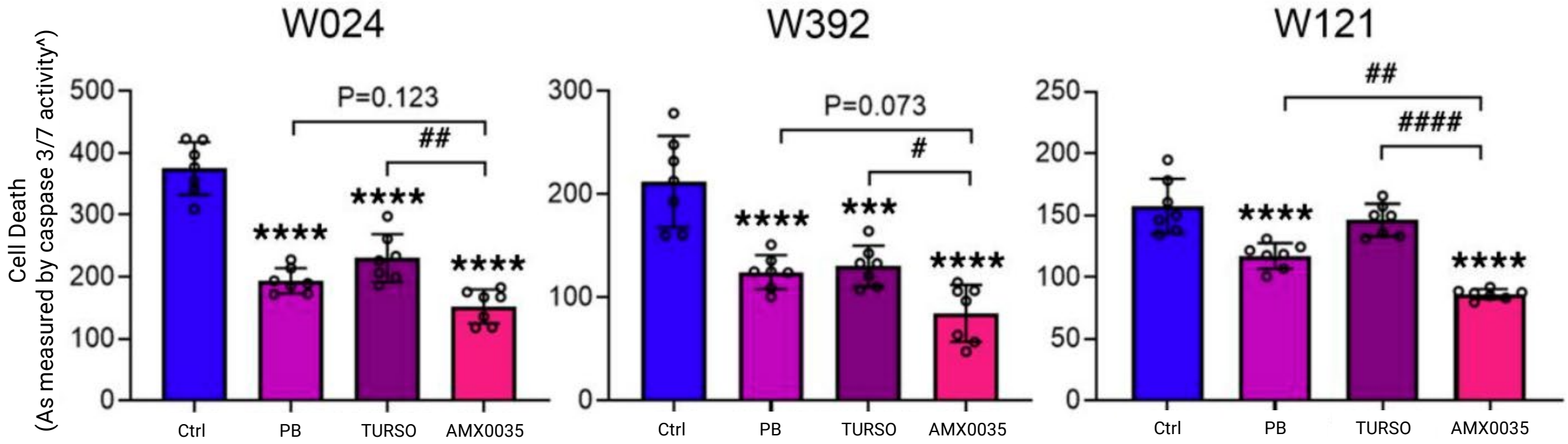
*P<0.05 by unpaired *t* test compared with Ctrl; ***P<0.001 and ****P<0.0001 by unpaired *t* test compared with Ctrl; #P<0.05 and ##P<0.01 by 2-way unpaired *t* test; ^Normalized by cell viability

Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549.

AMX0035 Rescues Wolfram Syndrome Phenotype In Patient-Derived Neuronal Cell Models



AMX0035 Prevented Cell Death (P<0.0001)
In Three Different Patient-Derived Neuronal Cell Models



W024, W392, W121 indicate cell lines from specific patients; **PB**, sodium phenylbutyrate; **TURSO**, taurursodiol.
***P<0.001 and ****P<0.0001 by 1-way ANOVA compared with Ctrl; #P<0.05, ##P<0.01, and ###P<0.0001 by 1-way ANOVA; ^Normalized by cell viability

Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549.

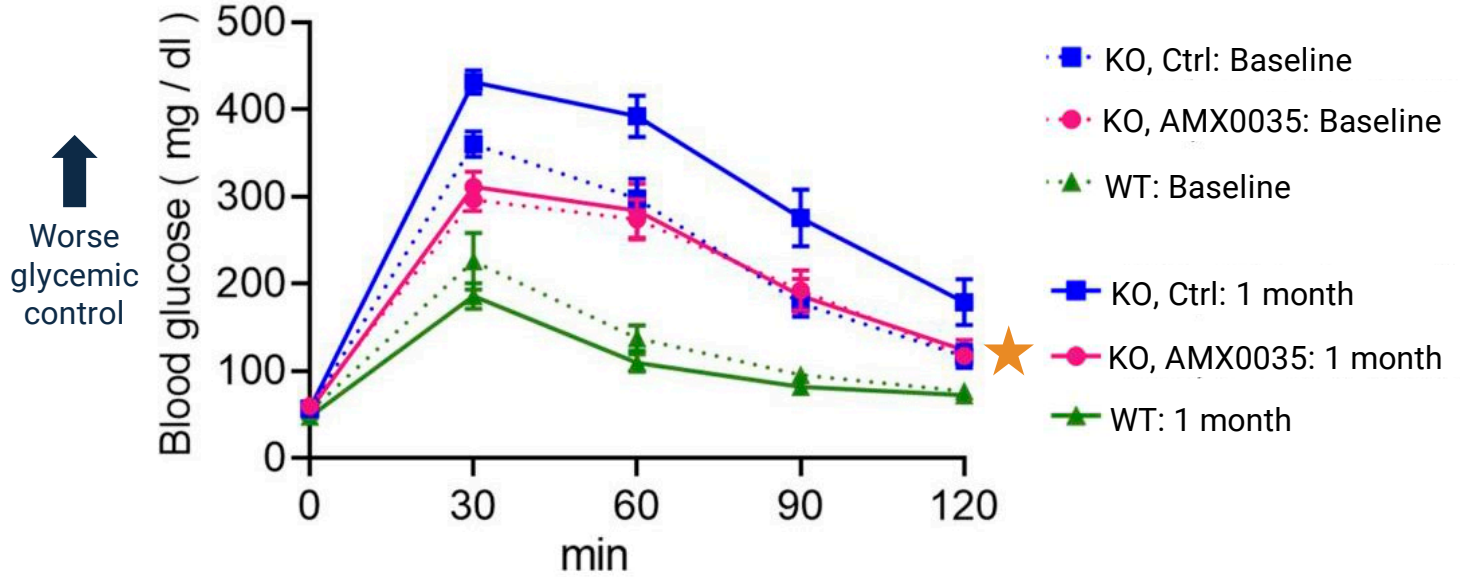
AMX0035 Significantly Delayed Onset of Diabetic Phenotypes in *Wfs1*-deficient mice

*Wolfram Syndrome Etiology Schematic**

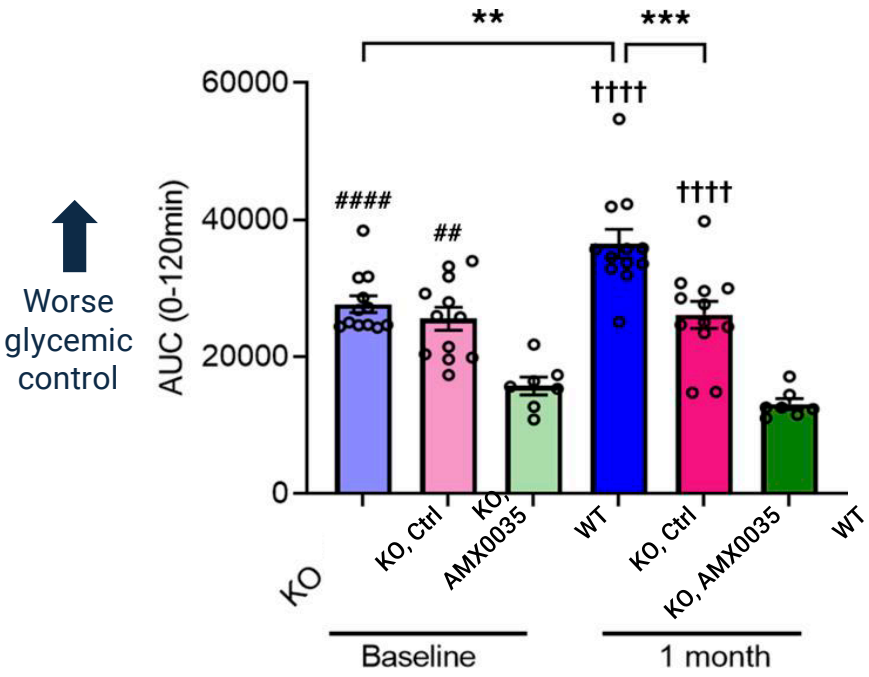
Mutant *WFS1* gene → Mutant *WFS1* mRNA → ↑ Mutant and ↓ WT WFS1 Protein → Dysregulated ER Ca^{2+} Homeostasis → ER Stress Mitochondrial Dysfunction → Pancreatic β Cell Death / Neuronal Cell Death → Clinical Manifestations

AMX0035-Treated Mice Showed Better Glycemic Control (P<0.001) than Untreated After 1 Month with Minimal to No Diabetes Progression Based on Glucose Tolerance Test (GTT)

IP-GTT with WT or Wfs1-KO Mice at Baseline and 1 Month



Area Under the Curve of the Glucose Tolerance Test



IP-GTT, intraperitoneal glucose tolerance test (IP-GTT)
**P < 0.01 and ***P < 0.001 by 1-way ANOVA; ##P < 0.01 and ####P < 0.0001 by 1-way ANOVA compared with WT: Baseline; ††††P < 0.0001 by 1-way ANOVA compared with WT: 1 month)

Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549.

Pre-Clinical Evidence for AMX0035 in Wolfram Syndrome Summary

AMX0035 has been Extensively Studied in Wolfram Syndrome Models including Patient-Derived Cells and Mouse Model

- Clear Improvement in Insulin Secretion in Patient-Derived Beta Cells
- Clear Improvement in Cell Viability in Patient-Derived Beta Cells
- Clear Improvement in Cell Viability in Patient-Derived Neuronal Cells
- Highly Statistically Significant Delay in Glycemic Progression in Wolfram Mice

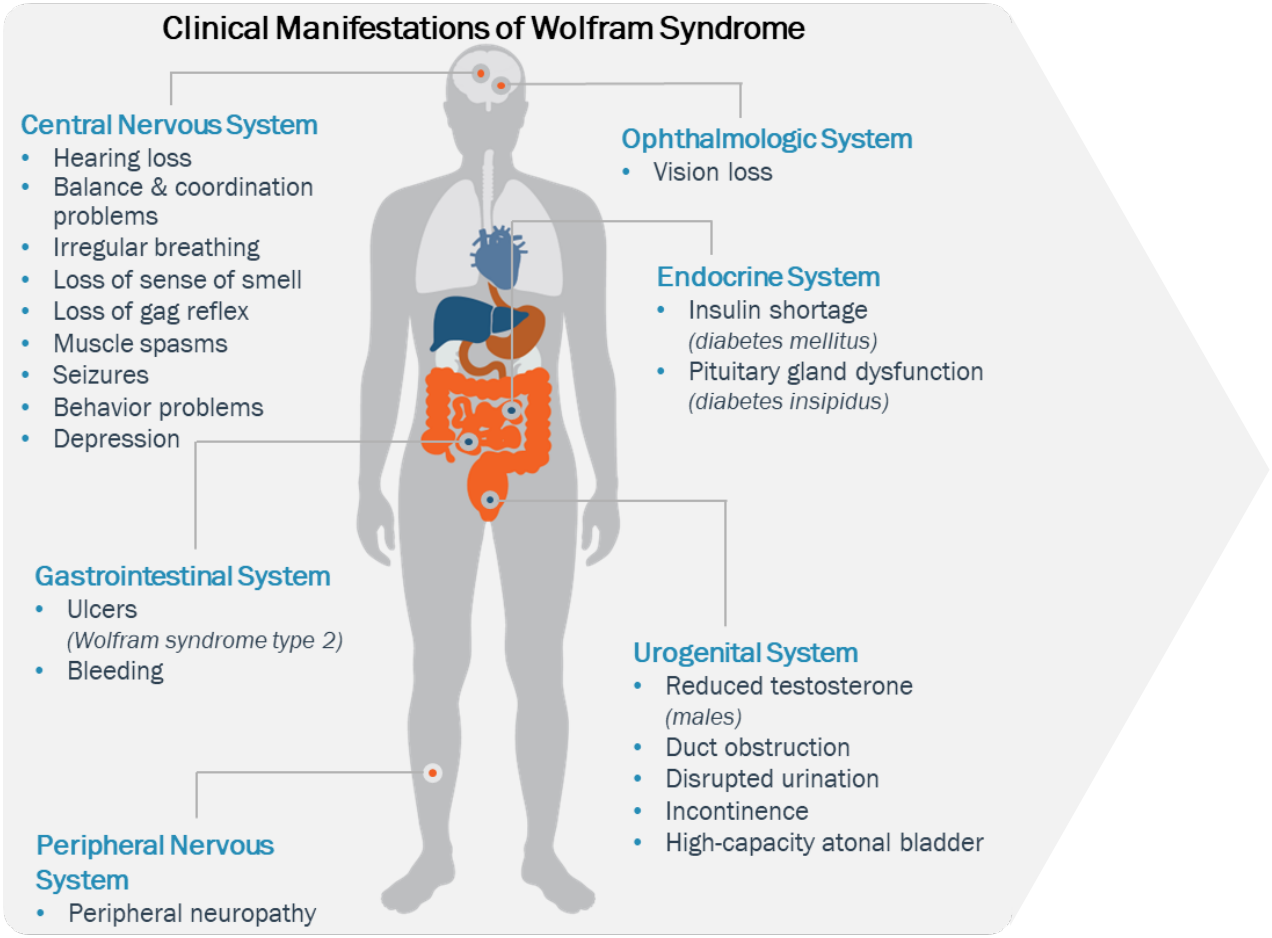
Kitamura RA, et al. *JCI Insight*. 2022;7(18):e156549.

AMYLYX

Measurement of Progression in Wolfram Syndrome

In memory of Lauren, a beautiful daughter and passionate Wolfram syndrome warrior.

Progression Measurements in Wolfram Syndrome Typically Focus on Disease Manifestations with Greatest Prevalence and Impact



Key Focus Areas for Wolfram Syndrome Progression Measurement

Diabetes Mellitus

Vision

Other Measures of Wolfram Syndrome Progression

Overall Wolfram Syndrome Symptom Burden

What is Wolfram syndrome? Snow Foundation. Accessed February 24, 2023. https://thesnowfoundation.org/wolfram-syndrome/

Measures of Diabetes Mellitus Progression: C-Peptide

C-Peptide

- The pancreas produces insulin over a series of steps:[1]
  - Preproinsulin is cleaved into proinsulin which is cleaved into insulin and C-peptide
- C-peptide levels are often used as a surrogate marker of pancreatic function and glycemic control as C-peptide[2,3]
  - Is secreted in a 1:1 ratio with insulin and degraded at a slower rate
  - Is not cleared by the liver and can be measured in the blood
  - Is produced endogenously and is not confounded by external insulin use
  - Has been shown to predict future diabetic complications and glycemic control
- C-peptide levels have been used as the primary outcome in several major diabetes trials and multiple publications consider it to be a validated surrogate marker[4,5]

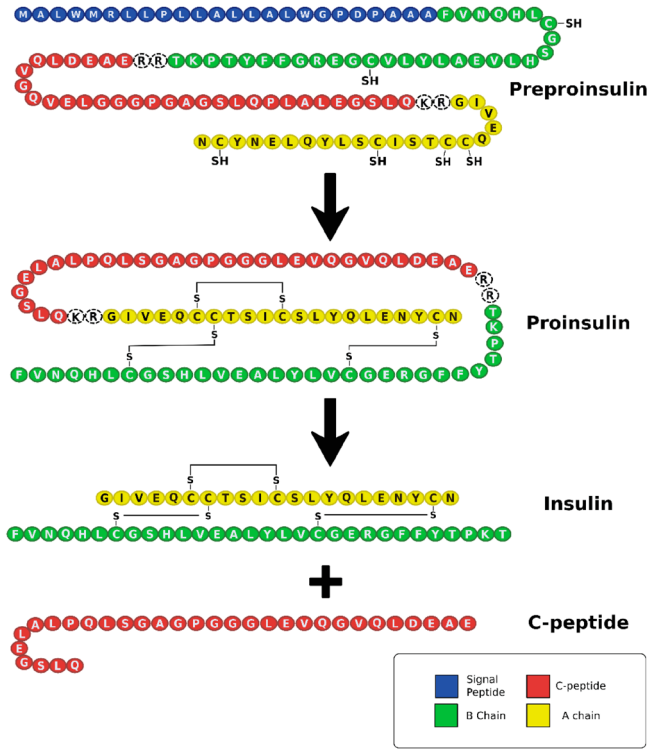


Image From: Washburn RL, et al. Biomedicines. 2021;9(3):270.

1. Washburn RL, et al. *Biomedicines.* 2021;9(3):270. **2.** Leighton E, et al. *Diabetes Ther.* 2017; 8(3):475-487. **3.** Iafusco D, et al. Int J Environ Res Public Health. 2022; 19(5):2755. **4.** Latres E, et al. Diabetes (manuscript in preprint server). 2024. **5.** Herold KC et al. Diabetes. 2013;62(11):3766-74.

C-Peptide Declines in Wolfram Syndrome—HELIOS was Designed to Measure a Slowing in Decline

- C-peptide levels are an objective laboratory measure assessed during a mixed meal tolerance test (MMTT), a physiological stimulation test using a standardized liquid meal ingested in the morning followed by timed measurements over the subsequent pre-determined time period[1]
- 4-hour MMTT is expected to have less variance and be a better measure
  - **Amylyx is the first to conduct 4-hour MMTT in Wolfram syndrome**
- The 90-minute MMTT has been shown to be a highly sensitive and specific measure of peak insulin secretion and AUC C-peptide and is considered to be a useful alternative to a full 2-hour MMTT[2]
- A recent natural history study demonstrated decline in C-peptide (as measured by 30-minute MMTT) after diabetes mellitus onset in Wolfram syndrome[3]
  - **In the first ~2 years:** Average decline of 0.37 ng/mL per year of diabetes mellitus
  - **After the first ~2 years:** Average decline of 0.13 ng/mL per year of diabetes mellitus

WS Natural History Expectations: C-peptide progressively decreases

1. Forbes S, et al. *Clin Transplant.* 2018;32(8):e13301. **2.** Besser REJ, et al. *Diabetes Care.* 2013;36(2):195-201. **3.** Ray MK, et al. *Pediatr Diabetes.* 2022;23(2):212-218.

Measures of Diabetes Mellitus Progression: HbA1c

Hemoglobin A1C (HbA1c)

- The level of glycosylated hemoglobin (HbA1c) provides a measure of the glycemic control of diabetes during the preceding 2-3 months[1]
- HbA1c is inversely correlated to C-peptide; improved metabolic function is associated with higher C-peptide and lower HbA1c[2]
  - In Wolfram syndrome, HbA1c levels may remain stable, if blood glucose is well-controlled with available diabetes mellitus treatments, however it may get more difficult for levels to remain stable as the disease progresses[3,4]

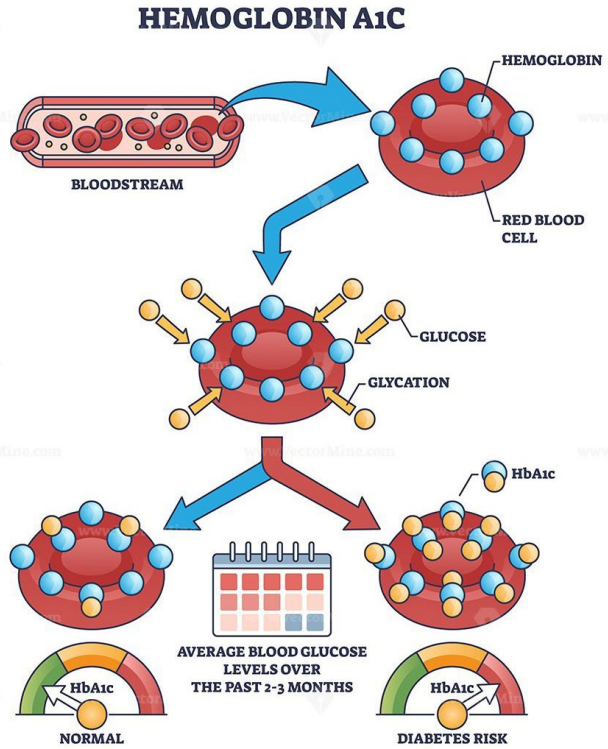
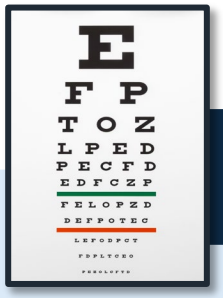


Image from: Lind M, et al. *PLoS One.* 2009;4(2):e4412.

WS Natural History Expectations: HbA1c gets more challenging to control over time

1. Sherwani S, et al. Biomark Insights. 2016;11:95-104. **2.** Ismail HM, et al. Pediatr Diabetes. 2019;20(4):408-413.**3.** Kondo M, et al. *Diabetologia.* 2018;61(10);2189-2201. **4.** Ray MK, et al. *Pediatr Diabetes.* 2022;23(2):212-218.

Measures of Vision: Best Corrected Visual Acuity

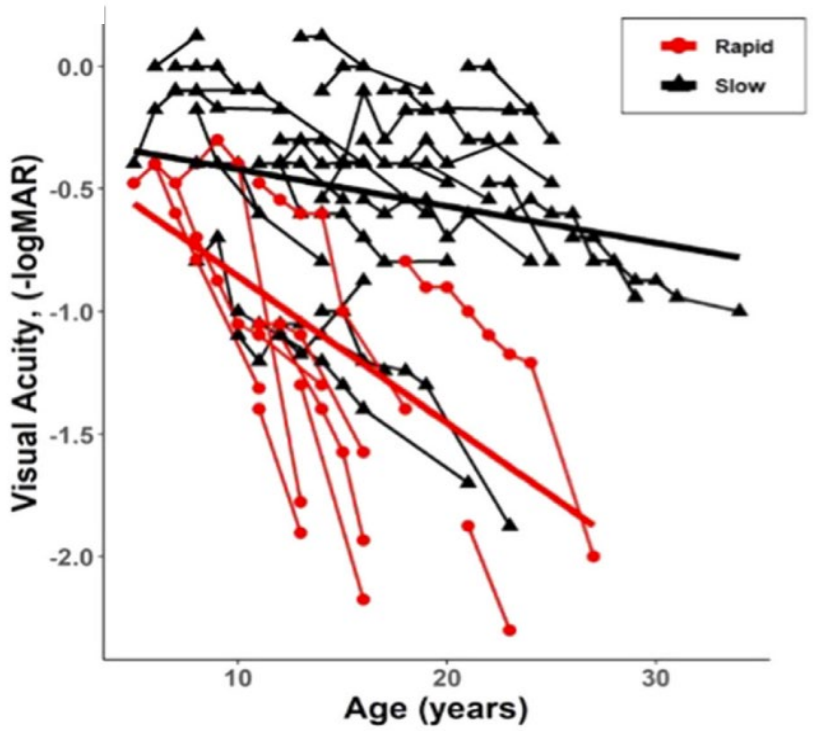


Best Corrected Visual Acuity

- Measurement of visual acuity for both eyes after correction, using the Snellen chart
- LogMar values range from 0 (perfect vision) to +2 (near blindness)*
- In a recent 10-year analysis of 38 individuals with Wolfram syndrome, **visual acuity declined over time in all participants with a mean slope of 0.059 logMar/year** (95% CI: 0.07 to 0.05 logMar/year)
  - > A subset of individuals (26%) had rapid decline in visual acuity; mean rate of decline was 0.16 logMar/year (SD 0.05)

*Values of -0.1 and -0.2 are also possible representing better than perfect vision

Visual Acuity in WS Over Time (n=38)



WS Natural History Expectations: Visual acuity progressively decreases

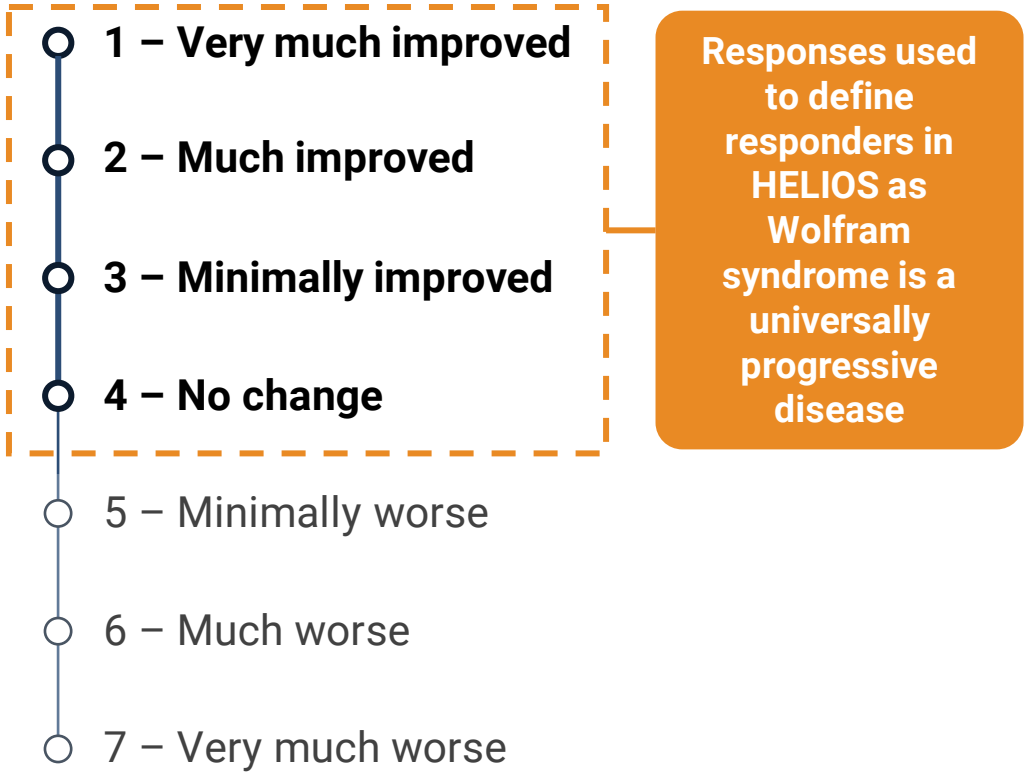
O'Bryhim BE, et al. Am J Opthalmol. 2022:243:10-18.

Measures of Overall Symptom Burden: PGI-C and CGI-C

PGI-C and CGI-C

- **PGI-C:** Patient-reported global impression of change
  - Participants evaluate the change in their WS-related symptoms since initiation of study drug
  - Asked by the investigator or qualified designee to rate their change in status using a 7-point scale
- **CGI-C:** Clinician-reported global impression of change
  - The CGI-C rates improvement by the same 7-point scale
- While not specific to WS, these measures have been used across multiple disease states to provide a holistic assessment of treatment benefit

PGI-C and CGI-C 7-Point Scale



Data on File. Amylyx Pharmaceuticals Inc. 2022.

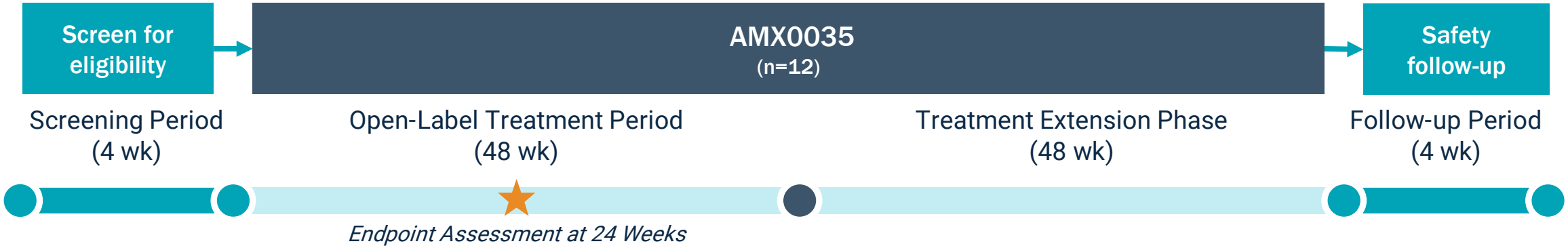
Interim Efficacy and Safety Results of AMX0035 in Wolfram Syndrome

HELIOS Study Design[1,2]

Primary Goal of HELIOS:
Achieve slowing of Wolfram syndrome progression

Primary Objectives:

- To assess the safety and tolerability of AMX0035 administered orally for up to 96 weeks
- To evaluate the effect of AMX0035 on residual beta cell function over 24 weeks by monitoring C-peptide levels



Key Trial Entry Criteria[1,2]

- Aged ≥17 years
- Definite diagnosis of Wolfram syndrome[a]
- Stimulated C-peptide level of ≥0.2 ng/mL at screening
- Insulin-dependent diabetes mellitus due to Wolfram syndrome
- Must be willing to wear a CGM device for the study duration
- No GLP-1 Agonist Use

CGM, continuous glucose monitoring.

[a]Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene based on historical test results (if available) or from a qualified laboratory at screening

1. ClinicalTrials.gov identifier: NCT05676034. Updated November 21, 2023. Accessed April 9, 2024. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2024.

HELIOS Study Design[1,2]

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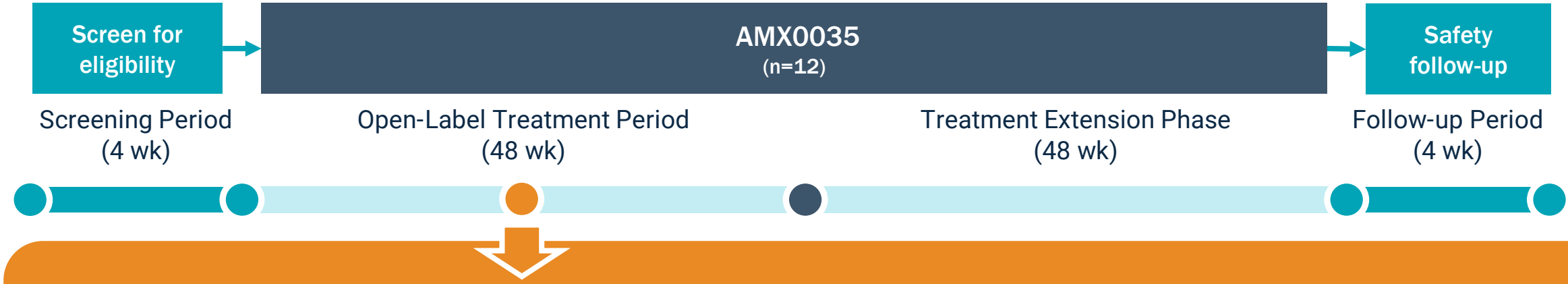


Data shared today are from an interim analysis performed as of March 5, 2024, when 8 participants had completed their Week 24 assessments

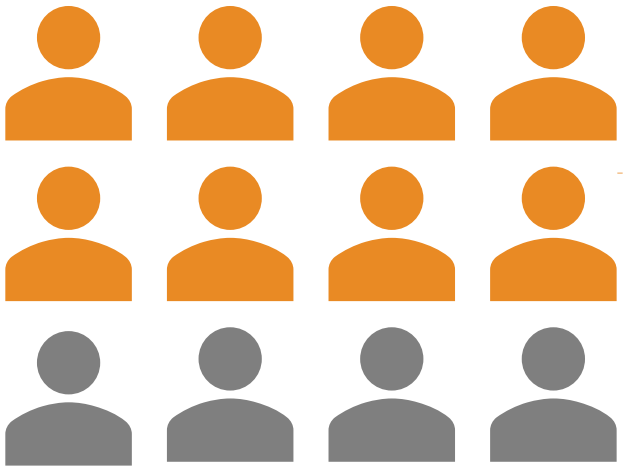
CGM, continuous glucose monitoring.

[a]Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene based on historical test results (if available) or from a qualified laboratory at screening

1. ClinicalTrials.gov identifier: NCT05676034. Updated November 21, 2023. Accessed April 9, 2024. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2024.

Interim Analysis Has Complete Efficacy for 8 Participants at Week 24 and Demographic and Available Safety Data for All 12 Enrolled

HELIOS



12 Individuals Enrolled
With No Dropouts or Discontinuations Thus Far

Today's Data

8 Participants with Data Fully Cleaned Through Week 24

- ✓ **Demographics**
- ✓ **Efficacy**
- ✓ **Safety**

4 Recently Enrolled Participants, Have Not Yet Reached Week 24

- ✓ **Demographics**
- ✓ **Available Safety**

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Patient Baseline Characteristics

Median Age:
25 years (range: 18-39)

Male:
2 (17%)

Female:
10 (83%)

Median Duration of WS:
5 years (range: 1 to 24)

Median Age at Diagnosis
20 (range: 8 to 35)

Median Age of Onset, Years (Range)

Diabetes Mellitus
9 (3 to 32)

Diabetes Insipidus*
11 (7 to 24)

Vision Loss
11.5 (5 to 29)

Hearing Loss
16 (7 to 33)

Diabetes Medications at Baseline

Medication	Frequency (count)
Insulin Lispro	8
Insulin Glargine	5
Metformin	3
Insulin Aspart	2
Glucagon	1
Insulin Degludec	1
Insulin Lispro-aabc	1

* N=4

HELIOS Endpoints

Primary Efficacy

- Change from baseline in C-peptide (ΔC-peptide, AUC c-peptide)

Secondary Efficacy

- Change in baseline **best-corrected visual acuity** on the LogMar scale using the Snellen chart
- Change from baseline in **exogenous insulin dose**
- Change from baseline in **overall time in target glucose range (70–180 mg/dL)**
- Change from baseline in **HbA1c level**

Exploratory

General

- Wolfram United Rating Scale
- Clinician-reported Global Impression of Change
- Patient-reported Global Impression of Change
- Most bothersome symptom

Visual

- Visual Functioning Questionnaire–25
- Optical Coherence Tomography measurements

Additional Pancreatic

- Diabetic measurements, including fasting glucose, fasting proinsulin, AUC C-peptide/ AUC glucose, delta proinsulin
- Change from Week 96 to Week 100 in C-peptide levels

Neurological

- Blood biomarker (panel) levels of neurodegeneration and neuroinflammation
- Scale for the Assessment of Rating Ataxia

Interim Analysis Results Focus on Diabetes and Vision Assessments in 8 participants (Week 24)

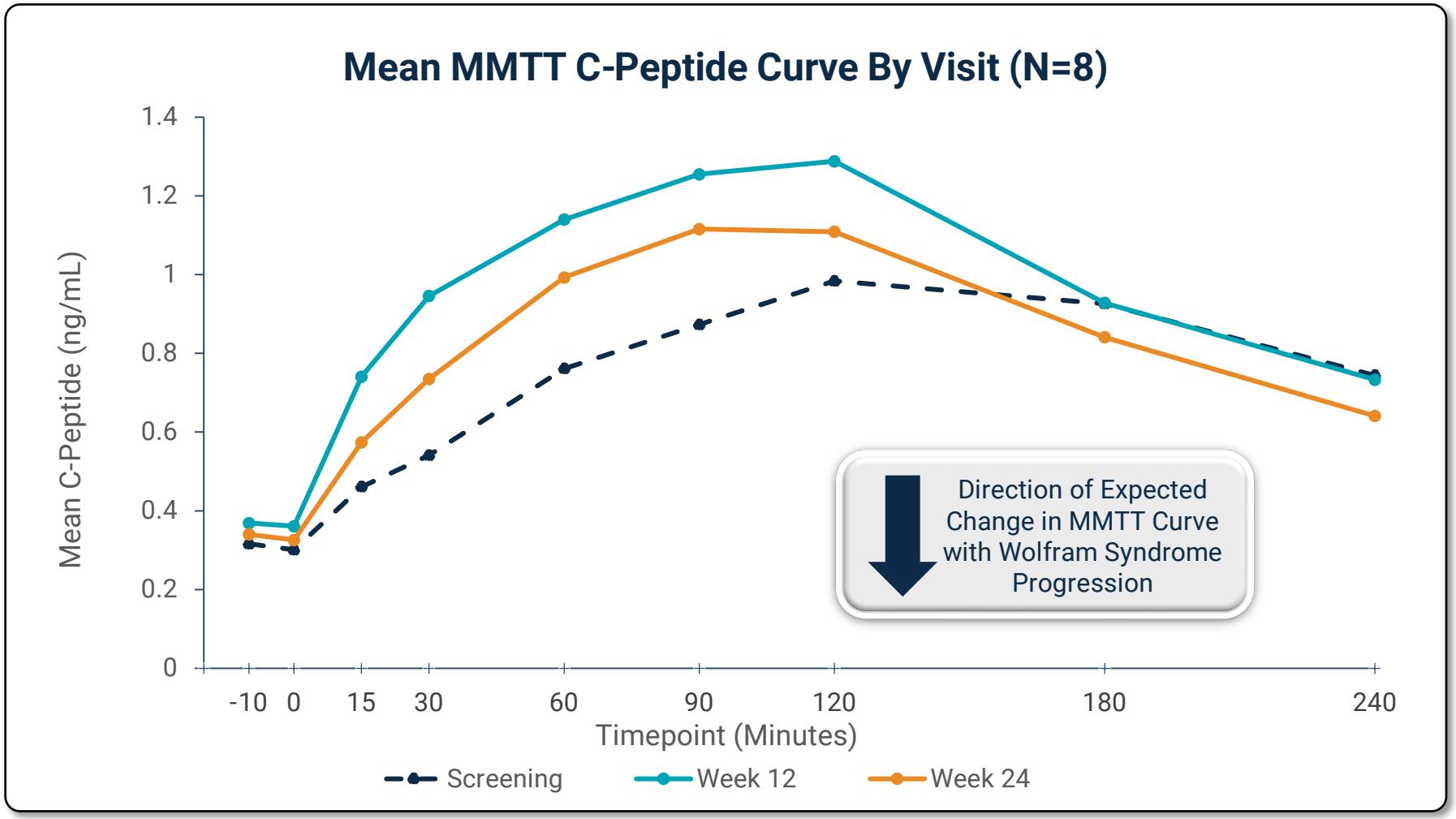
- Final Week 24 data will report all 12 participants and include additional assessments

AUC, area under the curve; MMTT, mixed-meal tolerance test.

1. ClinicalTrials.gov identifier: NCT05676034. Updated November 21, 2023. Accessed April 9, 2024. https://www.clinicaltrials.gov/ct2/show/NCT05676034. **2.** Data on File. Amylyx Pharmaceuticals Inc. 2022.

Primary Endpoint: Improvement in C-Peptide Response at Weeks 12 and 24

Overall increase in mean C-peptide (Total Production/Area Under Curve) when decrease expected



Partial Reversal in C-peptide Phenotype Observed at Weeks 12 and 24 Compared to Screening

Data on File. Amylyx Pharmaceuticals Inc. 2024.

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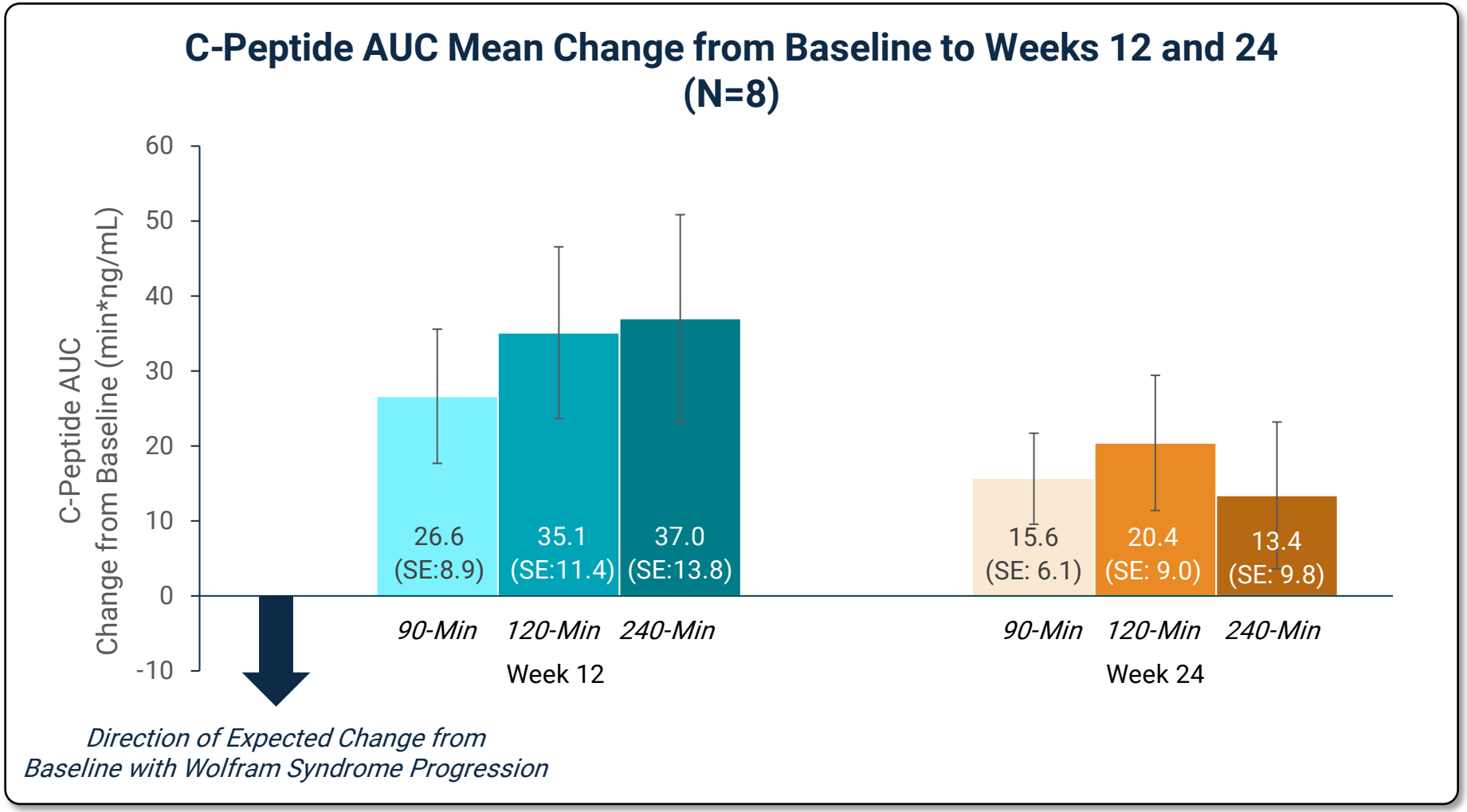
Overall increase in mean C-peptide (Total Production/Area Under Curve) when decrease expected

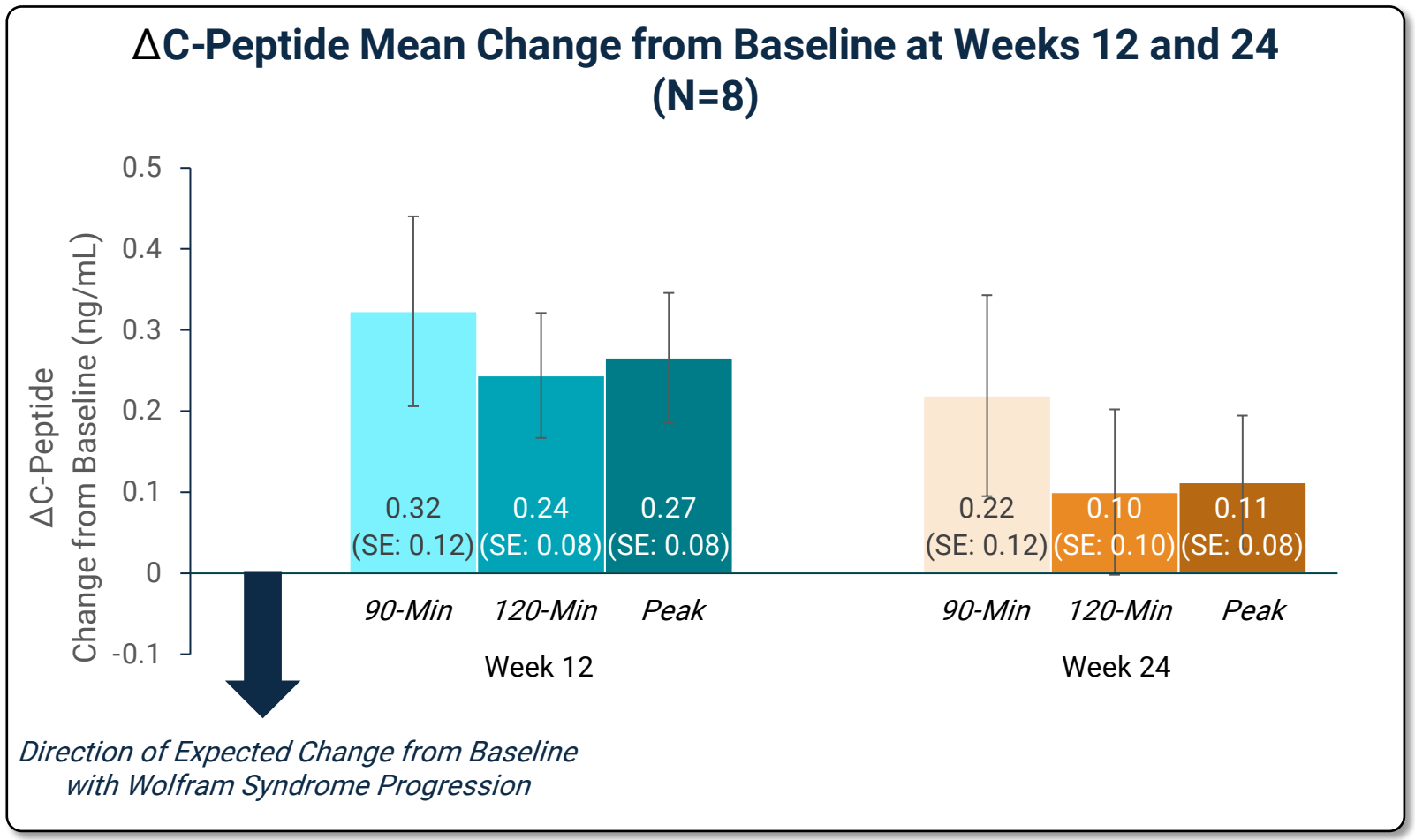


Partial Reversal in C-peptide Phenotype Observed at Weeks 12 and 24 Compared to Screening

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Primary Endpoint: Δ C-Peptide Change from Baseline Improved

Overall increase in numerical response at 90-, 120-minutes and Peak, when decrease expected



Improvement in Average Beta Cell Responsiveness at 12 and 24 Weeks Compared to Screening

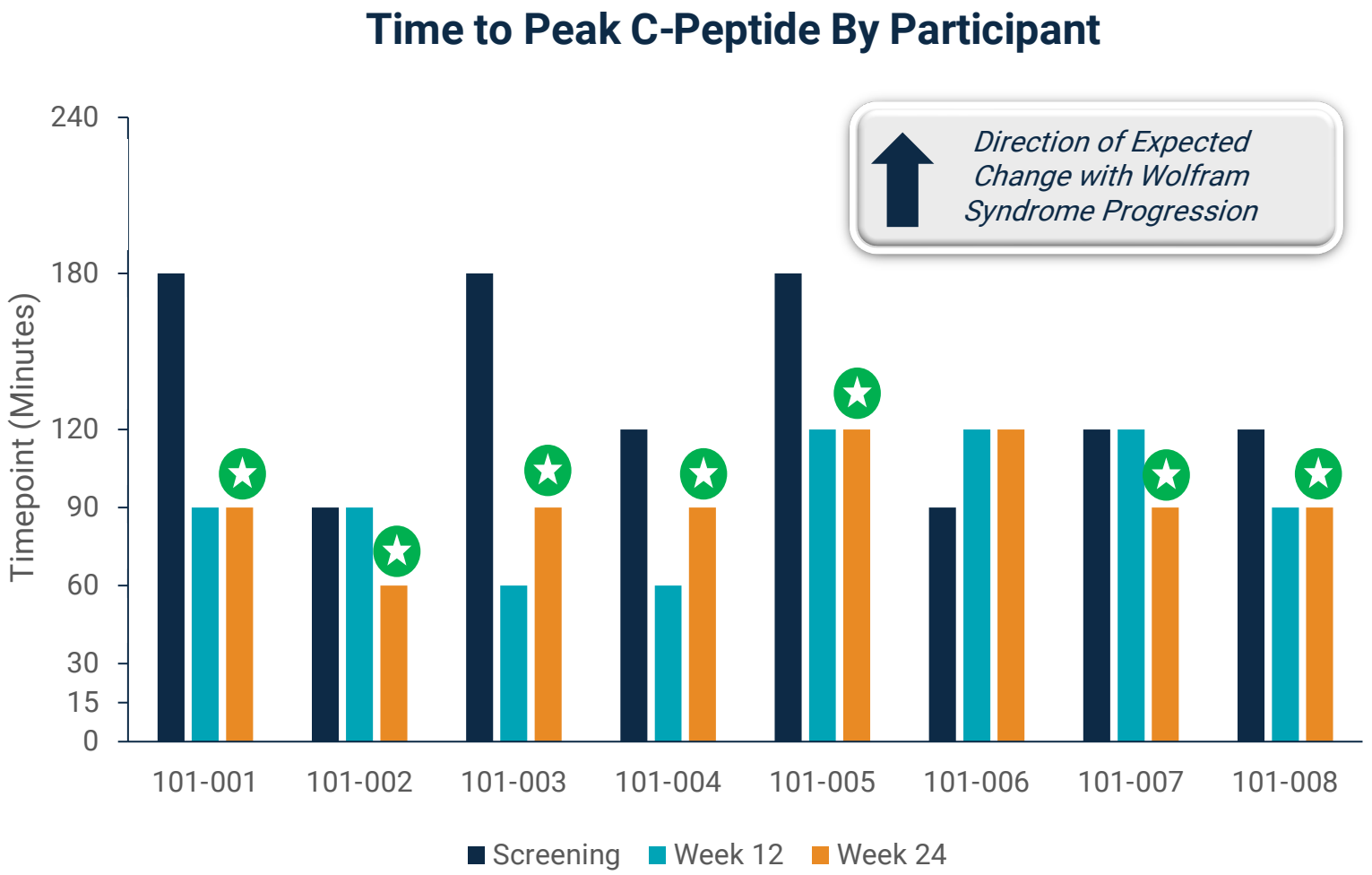
*5 of 8 participants demonstrated increased **ΔC**-Peptide change at peak from baseline*

Change in C-Peptide (or ΔC-Peptide) = (C-peptide at Specific Timepoint in MMTT [e.g., 90 minutes]) – (C-peptide at 0 minutes)
Change in ΔC-Peptide (or ΔΔC-Peptide) = (ΔC-Peptide over MMTT at Timepoint of Interest [e.g., 24 weeks]) – (ΔC-Peptide over MMTT at Baseline)

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Primary Endpoint: Time to Peak C-Peptide Improved with AMX0035

Shorter time to peak C-peptide suggesting more rapid beta-cell response to glucose challenge

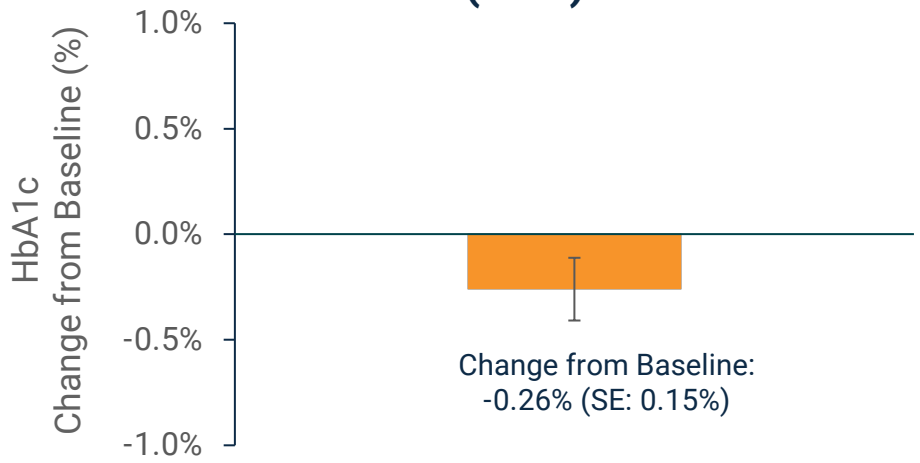


7 of 8 Participants Demonstrated Improved Pancreatic Function (at Least 30 min Shorter Time to Peak C-Peptide) at Week 24 Compared to Screening

Data on File. Amylyx Pharmaceuticals Inc. 2024.

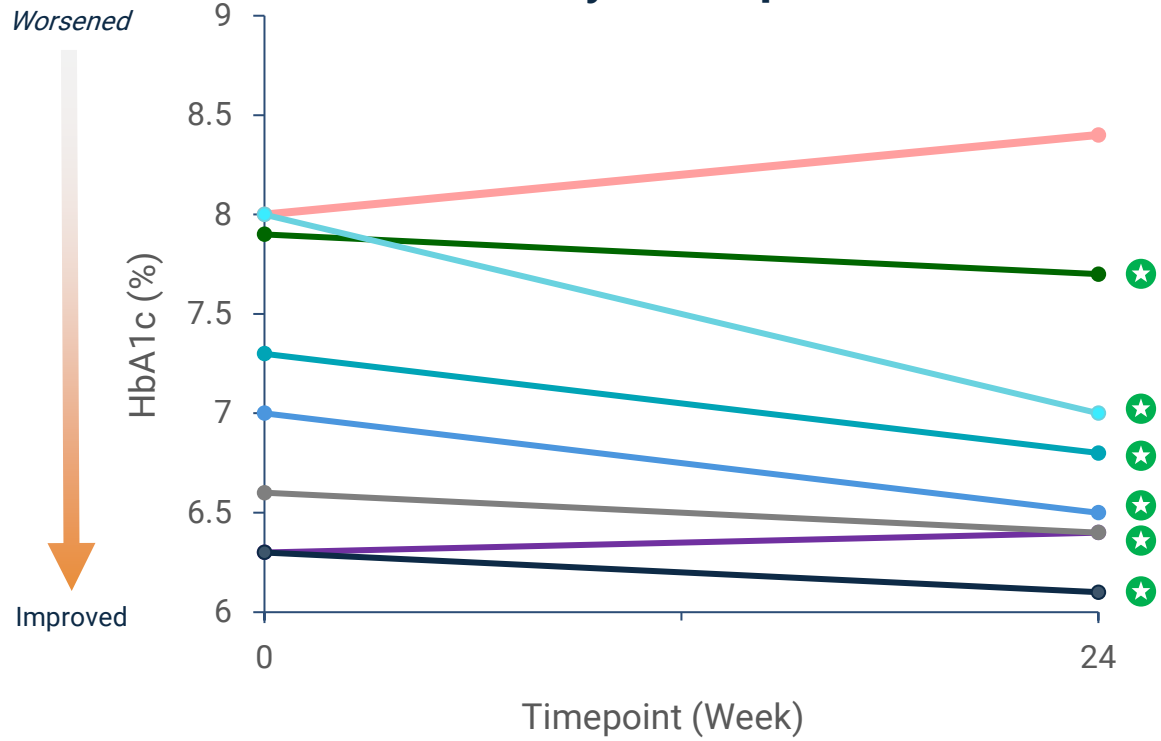
Secondary Endpoint: HbA1c

HbA1c Mean Change from Baseline to Week 24 (N=8)



Improved Glycemic Control as Measured by HbA1c at Week 24 Compared to Screening

HbA1c By Participant

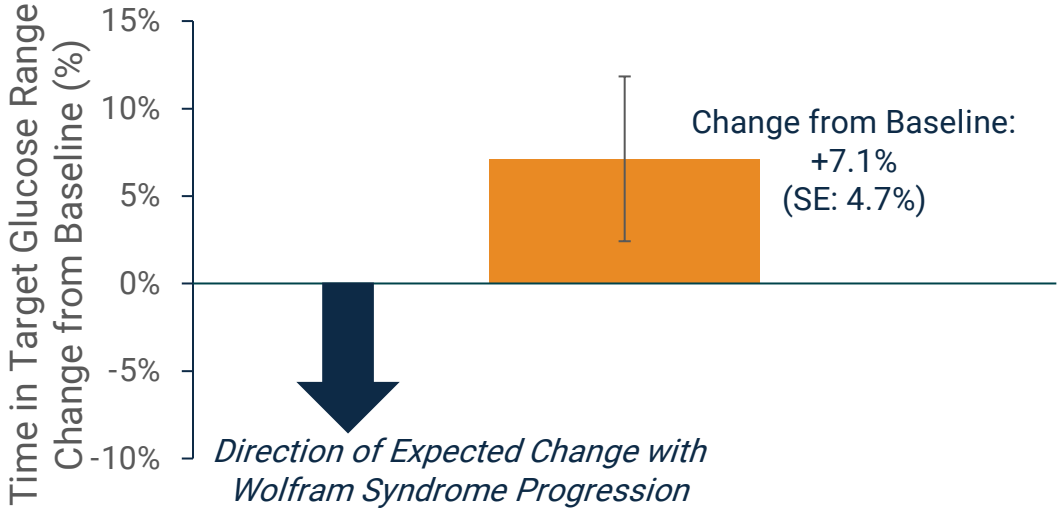


6 of 8 participants demonstrated reduced HbA1c from Screening to Week 24

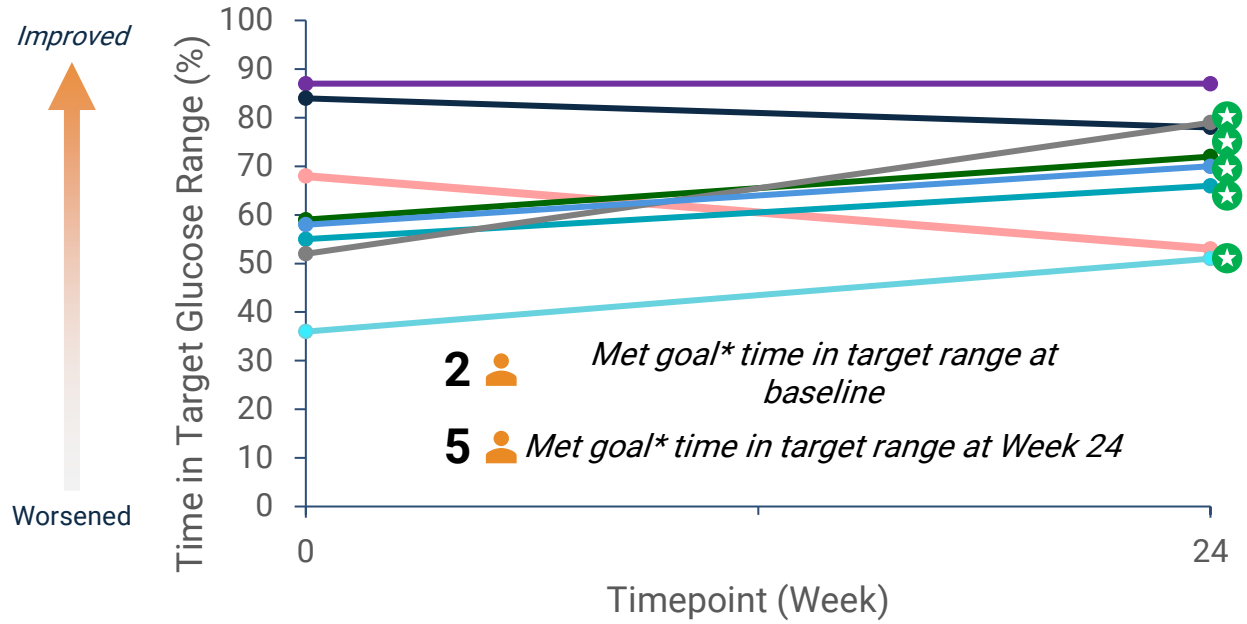
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Secondary Endpoint: Overall Time in Target Glucose Range

Time in Target Glucose Range Change from Baseline to Week 24 (N=8)



Mean Time in Target Glucose Range by Participant



Improved Glycemic Control as Assessed by Continuous Glucose Monitoring at Week 24 Compared to Screening

5 of 8 participants demonstrated increased time in target glucose range from Screening to Week 24

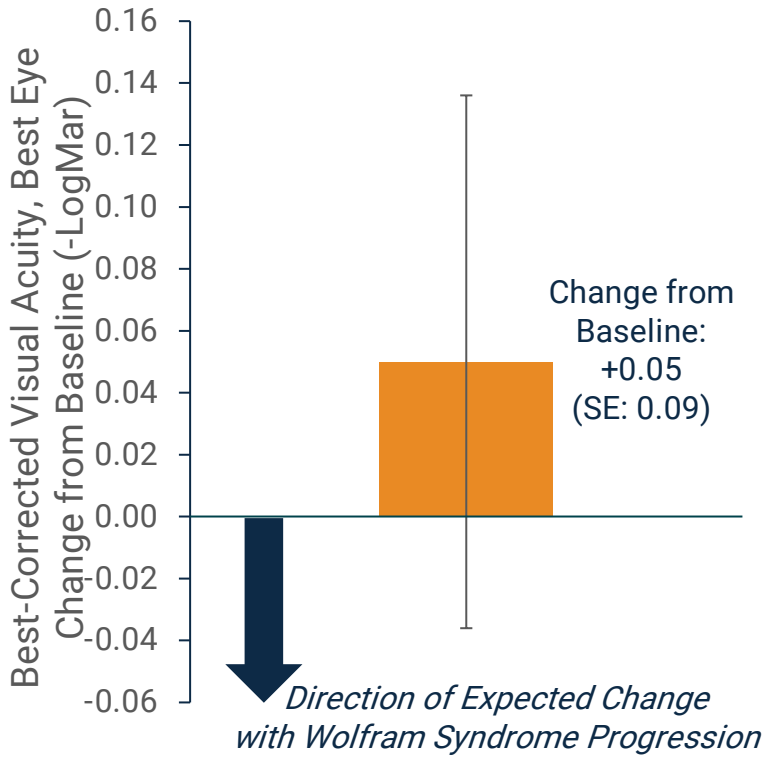
Of remaining 3 participants, 1 stable over time and 2 progressed

*Goal as defined by Recommendations from the International Consensus on Time in Range (Battelino T, et al. *Diabetes Care.* 2019;42(8):1593-1603.)

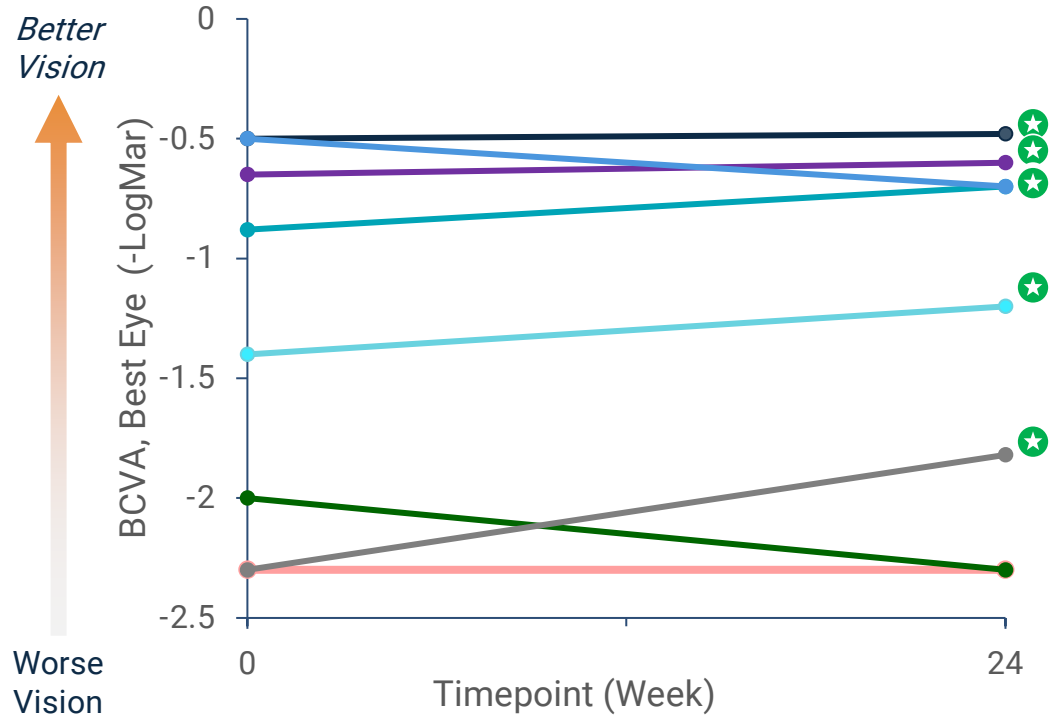
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Secondary Endpoint: Best Corrected Visual Acuity (BCVA)

BCVA, Best Eye Mean Change from Baseline to Week 24 (N=8)



Change in BCVA, Best Eye by Participant



5 of 8 demonstrated improved visual acuity in at least one eye from Screening to Week 24

Includes 1 participant blind at baseline who now has vision in one eye

Of remaining participants:

- *1 stable in one eye*
- *1 progressed in both eyes*
- *1 legally blind with no change*

Trend Indicating Potential Visual Acuity Improvement at Week 24 Compared to Screening

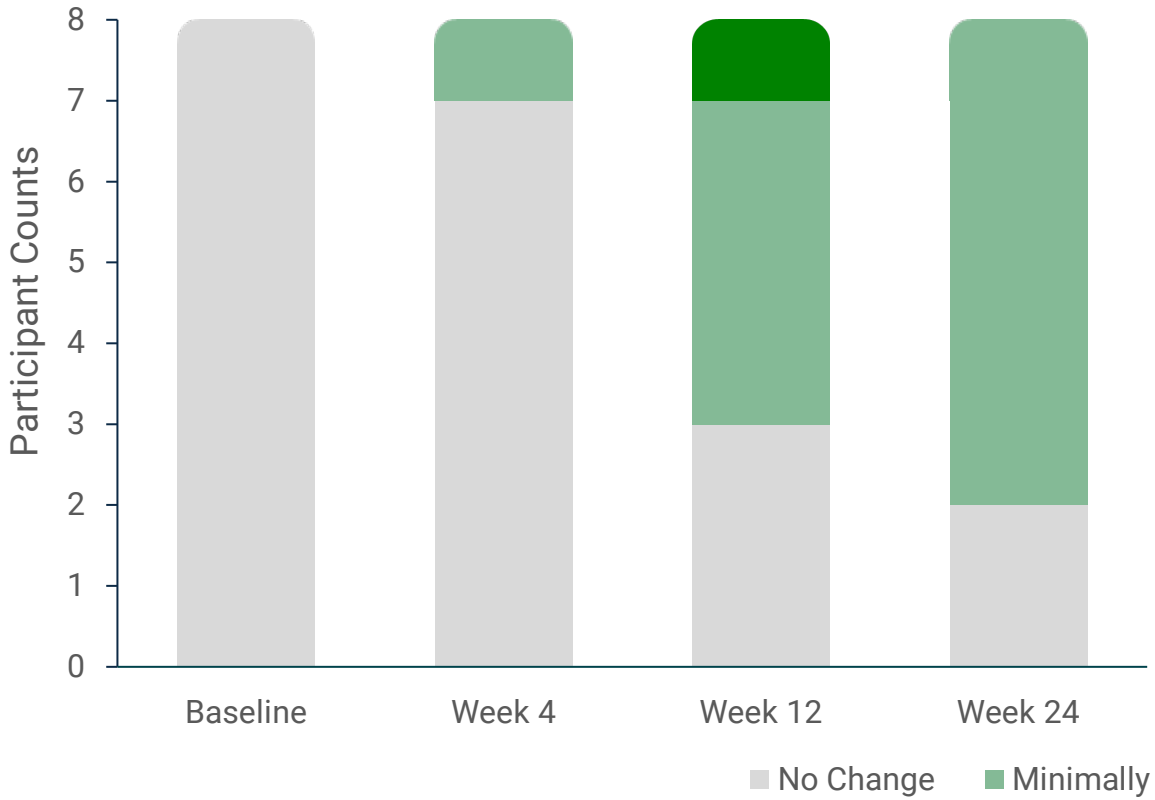
Data on File. Amylyx Pharmaceuticals Inc. 2024.

Exploratory Endpoint: PGI-C and CGI-C

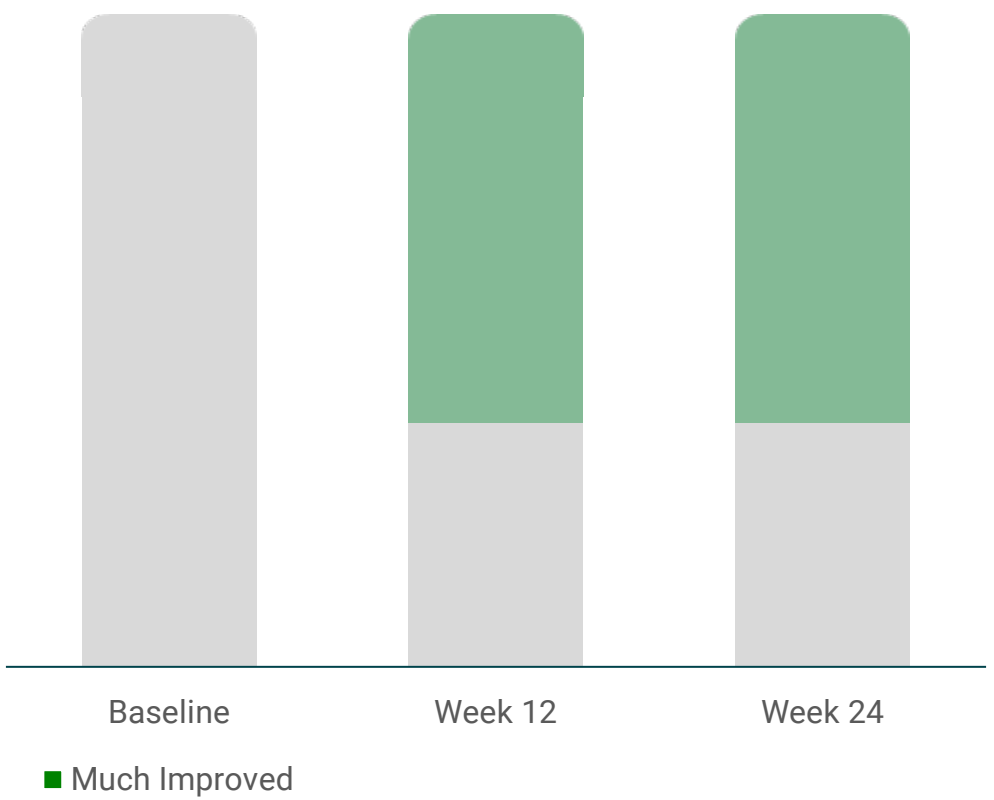
100% of Participants Met Responder Criteria by Self and Clinician Assessment

75% of participants claim to improve on AMX0035; clinician reports 62.5% of patients improving

Patient-Reported Global Impression of Change (PGI-C) (N=8)



Clinician-Reported Global Impression of Change (CGI-C) (N=8)



No Change Minimally Improved Much Improved

Data on File. Amylyx Pharmaceuticals Inc. 2024.

AMX0035 Safety and Tolerability in HELIOS (N=12)

- AMX0035 was **generally well tolerated**
  - Diarrhea was the most common TEAE (41.7%)
- **No new safety signals** were identified
- Nearly all participants reported ≥1 TEAE during the trial
  - Most did not lead to modification or interruption of AMX0035 dosing and **none led to drug discontinuation**

Summary of Treatment Emergent Adverse Events (TEAEs)

	AMX0035 (N=12)
Participants with ≥1 TEAE— n (%)	11 (91.7%)
TEAE related to study drug – n (%)	7 (58.3%)
Treatment-emergent serious adverse events – n (%)	0 (0%)
Drug interrupted owing to TEAE — n (%)	2 (16.7%)
Dose reduced owing to TEAE — n (%)	1 (8.3%)
Drug discontinued owing to TEAE — n (%)	0 (0%)

**N=8 with data through 24 weeks; For remaining 4, all available safety data as of March 5, 2024 used

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Summary of Interim Clinical Evidence: Potential of AMX0035 in Wolfram Syndrome

	Expected Progression of Wolfram syndrome	HELIOS Trend*
C-Peptide AUC	↓ Progressive Decline	↑ Partial Reversal in C-Peptide Phenotype
Δ C-Peptide	↓ Progressive Decline	↑ Increase in Beta Cell Responsiveness
HbA1c	Progressively More Difficult to Remain Stable	↓ Improved Glycemic Control
Time in Target Glucose Range	↓ Progressive Decline	↑ Improved Glycemic Control
Visual Acuity	↓ Progressive Decline	↑ Improved Acuity
CGI-C and PGI-C	↓ Progressive Decline	↑ Participant and Clinician Reported Improvement

Diabetic Measures

Visual Measure

Symptom Burden

*Baseline to Week 24 in N=8 participants

Data on File. Amylyx Pharmaceuticals Inc. 2024.

Thank you!

HELIOS

We extend our deepest gratitude to the HELIOS trial participants, their loved ones, Dr. Fumi Urano, the Washington University site team, and the entire Wolfram Syndrome community for their support of this trial.

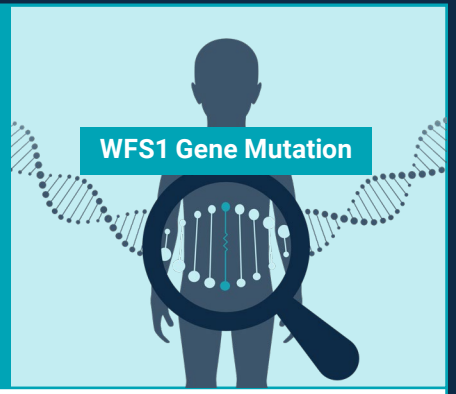
Members of the Wolfram syndrome community

Closing Remarks

Josh Cohen and Justin Klee
Co-CEOs, Amylyx

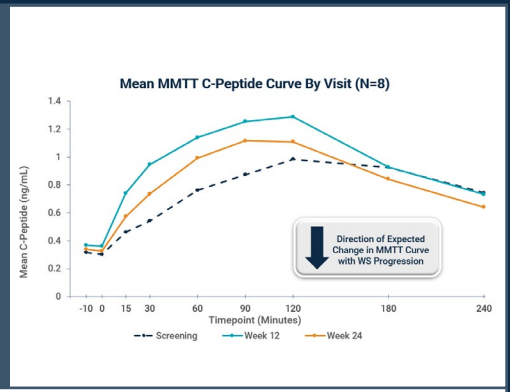
Key Takeaways

Strong Scientific Rationale



- Wolfram syndrome is a progressive, genetic disease caused by mutations in *WFS1* that cause endoplasmic reticulum (ER) stress and impaired mitochondrial dynamics
- AMX0035 has been shown to simultaneously mitigate ER stress and mitochondrial dysfunction
- Preclinical data have demonstrated the efficacy of AMX0035 in cell lines, patient-derived cells, and mouse models

Compelling Data Support AMX0035's Potential in Wolfram Syndrome



- Interim analysis demonstrated improvement in pancreatic function and glycemic control, as measured by C-peptide and other markers of glucose metabolism, rather than worsening typically expected with disease progression
- All participants met prespecified responder criteria demonstrating either improvement or stabilization of disease according to both patient- and clinician-reported scales
- Majority of participants reported some improvement in vision
- AMX0035 was generally well-tolerated in all participants

Urgent Unmet Need

- There are currently no disease-modifying therapies for Wolfram syndrome; treatment strategies focus on symptom management
- Wolfram syndrome impacts ~3,000 people in the U.S. and results in premature death

AMX0035 Wolfram Syndrome Program Next Steps

Orphan drug designation granted to AMX0035 for the treatment of Wolfram syndrome by U.S. FDA

Phase 2 HELIOS study of AMX0035 in Wolfram syndrome initiated in April 2023 and completed enrollment in Feb 2024

Continue to progress the Phase 2 HELIOS study and evaluate options for future development

Planning to engage with regulatory authorities to align on the development path

Topline data for all 12 participants at Week 24 are expected in the second half of 2024

Members of the Wolfram syndrome community