Lunch

The meeting will resume at 1:35 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Collecting Fit for Purpose Data to Inform Regulatory Decision Making

Presenters

Jennifer Farmer, MS
Friedreich's Ataxia Research Alliance

Collin Hovinga, PharmD, MS, FCCP
Critical Path Institute

Reactor Panel

Benjamin Forred, MBA, ACRP-CP, Sanford Research
Donna Rivera, PharmD, MSc, Oncology Center of Excellence, FDA
Kimberly Smith, MD, MS, Center for Drug Evaluation and research, FDA
Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH

REAGAN-UDALL FOUNDATION FOR THE FDA

CRITICAL PATH INSTITUTE

RARE AND ORPHAN DISEASE PROGRAMS

Collecting Fit for Purpose Data to Inform Regulatory Decision Making

Collin Hovinga, PharmD, MS, FCCP

VP Rare and Orphan Diseases

Building a rare disease community that works. Together.

c-path.org

5-13-2024

Practical Considerations

- Non-interventional/observational studies or registries to understand the clinical course of a rare disease
- Capture of real world data longitudinally with an intended regulatory use
- Data sharing considerations
- Examples (trial simulation, disease staging)

Fit for Use Data Considerations

Reliable

Represents the intended underlying medical concepts and thus are considered trustworthy and credible

Relevant

Represents the population of interest and can answer the research question in the clinical context of interest

First Step-Preparation Work

- Begin with the end in mind
- Gather input and landscape what has been done
  - Get input from persons with lived experience, clinicians
  - Literature review
  - Define the unmet need, avoid duplication
- How are you going to collect the data and from whom?
- Refine data collection strategy to sufficiently address your questions but not overly burdensome
- Use global unique identifiers to account for participation in multiple research efforts

Protocol Elements

Population*	• Inclusion/exclusion criteria • Demographics • Concurrent treatments	• Consider all comers vs subpopulations • Presymptomatic vs symptomatic
Disease-related*	• Signs and symptoms and severity • Age at onset/diagnosis • Family history • Genotype • Biomarkers	• Identify areas of interest in multiorgan impacted disease (brain vs liver?)
Outcome assessments	• Clinician/observer reported outcomes • Patient reported outcomes • Measurement scales • Assessments/tests (MRI, FVC, labs) • Interviews/free text diaries	• Exploratory, clinical vs regulatory grade • Qualitative • Describe measurement methods and how the test was performed

* Variables that could be covariates or be used to enrich the study population or usefully for matching criteria (external controls)

Protocol Elements

General methods	• Who/where/how/data collected? • Duration of study overall and for the subject • Schedule of events • Number of sites • Total N	• Clear, standards, definitions and measurement methods • Consider forms with structured data elements
Analysis Plan	• Statistical methods will be based upon your questions • Inter/intra-rater reliability for assessments • Plan for analyzing with missing data or subjects lost to follow up	• Consider sources of bias • Interim analysis plans may help identify high sources of variability • Are raw measurements being collected vs algorithm derived data?
Quality	• Audit plan and documentation/trail • Quality checks and correction • Data access and reproducibility • Amendments-continued relevance and updates	• Documentation of amendments and justification • Can the data be readily reproduced? • Includes security • Protections

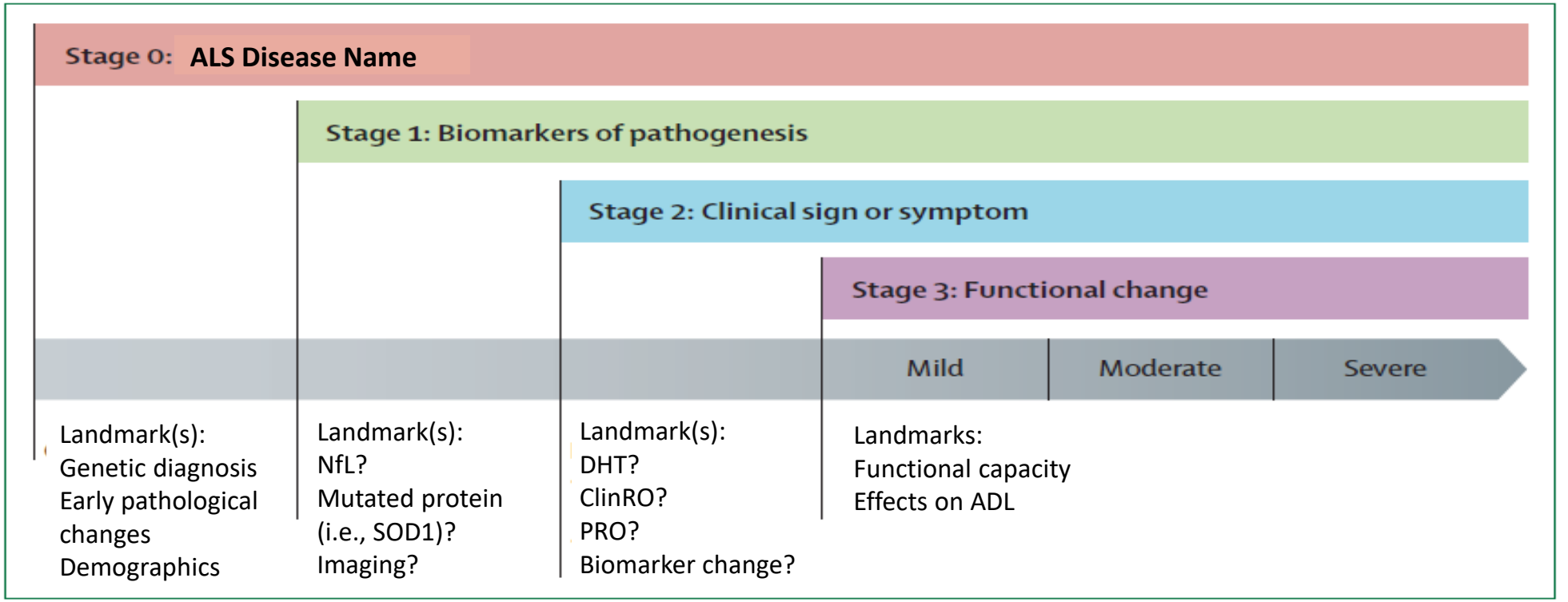
Clinical Outcome Assessments

- Priorities in natural history studies should consider those that have been associated with measuring clinical benefit (improvement in how a patient feels, functions or survives)
- Should be meaningful to the patient
- Example: May not provide a clinically meaningful information
  - Clinician reporting exam changes of decreased vibratory sense
  - Changes may suggest a change in the disease status but do not reflect any impact on patient symptoms or daily functioning

- Example: Does provide clinically meaningful information
  - Numbness in hands that interferes with the ability to button clothes
  - Weakness in hands that interferes with ability to hold spoon and eat

- Make sure that the COA has support for its use in your rare disease population (unless that's planned)
- Methods to collect and assure reproducibility should be described

Framework for Biology-Driven Disease Staging



Each data field should have descriptions and information (meta data) about how and when it is collected.

Abbreviations:
NfL = neurofilament light chain
DHT = digital health technology
ClinRO = clinician reported outcome
PRO = patient reported outcome
ADL = activities of daily living

Modified from Ref.: Sarah J. Tabrizi…HD-RSC et al., *Lancet Neurol.* July 2022 PMID: 35716693

Clinical Trial Simulation Tool

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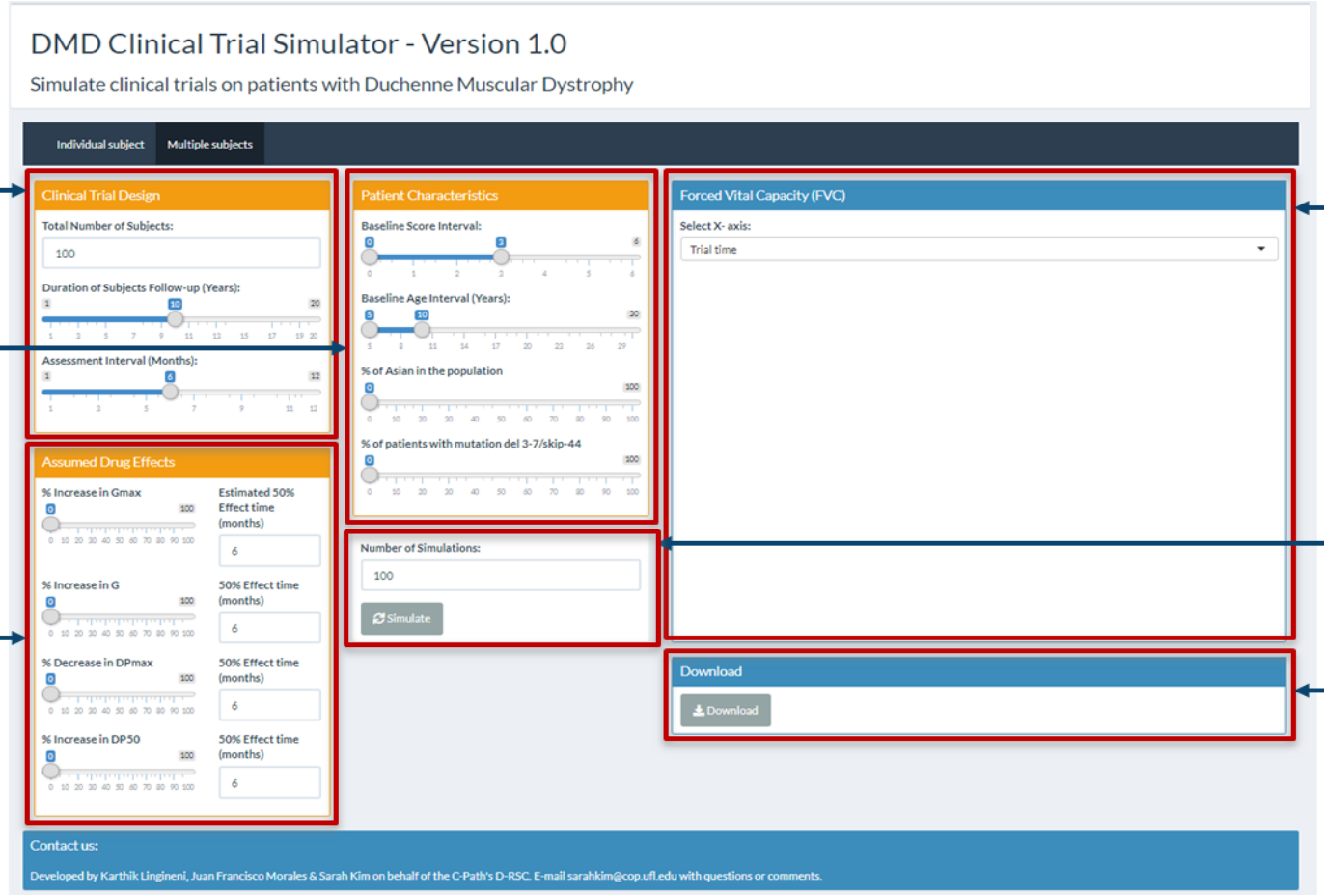
Trial design parameters:
- Study duration
- Assessment frequency

Baseline Patient features:
- FVC
- Age
- Race
- del 3-7/skip-44 mutation

Assumed drug effects:
- % changes to model parameters to mimic drug effects
- Adjustable times to effect



Plotting window by user chosen time metric:
- Plots by age groups
- Plots by time in study
- Provides mouse-over quantitative values

Number of trials to simulate

Simulation output export feature:
- Export virtual patient data
- Export plots
- Export power estimates

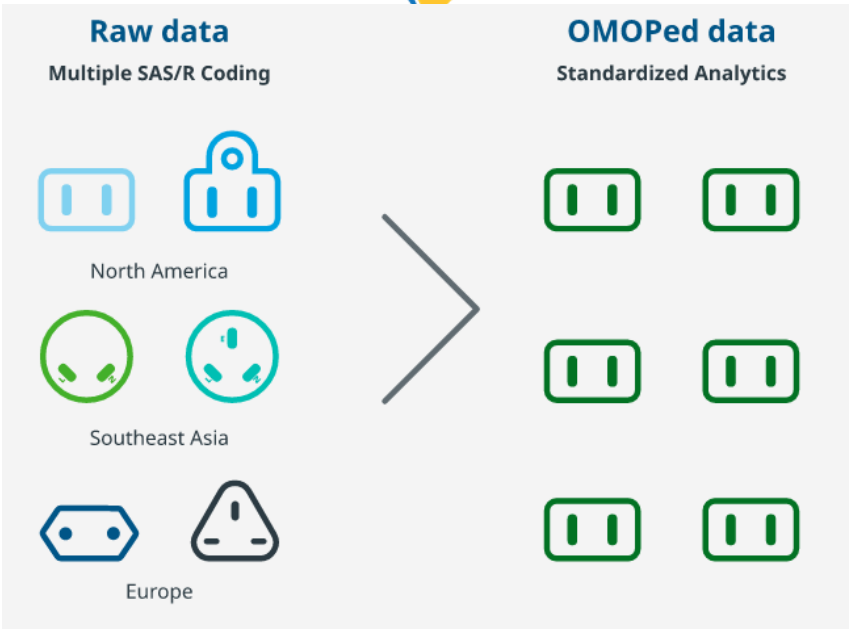
A Model-based Clinical Trial Simulation Tool to Optimize Clinical Trial Design of Studies to Investigate Efficacy of Potential Therapies for Duchenne Muscular Dystrophy Briefing Document submitted to the FDA's Fit-for-Purpose Initiative Consultation and Advice pathway. Revisions submitted to FDA/EMA

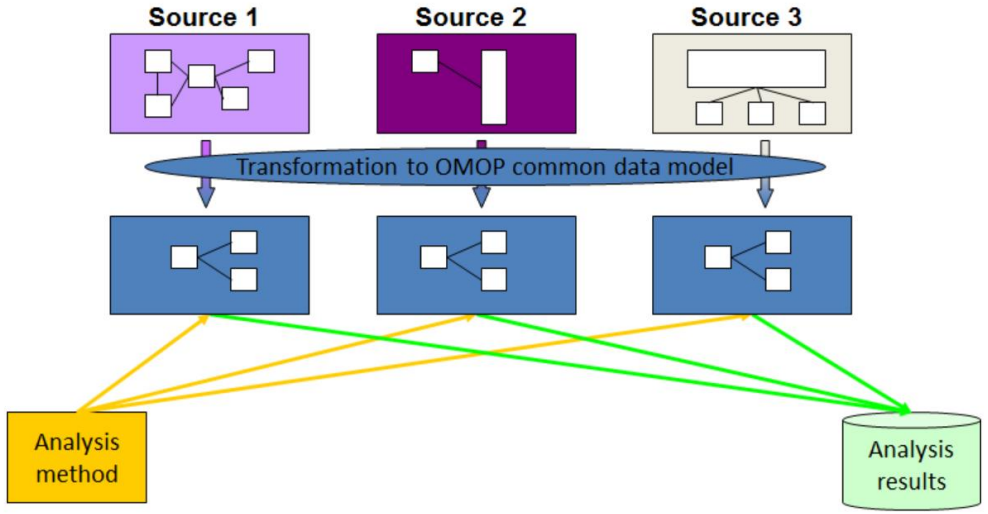
Data Standard Considerations

- Data dictionary (meta data) describing database/tables, variable definitions and standards should be outlined prior to collection of data is essential

- Data can be further standardized to a common data model to depending on the intended audience and use case

- Common data models (including terms, format and vocabularies) allow for data from different sources to be combined more reproducibly
  - SDTM-CDISC
  - OMOP





Sharing of Data IRB-Considerations “Anonymized” vs. “De-identified” Data

- **Anonymized**: Identifiers are removed from patient data, and ***no code exists*** to link patient identifiers to patient data
- **De-identified**: Direct identifiers are removed from patient data, but ***a link exists*** between coded data and identifiers
  - ***Coded link not shared***: *Individuals associated with the creation of the data maintain a link, but the link is not shared with investigators using the data for research.*
  - **Coded link shared**: The link is shared with investigators using the Study/Registry data for research.

Example Consent Form Language for Data Sharing

- *"To ensure that your information collected for this Natural History/Registry will be kept private, your name or other information that could be used to identify you will not be used whenever possible. A code will be used to identify your information, and the key linking the code to information that could be used to identify you will not be shared, except with others as needed to manage the Registry."*

- *"Identifiers will be removed from your identifiable private information or identifiable biospecimens collected for this Study/Registry and then your information/biospecimens will be used for future research studies or distributed to other investigators for future research studies without additional informed consent."*

THANK YOU!

Questions?

Building a rare disease community that works. Together.

c-path.org

Case Example:
Nulibry for molybdenum cofactor deficiency

Presenters

Ronen Spiegel, MD
Emek Medical Center

Liza Squires, MD
Sentynl Therapeutics

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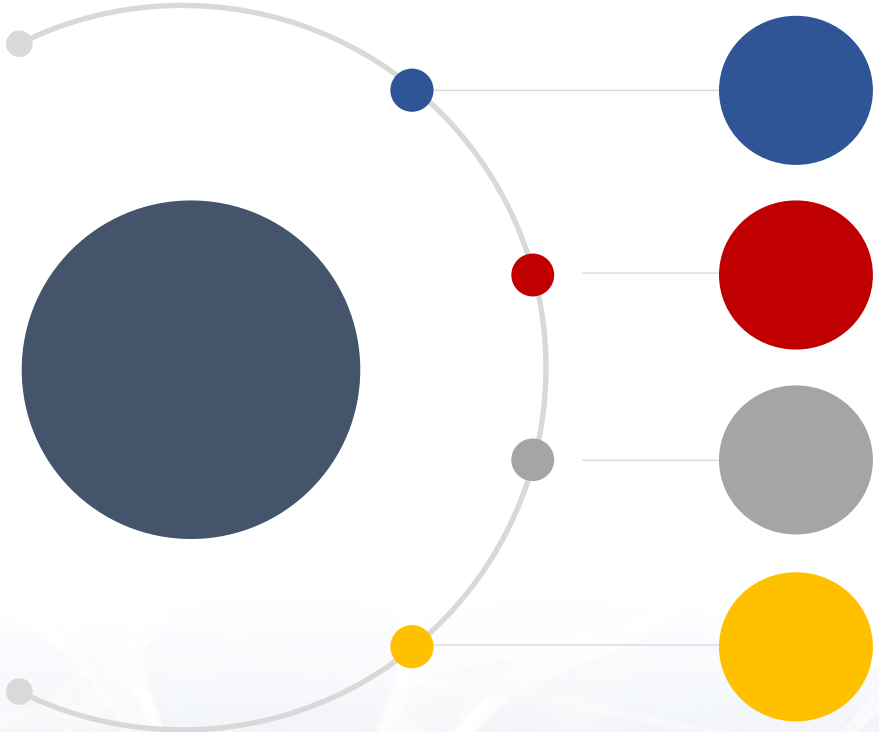
REAGAN-UDALL FOUNDATION FOR THE FDA

Collecting Fit-for-Purpose Data to support Regulatory Decision Making

Reagan Udall, May 2024

Jen Farmer, CEO, Friedreich's Ataxia Research Alliance (FARA)

Disclosures



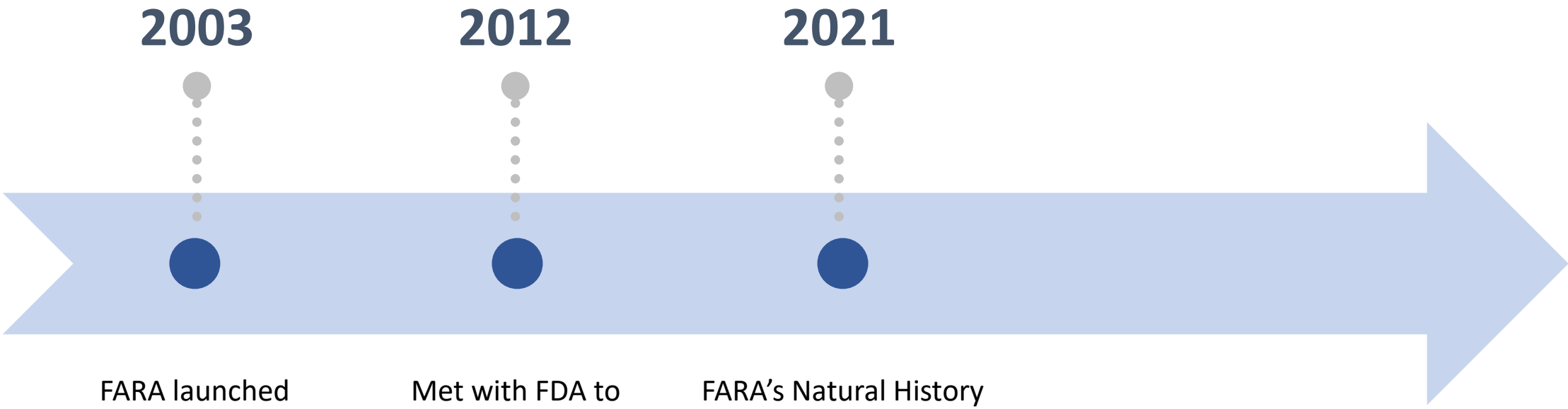
FA-COMS is primarily funded by community fundraising events

FDA funded a 3-year FA-CHILD pediatric study

Industry sponsorships do not directly fund the FA-COMS study

FARA has no additional disclosures to report

FARA's Natural History study began 20+ years ago



How FA-COMS began:

COAs for FA

MDA Muscular Dystrophy Association & FARA Friedreich's Ataxia Research Alliance

2003: Co-funded grant

- *Original to FA*
  FARS, ADL, staging scale
- *Borrowed measures from MS*
  9HPT, T25FW, PATA, Low Contrast Letter Acuity, MSQLI

Natural History Visits Begin

2006 : FARA commits to funding the natural history study and network

NOTE: Not designed to be a control arm for trials

Goal 1

Systemic Data Collection

Understand natural history of FA through systemic collection of clinical data

Goal 2

Disease Measures

Develop outcome measures and inform clinical trial design

Goal 3

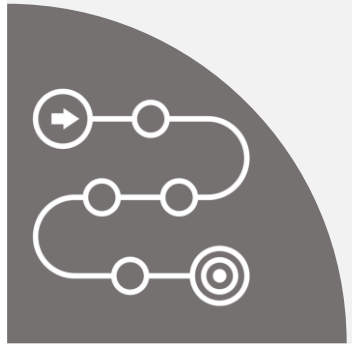
Clinical Network

Create a network of clinical research centers in FA that will provide quantitative clinical data on patients.

FA-COMS Study Design

Inclusion

Genetically confirmed FA
All ages and stages
Representative population



Prospective, Longitudinal

Intentionally forward-looking
Long-term commitment commensurate with the rate of disease progression

Annual Visits

Nearly all in-person visits (except some from 2020-2022 due to COVID)

Consistency

Treated it as a non-interventional trial – same protocol, visit schedules, sops/standardized procedures, data collection across all sites

Quality of the Data

NIH NINDS

Common data elements

Peer-reviewed publications share longitudinal data with the FA research community

Multicenter Study > Diabetes Res Clin Pract. 2022 Apr;186:109828.
doi: 10.1016/j.diabres.2022.109828. Epub 2022 Mar 14.

Friedreich's Ataxia related Diabetes: Epider and management practices

Jaclyn Tamaroff [1], Anna DeDi
Karla Leavens [4], Christian Ru

> J Neuroophthalmol. 2020 Jun;40(2):213-217. doi: 10.1097/WNO.0000000000000878.

Correlation of Visual Quality of Life With Clinical and Visual Status in Friedreich Ataxia

Parisa Afsharian [1], Rachel Nolan-Kenney, Abigail E Lynch, Laura J Balcer, David R Lynch

Observational Study > Ann Clin Transl Neurol. 2021 Ju
doi: 10.1002/acn3.51352. Epub 2021 May 5.

Scoliosis in Friedreich's ataxia: characterization in a large heter

Christian Rummey [1], John M Flynn [2],
George Wilmot [5], Sub H Subramony [6]

> Ann Clin Transl Neurol. 2020 Sep;7(9):1708-1712. doi: 10.1002/acn3.51118. Epub 2020 Aug 11.

Test–retest reliability of the F rating scale

> Neurol Genet. 2019 Oct 29;5(6):371. doi: 10.1212/NXG.0000000000000371.
eCollection 2019 Dec.

Psychometric properties of the Friedreich A Rating Scale

Christian Rummey [1], Louise A Corben [1], Martin B Delatycki [1], S H Subramony [1],
Khalaf Bushara [1], Christopher M Gomez [1], Joseph Chad Hoyle [1], Grace Yoon [1], Bernard R
Katherine D Mathews [1], George Wilmot [1], Theresa Zesiewicz [1], Susan Perlman [1],
Jennifer M Farmer [1], David R Lynch [1]

> EClinicalMedicine. 2020 Jan 8;18:100213. doi: 10.1016/j.eclinm.2019.1
eCollection 2020 Jan.

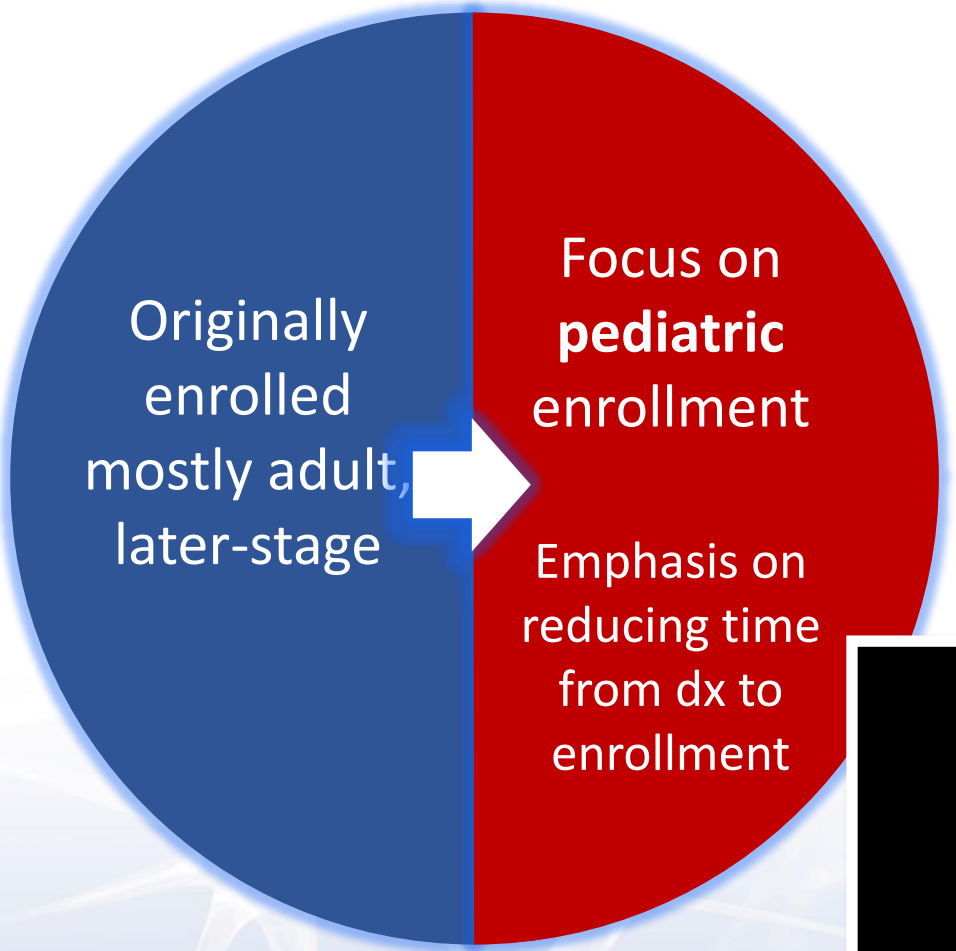
Predictors of loss of ambulation in Frie

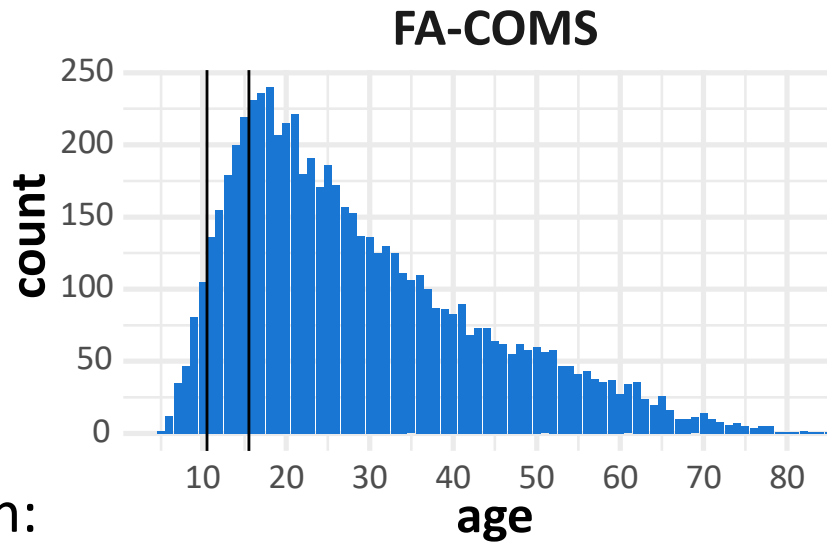
Christian Rummey [1], Jennifer M Farmer [2], David R Lynch [3]

>30 articles published based on the study's data

FARA Friedreich's Ataxia Research Alliance

Data Evolution : Population





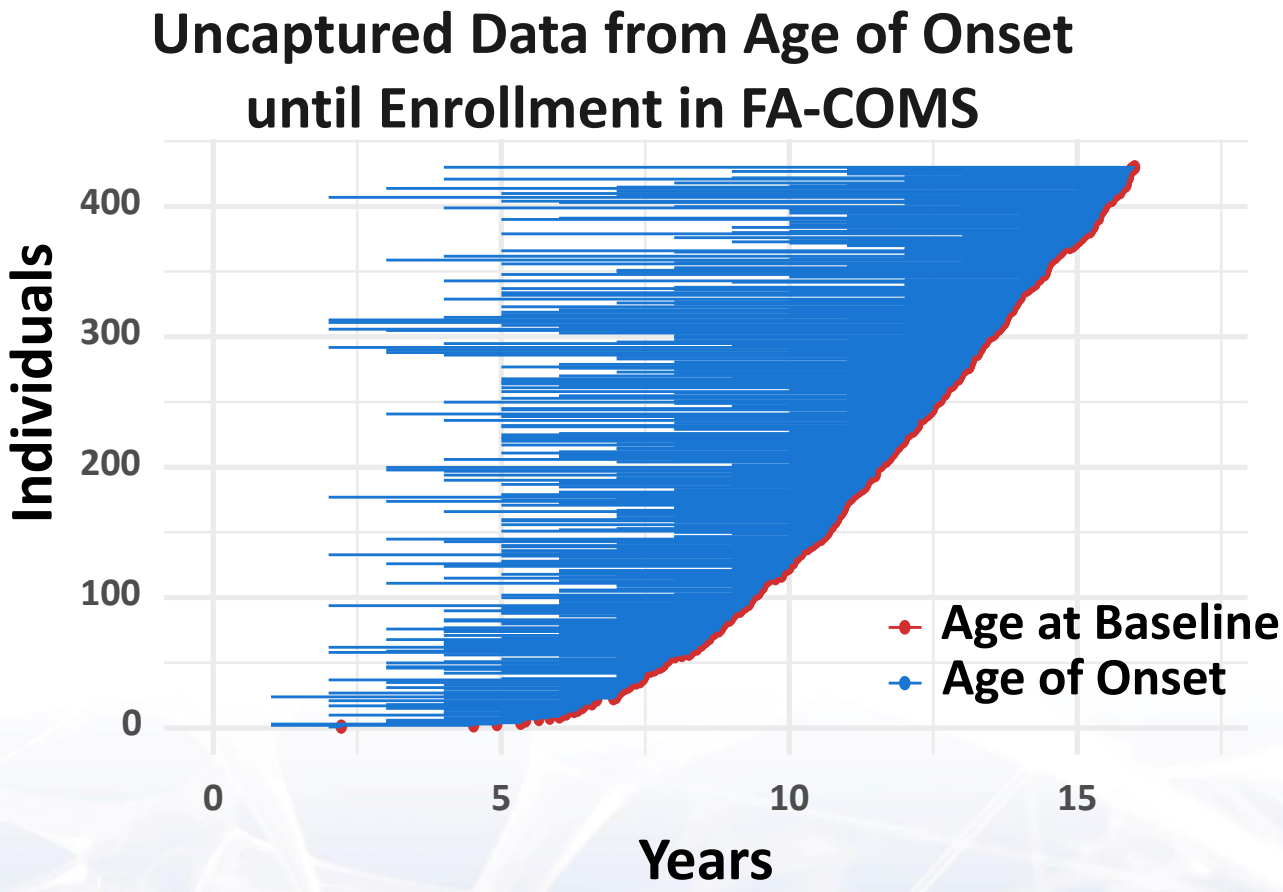
Achieved this shift through:

- Patient community outreach and education
- Added sites with pediatric neurologist PIs
- Additional funding – FDA/NIH grant

Goal:
An enrolled population representative of FA across all stages, genotypes and phenotypes

FARA Friedreich's Ataxia Research Alliance

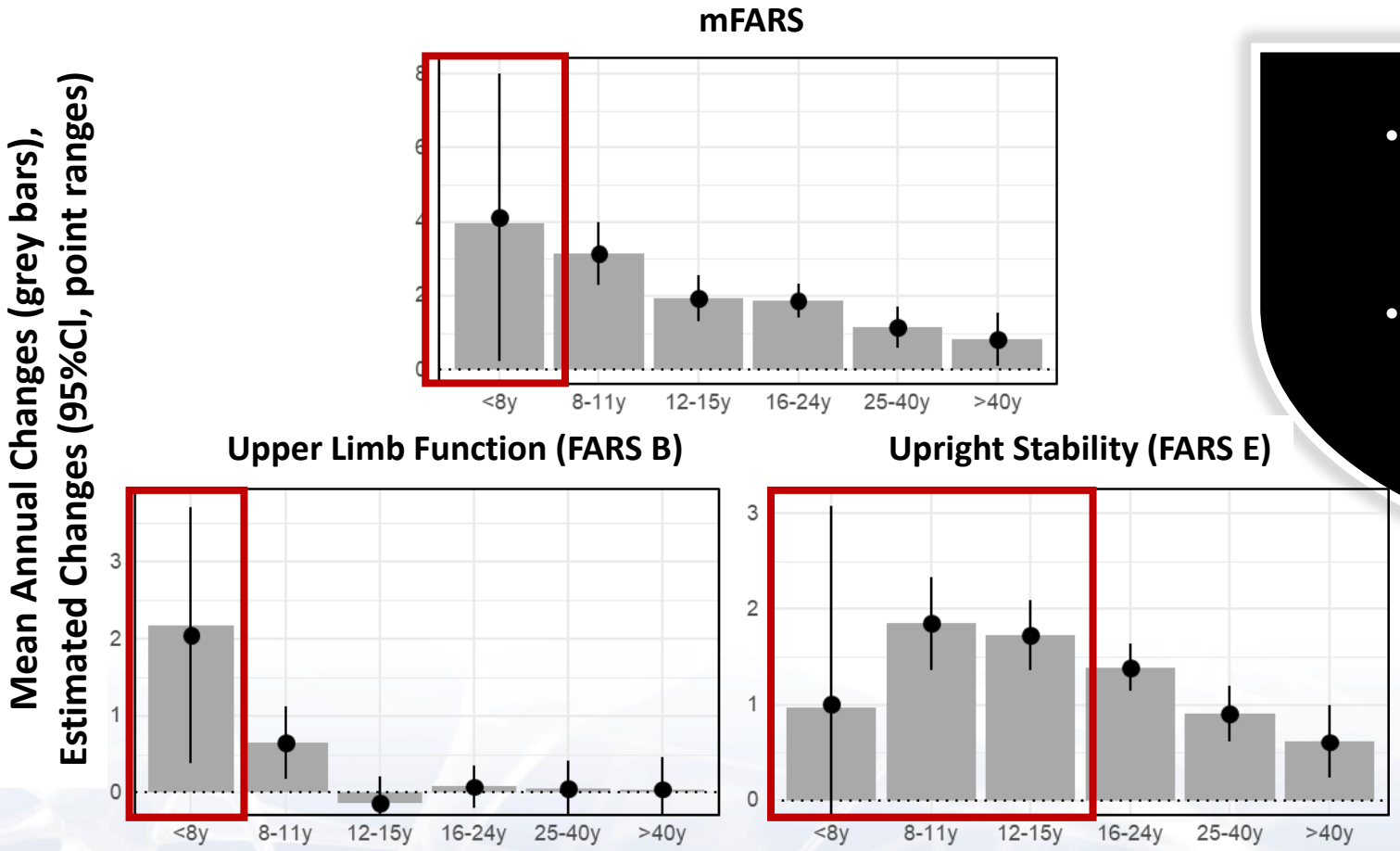
Data Evolution : Assessments



FA primarily begins in childhood

Goal: Capture data beginning at symptom onset

Data Evolution : Reducing variability and increasing consistency with our youngest children



- Variability in mFARS <8 yo
  - Working on more reliable measurements
- Change in Upright Stability reveals milestones gained from birth to 11yo and the tragedy of losing function after 11yo.

Rummey C, et al, Neurology 2022;99:e1499-e1510.

Consistency and Comparability

Duration

Study initiated in 2003 and still ongoing today with strong participant retention

Assessments

The natural history study uses the same assessments as clinical trials

Investigators

Same sites/investigators are conducting both the history study and clinical trials

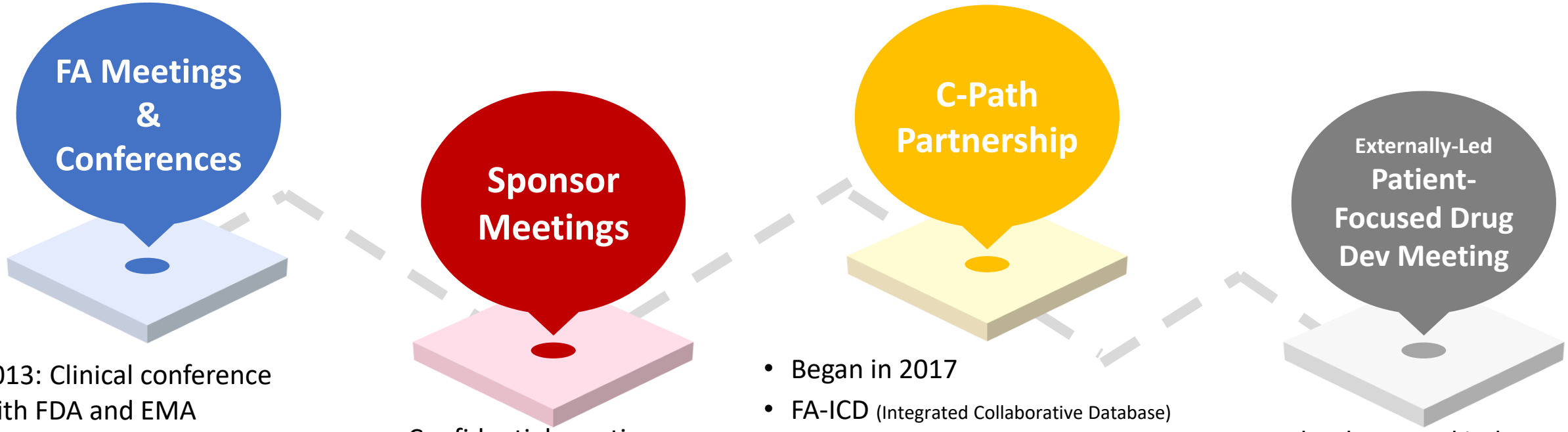
Contemporary Data

Collection of the natural history dataset is contemporary to clinical trials

Collecting Fit-for-Purpose Data **to support Regulatory Decision Making**

FARA Friedreich's Ataxia Research Alliance

Regulatory Engagement



2013: Clinical conference with FDA and EMA

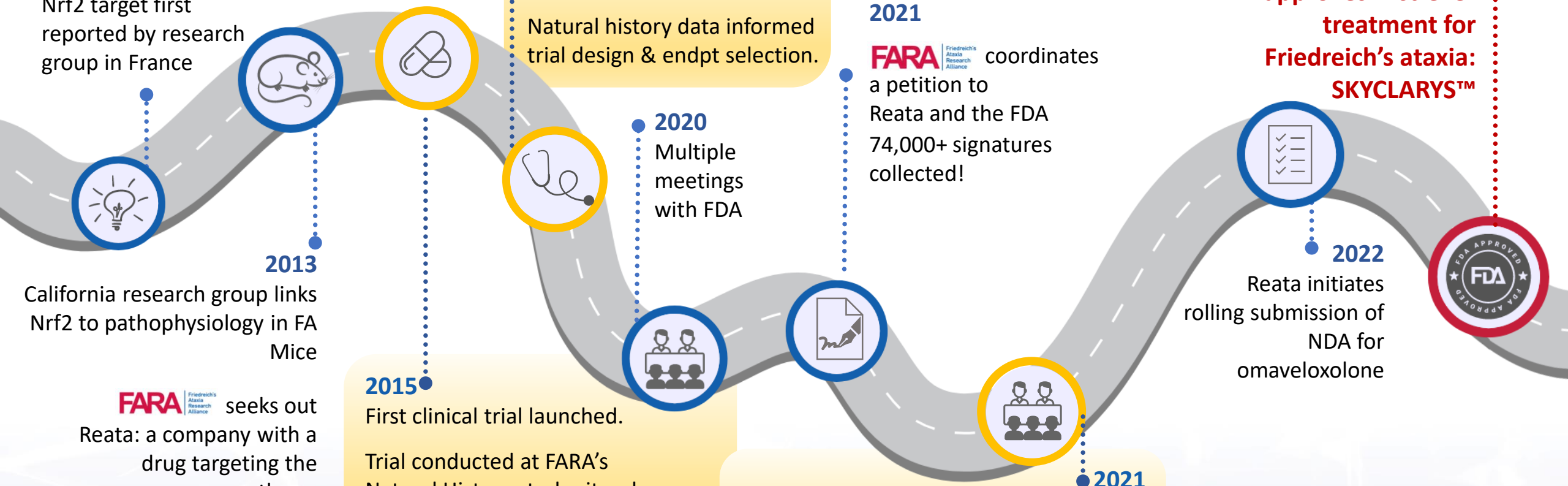
- Presented first 10 years of data
- Informal feedback
- Beginning of evolution from FARS to mFARS

- Confidential meetings
- FARA attends as a guest of our industry partner
- Opportunity to discuss how natural history data informs trial design and endpoints

- Began in 2017
- FA-ICD (Integrated Collaborative Database)
  - Includes FA-COMS & trial data
  - Available to industry sponsors, FDA, and RDCA-DAP
  - Data in CDISC STDM standard

- Helped FDA and industry partners understand the lived experience of FA
- Communicated outcomes that are valued by the community

The Path to the First Approval for Friedreich's Ataxia



2009
Nrf2 target first reported by research group in France

2013
California research group links Nrf2 to pathophysiology in FA Mice

FARA seeks out Reata: a company with a drug targeting the pathway

2015
First clinical trial launched.

Trial conducted at FARA's Natural History study sites, by Natural History study investigators.

2017
Second clinical trial launched.

Natural history data informed trial design & endpt selection.

2020
Multiple meetings with FDA

2021
FARA coordinates a petition to Reata and the FDA
74,000+ signatures collected!

2021
FARA Natural History study provides confirmatory evidence through a propensity-matched study.

2022
Reata initiates rolling submission of NDA for omaveloxolone

2023
FDA approves first-ever treatment for Friedreich's ataxia: SKYCLARYS™

FARA Friedreich's Ataxia Research Alliance

Use of Natural History in Skyclarys Approval

Propensity-Matched Analysis
Comparable Baseline Characteristics

Demographics and baseline characteristics balanced between the two groups

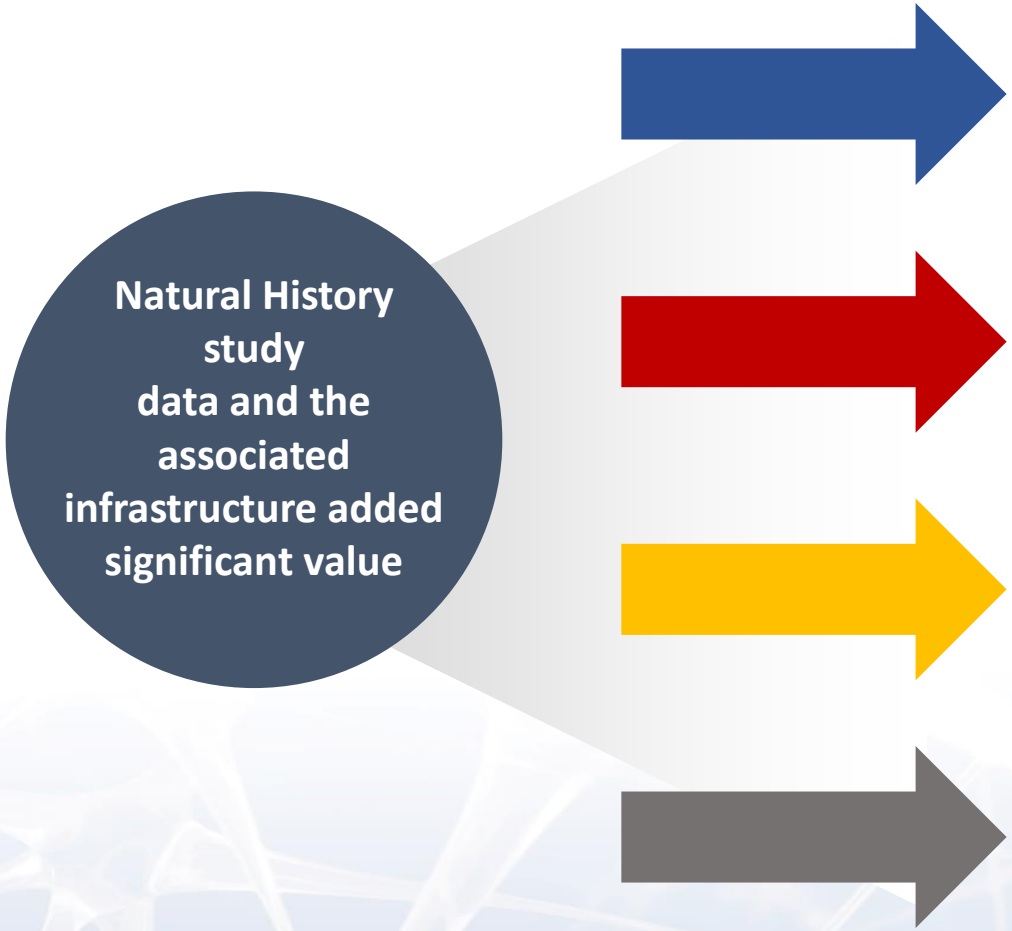
Median treatment/follow-up duration of approximately 3 years

Demographics and Baseline Characteristics for Primary Pooled Population

Characteristic	Statistic	Matched FA-COMS (n=136)	MOXIe Extension (n=136)
Age (years)	Mean (SD)	26.2 (13.72)	26.6 (7.26)
Age at FA Onset	Mean (SD)	15.2 (10.48)	15.5 (5.30)
Sex, Female	N (%)	70 (51.5%)	70 (51.5%)
mFARS	Mean (SD)	41.0 (16.10)	42.2 (12.60)
Gait	Mean (SD)	2.7 (1.69)	2.8 (1.36)

This analysis served as one piece of confirmatory evidence for the NDA submission

FARA's Natural History Study played a pivotal role in the path to the first approval



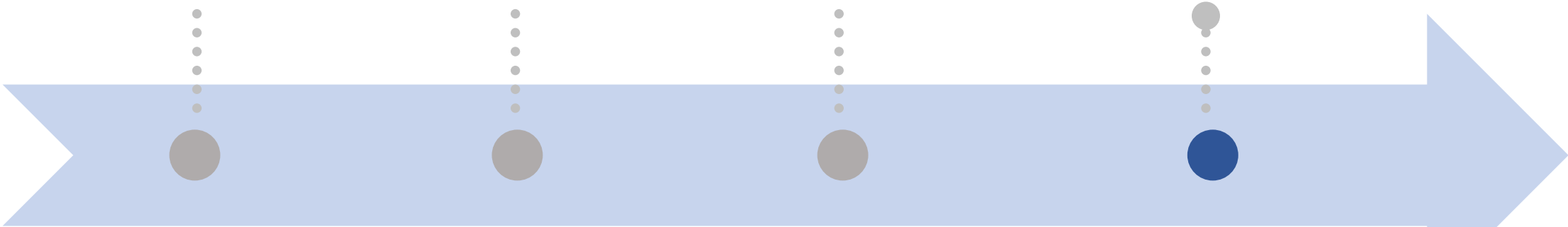
Trial Design: Data from natural history study informed power analysis

Primary Outcome Measure: Regulatory alignment

Data Quality and Consistency: Clinical trial sites were also Natural History Study sites. Study PIs were familiar with the endpoint measurement. Resulted in reduced variability, better confidence in the quality of the data.

Confirmatory evidence: Propensity-matched study was possible because there was a representative cohort enrolled in the natural history study

FARA's Natural History study began 20+ years ago



2003

FARA launches Clinical Outcome Assessments study.

2012

Meeting with FDA to validate endpoints.

2021

FARA's Natural History study provides confirmatory evidence through a propensity-matched study.

Leads to first approval for Friedreich's ataxia.

2024 & beyond

Continued investment.

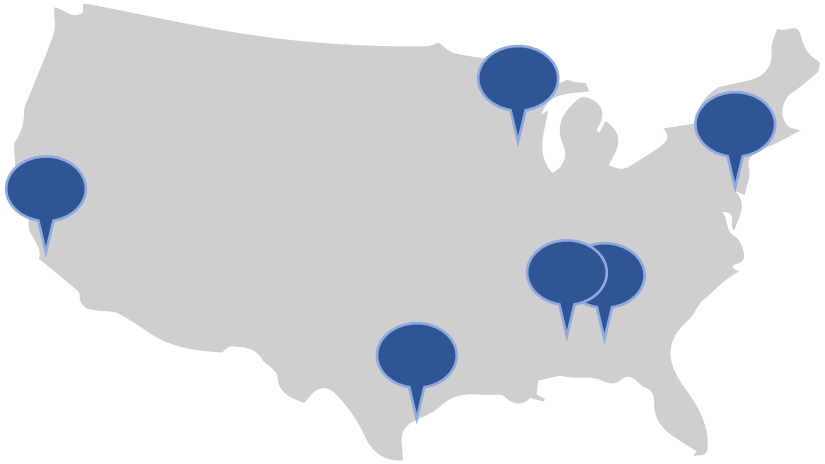
Positioning to support tomorrow's clinical trials.

Keeping the data contemporary.

Developing and validating the next generation of clinical trial endpoints.

Global reach.

Expanding Global Reach



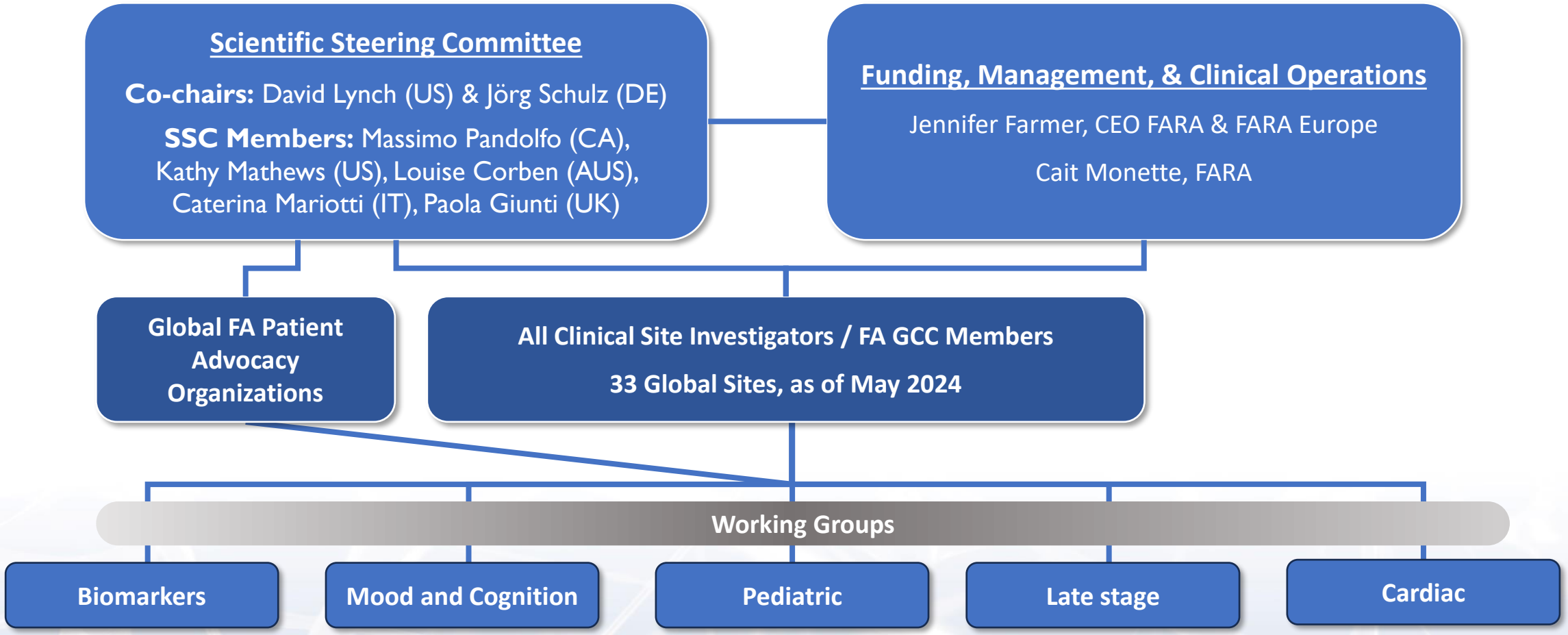
Started with 6 sites across the USA

Grown to 33 sites across 5 continents

Focused on:

- **Adding sites**
- **Funding for travel**
- **Enrolling subjects in multiple studies at the same visits**

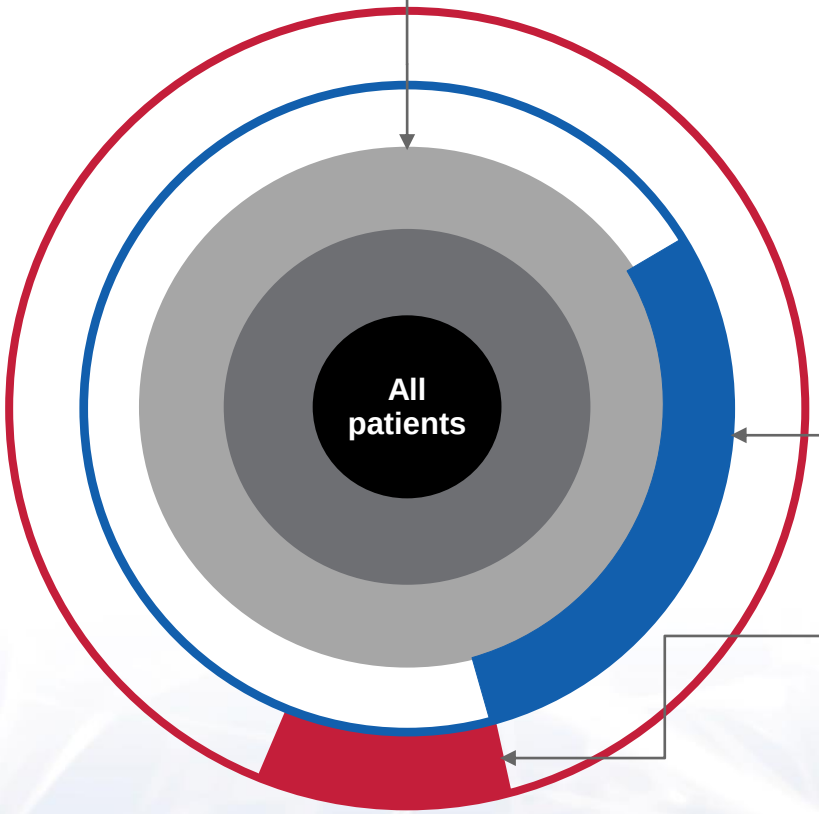
THE FA GCC GLOBAL CLINICAL CONSORTIUM



UNIFAI Study
Natural History Enrollments

Core data elements

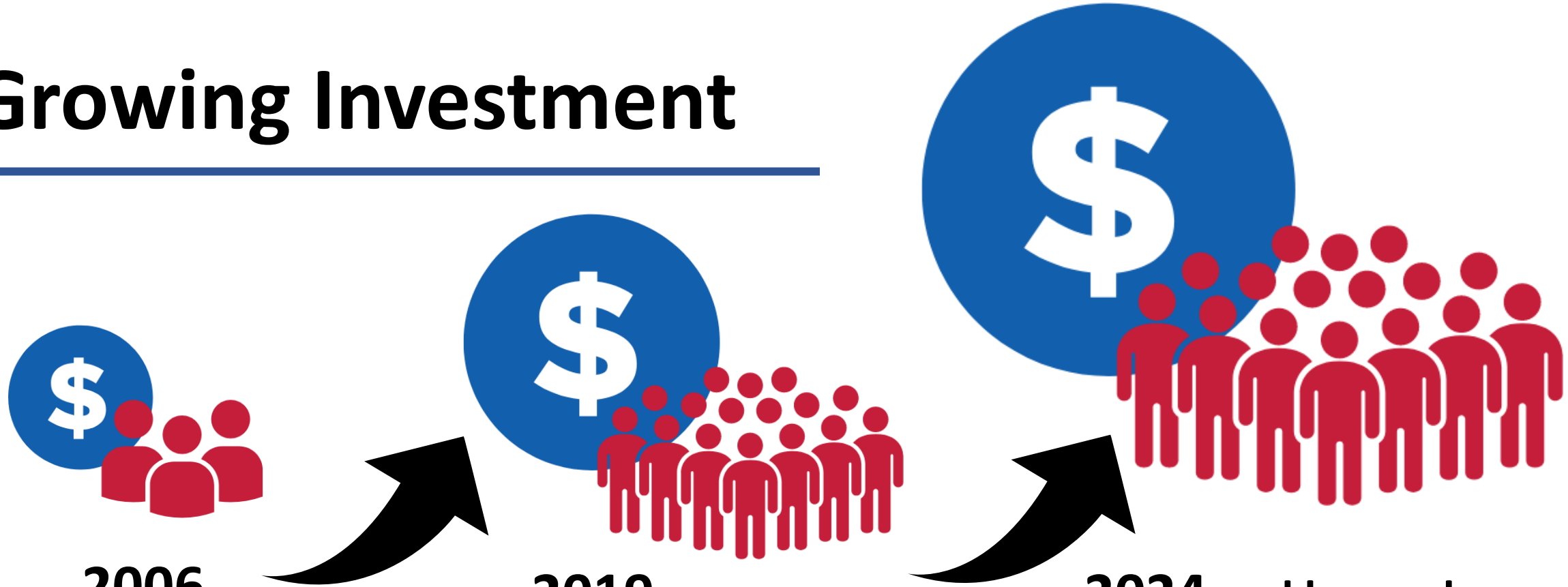
Supplemental tests and surveys



Other FA trials
(Industry and Academic Partnerships)

Other non-interventional studies
(e.g. Biomarker or Pediatric substudies)

Growing Investment



2006

$175,000

150 subjects

6 sites

2019

$1,000,000

>1,000 subjects

14 sites

2024 and beyond

$2,000,000

>3,000 subjects

33 sites

Looking ahead: Expanding and Improving

Capture data that describes the earliest onset of disease

Refine outcome measures for young children

Data collection in late stages of disease, despite the challenges of travel

Study population should be contemporary with the population

Longitudinal data answers basic questions and prompts a new round of deeper inquiries

Thank You!

Acknowledgements:

FA-COMS Site Investigators

Friedreich's Ataxia community

for participating in our natural history study, clinical trials, and for raising funds to enable these efforts

FARA Friedreich's Ataxia Research Alliance

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Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH

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Case Example:
Nulibry for molybdenum cofactor deficiency

Presenters

Ronen Spiegel, MD
Emek Medical Center

Liza Squires, MD
Sentynl Therapeutics

REAGAN-UDALL FOUNDATION FOR THE FDA

Leveraging Natural History Data for Rare Disease Drug Development and Approval:

Demonstrated Increased Survival in MoCD Type A Patients Treated With Fosdenopterin

Ronen Spiegel, MD

Clinical Associate Professor, Director of Pediatric B Department,
and Head of Center for Rare Diseases, Emek Medical Center, Afula, Israel

Liza Squires, MD

Former Chief Medical Officer, Origin Biosciences
Sentynl Therapeutics, Inc.

SENTYNL THERAPEUTICS, INC.

Molybdenum Cofactor Deficiency (MoCD) Type A

- Rare, autosomal-recessive in-born error of metabolism caused by pathogenic variants in the *MOCS1* gene[1,2]
- Rapidly progressive, irreversible neurologic damage due to loss of the MoCo-dependent enzyme sulfite oxidase, resulting in neurotoxic sulfite accumulation[1,3]
- Patients rarely survive beyond the first few years of life[1]
- Early diagnosis is crucial[4]
- Biomarkers[1,4]
  - Decreasing, low, or undetectable plasma or urinary uric acid
  - Increased plasma and urine xanthine/hypoxanthine
  - Increased urinary sulfites
  - Increased SSC in the plasma and urine

Signs and symptoms often present in the first hours to weeks of life[1]

Intractable Seizures

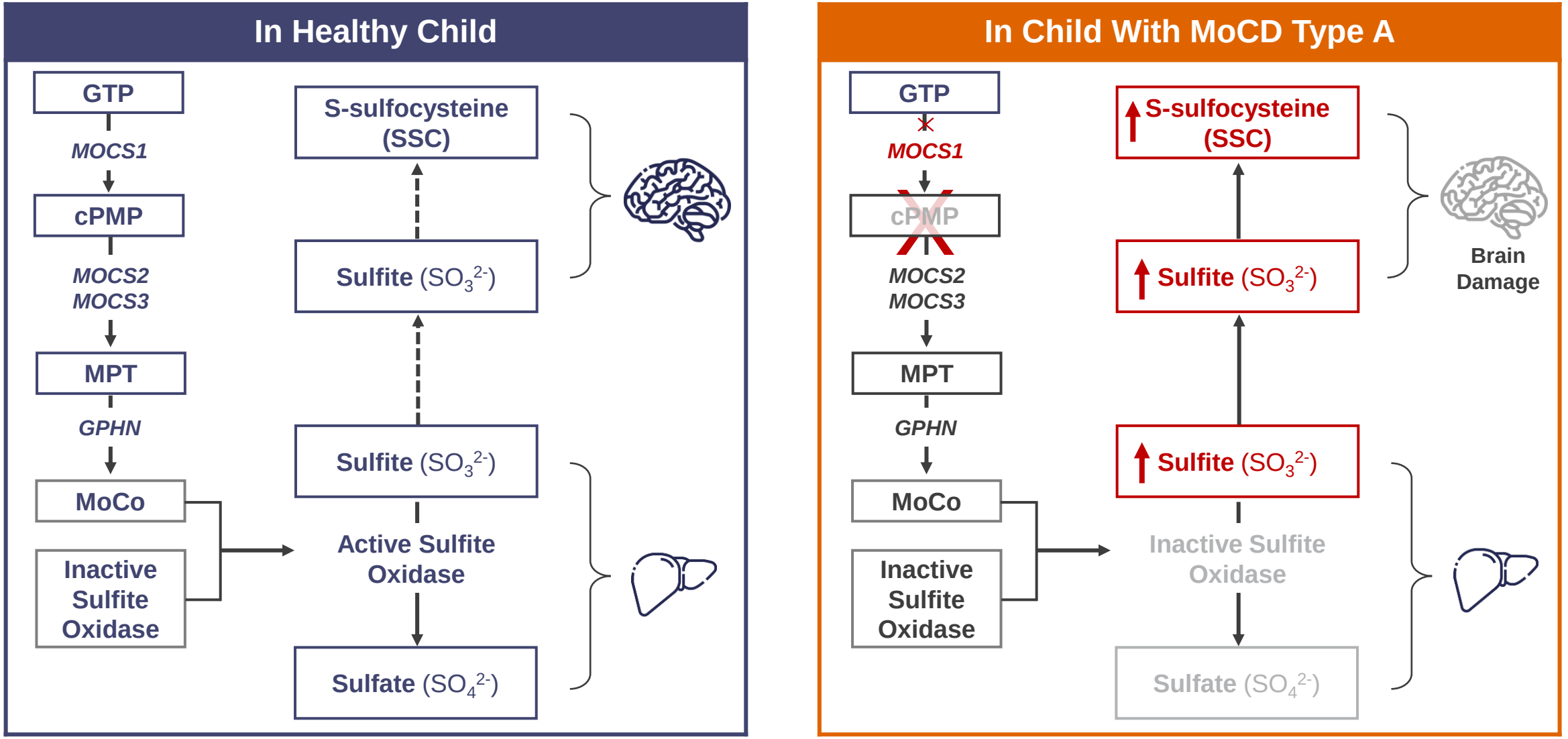
Feeding Difficulties

Abnormal Neuro Examination

MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; *MOCS1*, molybdenum cofactor synthesis 1; SSC, S-sulfocysteine.

1. Atwal PS, et al. *Mol Genet Metab*. 2016;117:1-4; 2. Reiss J, et al. *Hum Mutat*. 2011;32:10-18; 3. Mechler K, et al. *Genet Med*. 2015;17:965-970; 4. Kumar A, et al. *J Clin Invest*. 2017;127:4365-4378

Biochemical Pathology of MoCD[1-3]



cPMP, cyclic pyranopterin monophosphate; *GPHN*, gephyrin; GTP, guanosine triphosphate; MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; *MOCS1/2/3*, molybdenum cofactor synthesis 1/2/3; MPT, molybdopterin.

1. Reiss J, et al. *Hum Mutat*. 2011;32:10-18; 2. Atwal PS, et al. *Mol Genet Metab*. 2016;117:1-4; 3. Kumar A, et al. *J Clin Invest*. 2017;127:4365-4378.

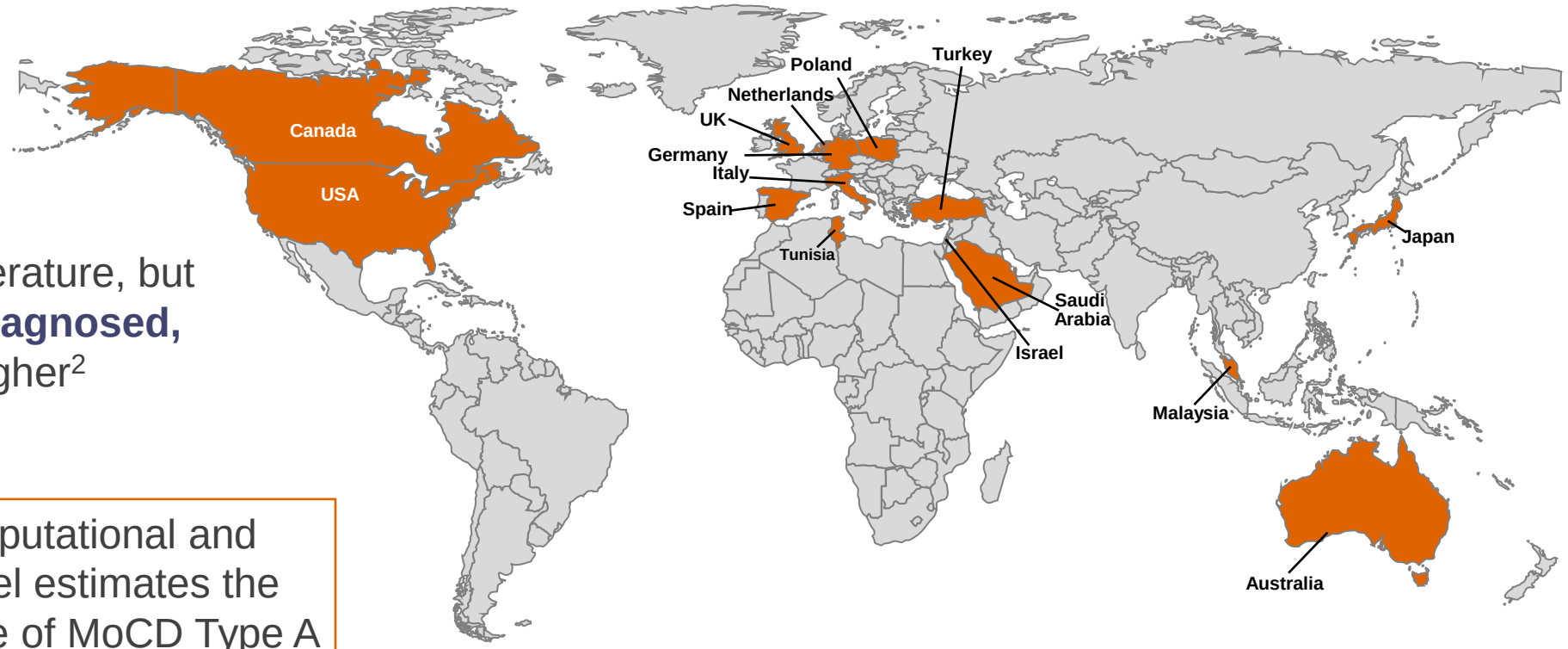
Epidemiology of MoCD: An Ultra-Rare Disease

MoCD Occurs Worldwide, With "Hot Spots" in Multiple Countries[1]

MoCD is an **ultra-rare, pan-ethnic** disease

>100

cases reported in the literature, but **MoCD is likely underdiagnosed,** and numbers may be higher[2]



An iterative computational and biochemical model estimates the worldwide incidence of MoCD Type A is **1:342,000 to 411,000** births[3]

MoCD, molybdenum cofactor deficiency.

1. Spiegel R, et al. A natural history study of molybdenum cofactor and isolated sulfite oxidase deficiencies. Presented at the 2019 SSIEM meeting; September 3-6, 2019; Rotterdam, The Netherlands; 2. NIH. https://ghr.nlm.nih.gov/condition/molybdenum-cofactor-deficiency. Accessed April 25, 2024; 3. Mayr SJ, et al. Forecasting the incidence of rare diseases: an iterative computational and biochemical approach in molybdenum cofactor deficiency type A. Presented at the 2019 SSIEM meeting; September 3-6, 2019; Rotterdam, The Netherlands.

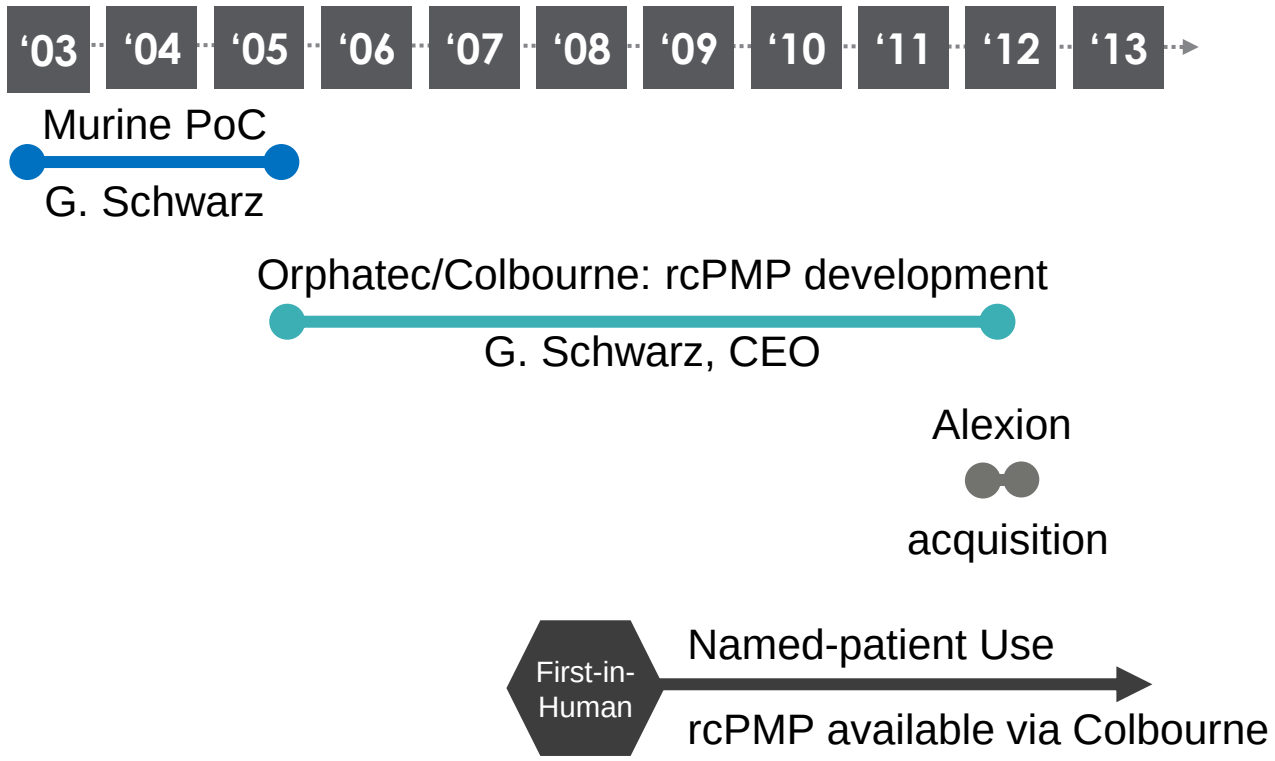
cPMP Replacement Therapy | First-in-Human Experience

- Prof Guenter Schwarz in Cologne, Germany, discovers that **cPMP is produced as a natural chemical byproduct** by *Escherichia coli*
- Selects for **strains of *Escherichia coli*** to manufacture **recombinant form of cPMP**
- Dr Schwarz's lab **tests cPMP in *MOCS1*-knockout mouse model**, showing its potential as replacement therapy
- **First baby is treated** with recombinant cPMP and **shows rapid biochemical response in 2008**
- Colbourne Pharmaceuticals **begins named-patient program** with recombinant cPMP

Dr Guenter Schwarz

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; *MOCS1*, molybdenum cofactor synthesis 1.

First 10 Years of Recombinant cPMP Therapy



- **No approved treatments**; supportive care only
- **No patient advocacy group**
- 10 patients with MoCD Type A **treated with recombinant cPMP** gave consent for retrospective data
- Named-patient use, with **each dose prepared by fermentation** in the lab
- **Unethical to initiate a randomized, placebo-controlled trial** in patients with an ultra-rare and fatal disease

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant cyclic pyranopterin monophosphate.

Natural History Study Design (MCD-502)

Multinational, multicenter, retrospective, and prospective study in patients with MoCD or isolated SOX deficiency

Primary Objective

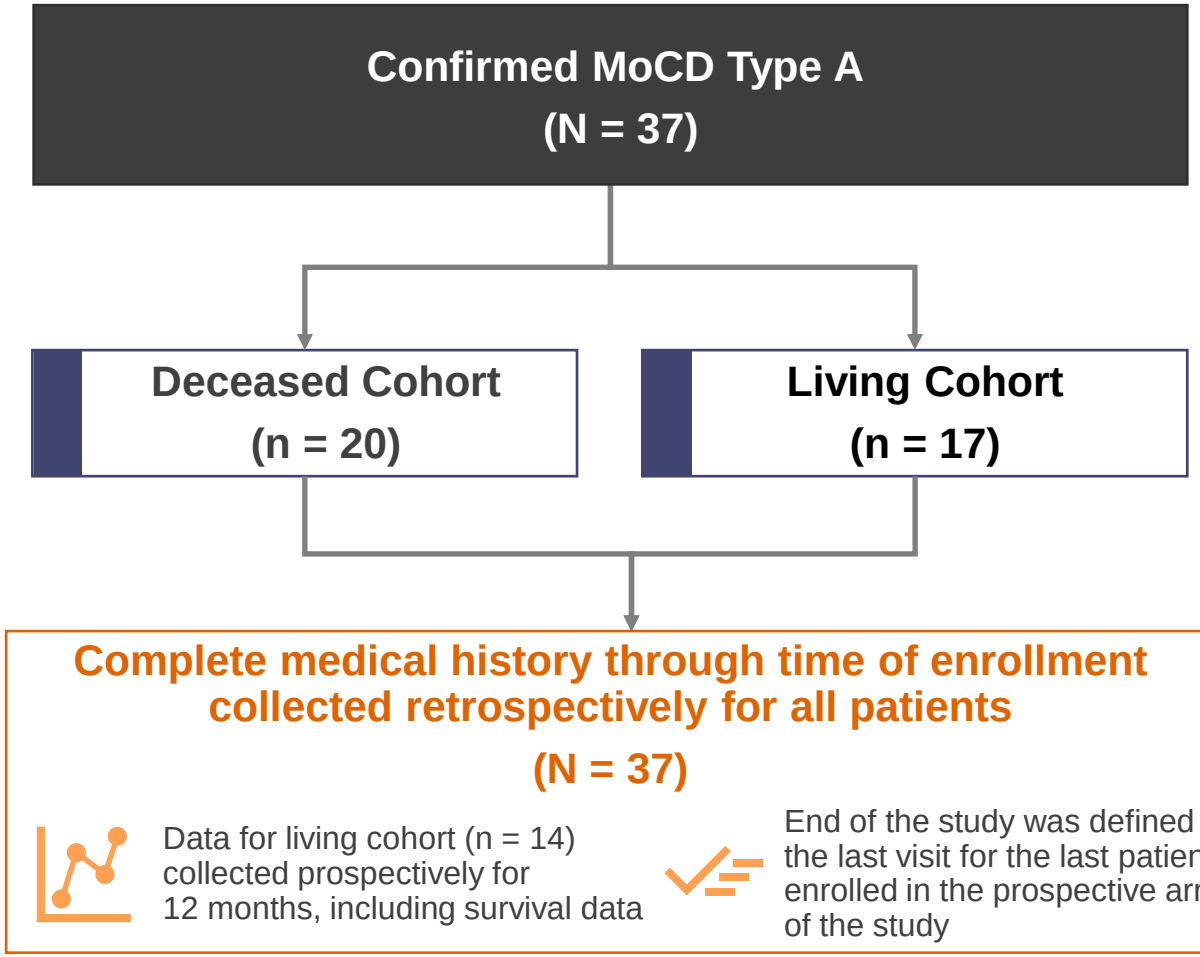
- ✓ To characterize the natural history of patients with MoCD by
  - Documenting the natural progression of the disease
  - Developing a more complete understanding of the phenotype
  - Describing the clinical and biochemical variability of the condition

Inclusion Criteria

- ✓ MoCD or isolated SOX deficiency
  - Clinical and biochemical diagnosis
    - Elevated SSC levels in urine, serum, or plasma
    - Positive urine sulfite dipstick

OR

- ✓ Genetic diagnosis



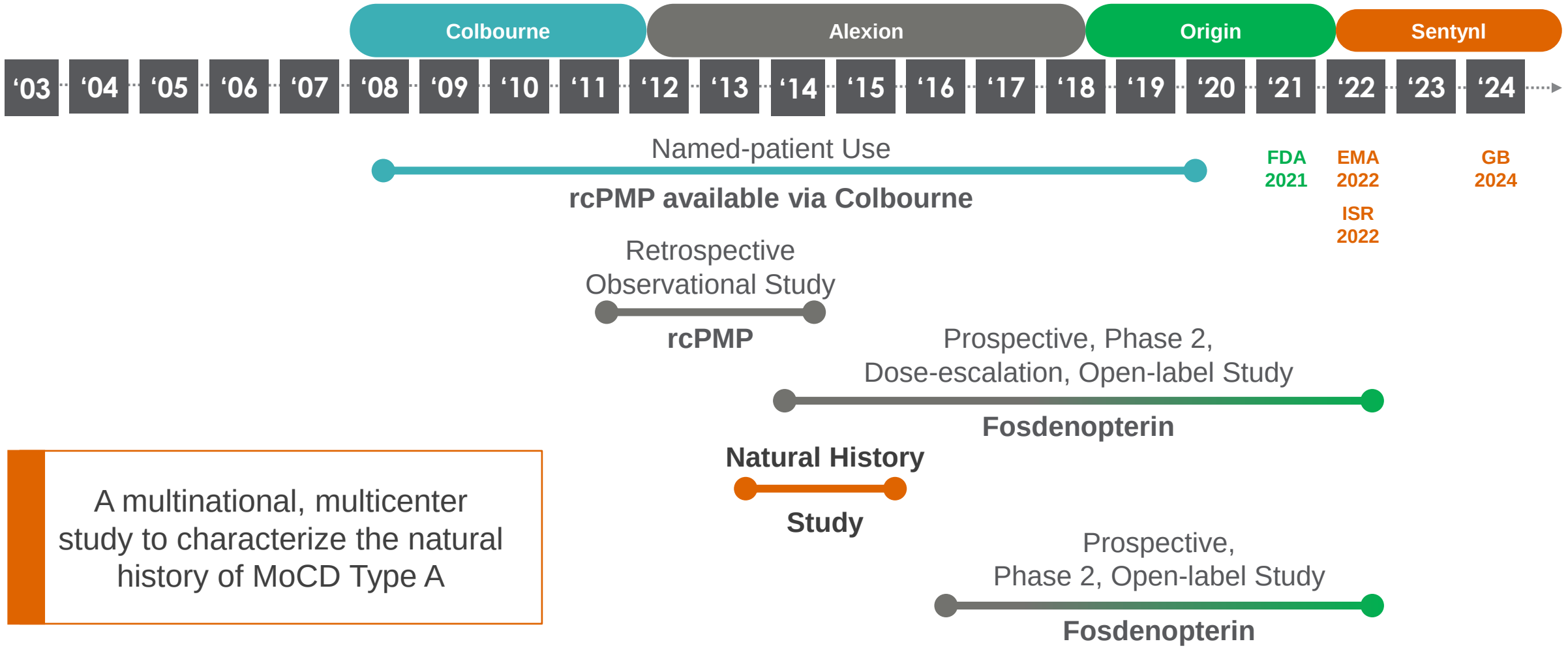
MoCD, molybdenum cofactor deficiency; SOX, sulfite oxidase.

Natural History Data as a Surrogate Placebo Group

SENTYNL THERAPEUTICS, INC.

Developed and approved for use in the US only.

Clinical Development of Fosdenopterin (cPMP)



A multinational, multicenter study to characterize the natural history of MoCD Type A

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant cyclic pyranopterin monophosphate.

cPMP Clinical Development Program: Using Natural History Data

Objectives

- Summarize clinical efficacy of cPMP (inclusive of both recombinant cPMP and fosdenopterin)
  - Retrospective, observational study (MCD-501)
  - Phase 2, open-label, dose-escalation study (MCD-201)
  - Phase 2/3 open-label study (MCD-202)
- Interpret the response to cPMP in patients with MoCD Type A
- Compare the survival rate of children with MoCD Type A treated with cPMP replacement therapy with the survival rate of untreated patients with MoCD Type A from a natural history study

Key Variables Assessed in the Clinical Studies

- Baseline characteristics
- Growth parameters
- Overall survival
- GMFCS-ER
- Biomarkers
- Seizures
- Feeding patterns
- Neurologic examinations
- Developmental assessments

cPMP, cyclic pyranopterin monophosphate; GMFCS, Gross Motor Function Classification System-Expanded and Revised; MoCD, molybdenum cofactor deficiency.

Full Analysis Set

Patients with MoCD Type A treated with cPMP replacement therapy (recombinant cPMP and/or fosdenopterin) from 1 retrospective, observational study and 2 prospective, open-label, single-arm studies (N = 13)

VS

Patients with MoCD Type A who were enrolled in a multinational, multicenter, retrospective/prospective natural history study (N = 37)

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

Patient Demographics

Characteristics, n (%)	cPMP-Treated Patients (N = 13)	Untreated Controls (N = 37)
Male	7 (53.8)	28 (75.7)
Female	6 (46.2)	9 (24.3)
Region of birth		
North America	2 (15.4)	3 (8.1)
Europe	6 (46.2)	14 (37.8)
Rest of world	5 (38.5)	20 (54.1)
Age of first MoCD symptom category		
≤ 28 days	13 (100)	33 (89.2)
> 28 days	0	4 (10.8)

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

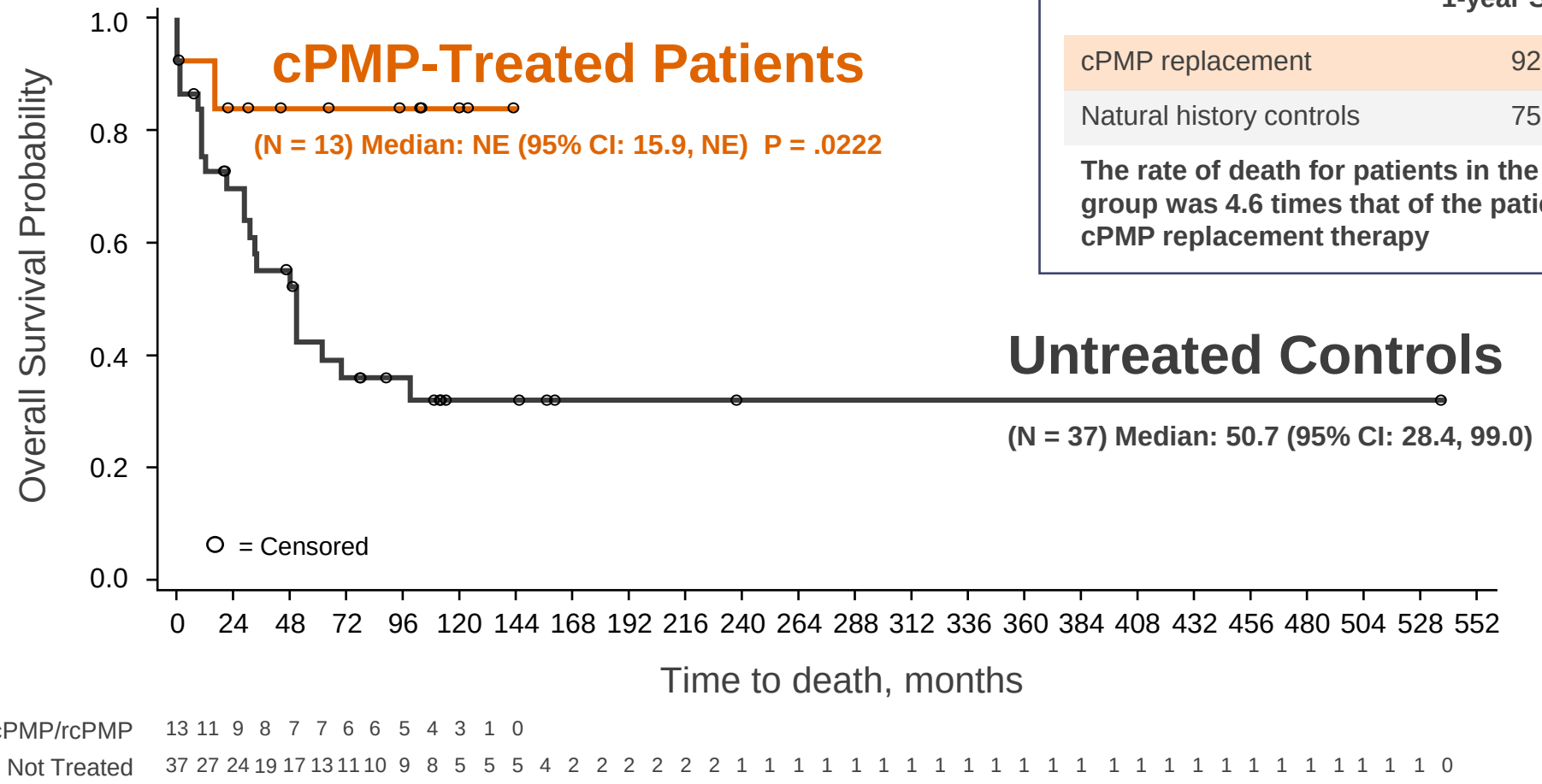
MoCD Presenting Signs and Symptoms

Parameters, n (%)	cPMP-Treated Patients (N = 13)	Untreated Controls (N = 37)
Seizures	9 (69.2)	34 (91.9)
Feeding difficulties	8 (61.5)	31 (83.8)
High-pitched cry	7 (53.8)	16 (43.2)
Exaggerated startle response	5 (38.5)	12 (32.4)
Number of reported other symptoms[a]	21	20

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

[a]Other signs and symptoms included but were not limited to metabolic acidosis, hypertonia, hypotonia, encephalopathy, intracranial hemorrhage.

cPMP Replacement Therapy Improves Overall Survival

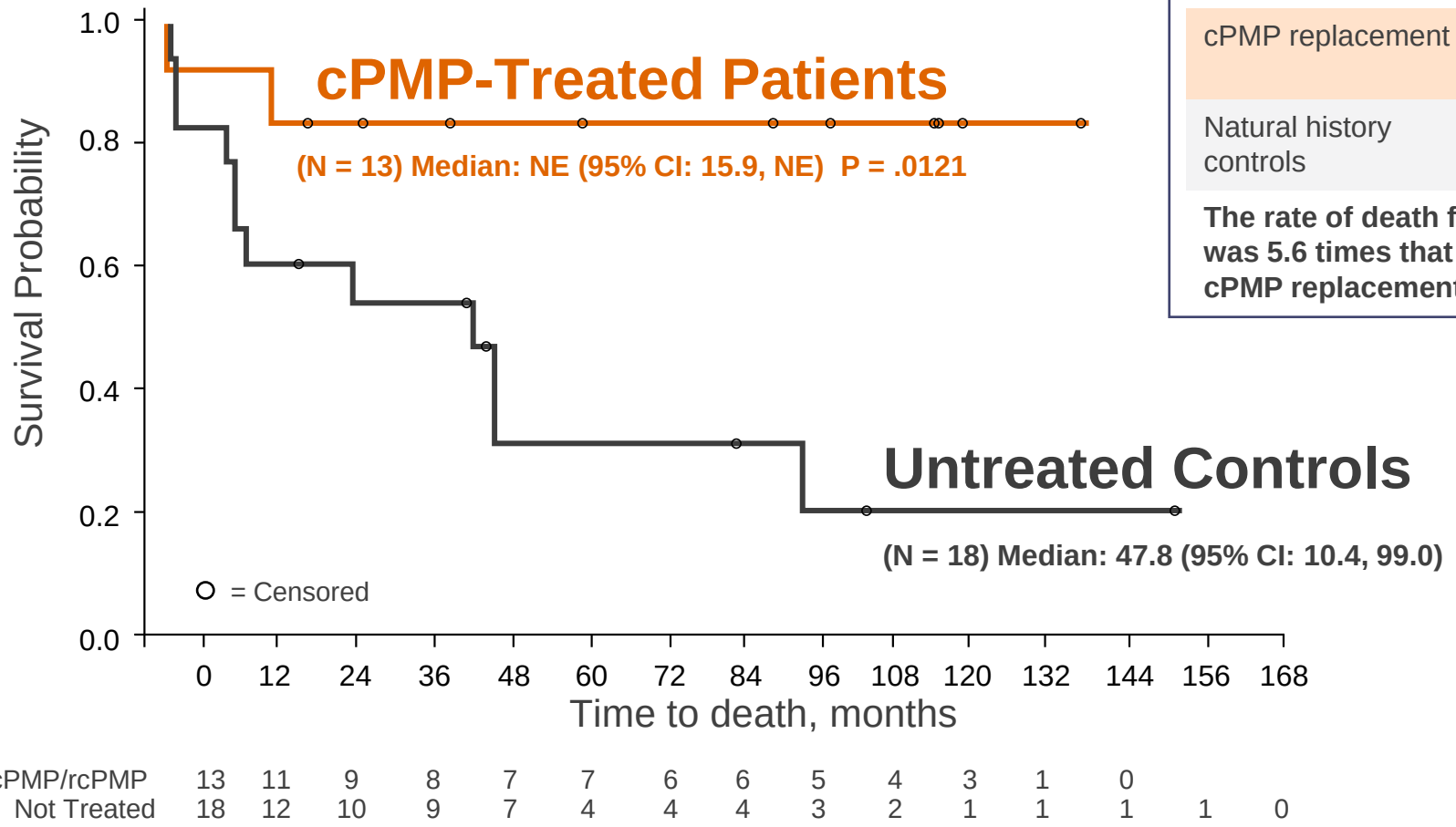


	1-year Survival	2-year Survival
cPMP replacement	92%	84%
Natural history controls	75%	70%

The rate of death for patients in the untreated control group was 4.6 times that of the patients who received cPMP replacement therapy

cPMP, cyclic pyranopterin monophosphate; NE, not evaluable; rcPMP, recombinant cyclic pyranopterin monophosphate.

cPMP Replacement Therapy Improved Overall Survival: Genotype-Matched Controls



	1-year Survival	2-year Survival	3-year Survival
cPMP replacement	92%	84%	84%
Natural history controls	67%	61%	55%

The rate of death for patients in the untreated control group was 5.6 times that of the patients who received cPMP replacement therapy

cPMP, cyclic pyranopterin monophosphate; NE, not evaluable; rcPMP, recombinant cyclic pyranopterin monophosphate.

Urine SSC Levels in cPMP-treated Patients vs Controls

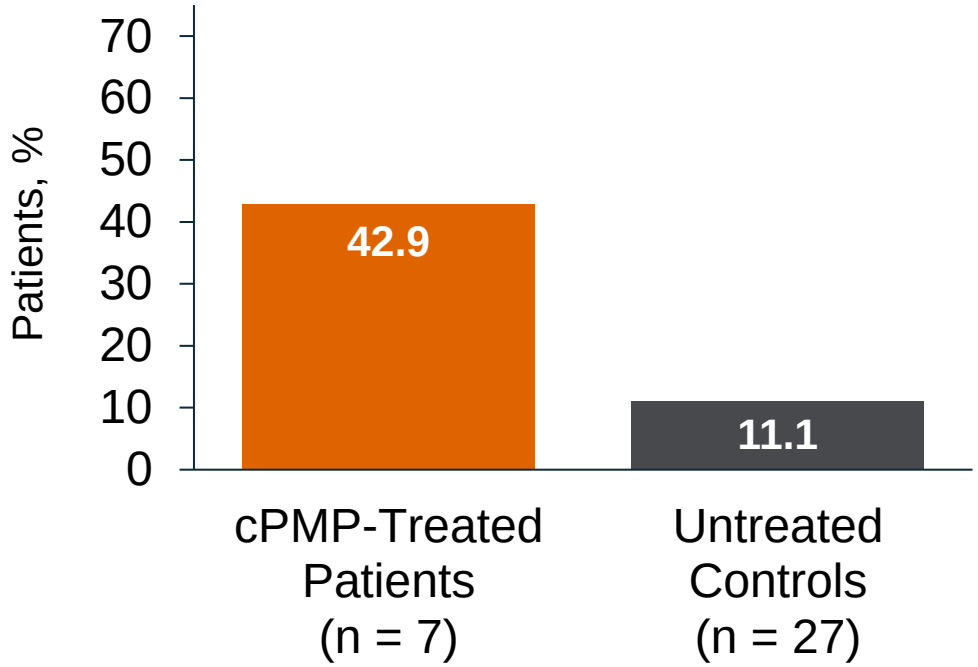
S-sulfocysteine/creatinine, µmol/mmol	cPMP-Treated Patients (N = 12)	Untreated Controls (N = 37)
Baseline, first value, n	12	22
Mean (SD)	181.1 (282.53)	136.3 (87.21)
Last visit, n	12	22
Mean (SD)	11.4 (6.87)	156.6 (100.70)
Change to last visit, n	12	18
Mean (SD)	−169.6 (282.44)	24.8 (104.61)

Pathological values of S-sulfocysteine are > 50 µmol/mmol creatinine

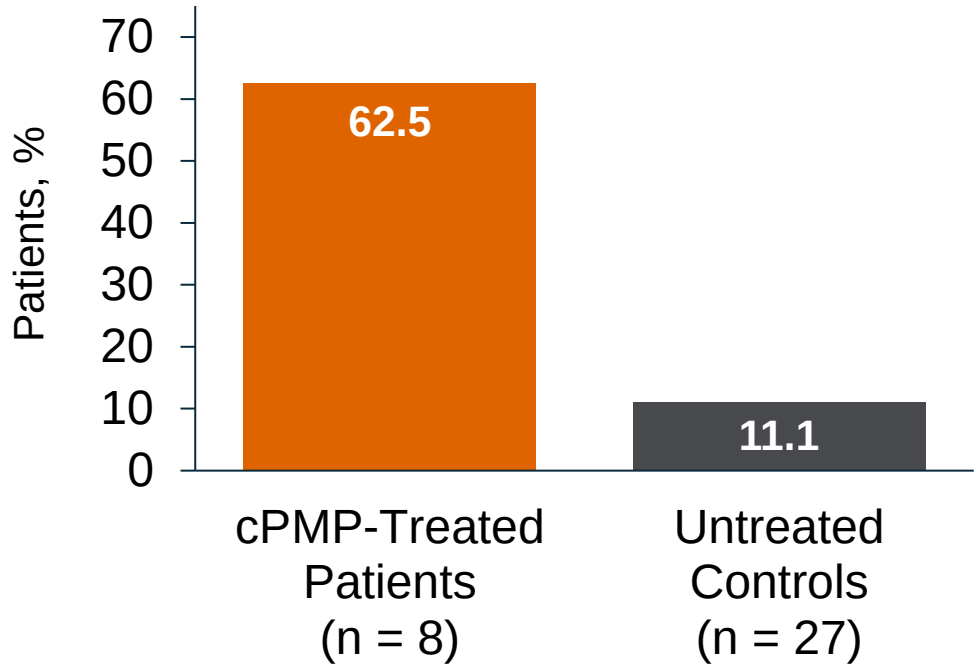
cPMP, cyclic pyranopterin monophosphate.

Sitting Unassisted in cPMP-Treated Patients vs Controls

Unassisted Sitting by 12 Months[a]



Unassisted Sitting at Any Time[a]

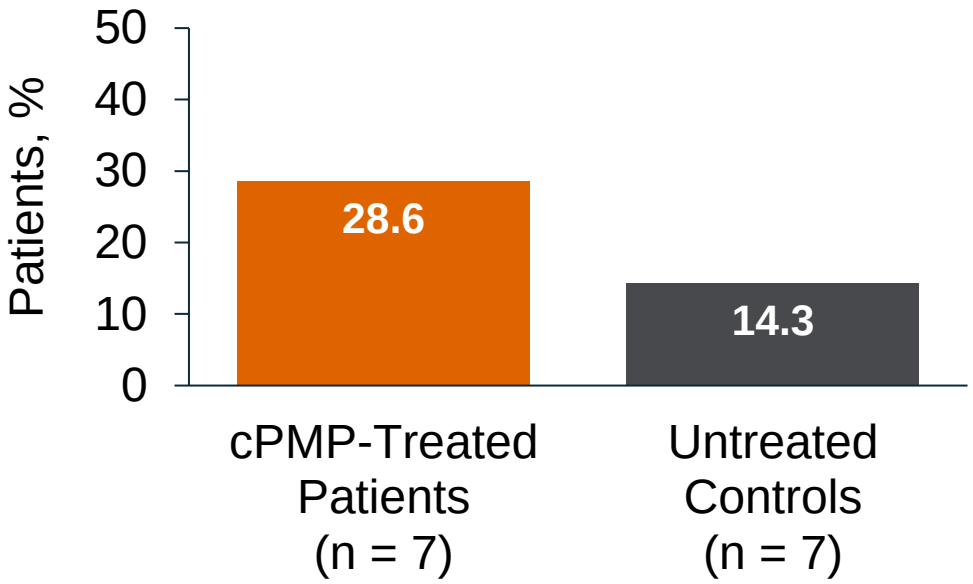


cPMP, cyclic pyranopterin monophosphate.

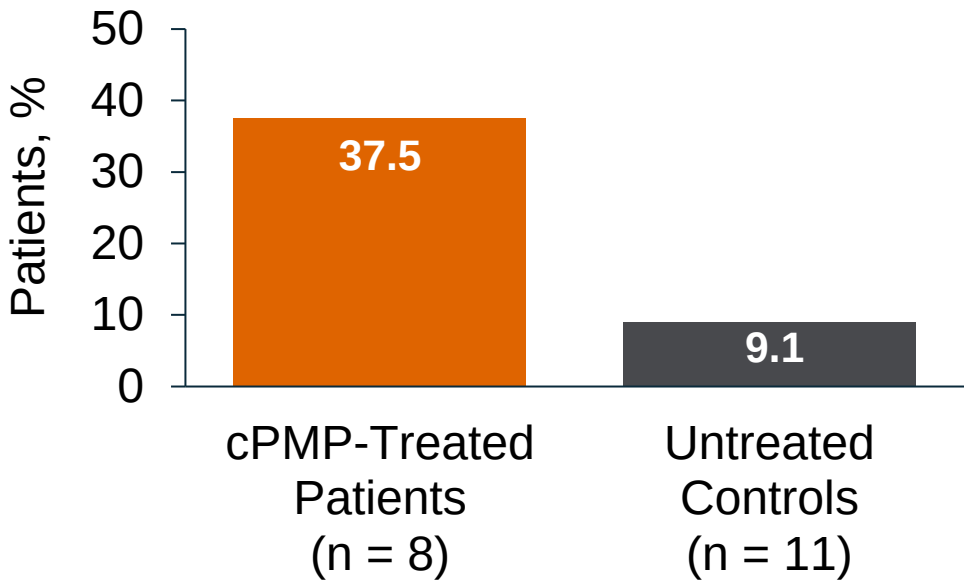
[a]Unassisted sitting was measured as ability to sit independently for 30 seconds.

Achievement of GMFCS Level 1 in cPMP-Treated Patients vs Controls

Achieving GMFCS-ER Level 1 at Month 12



Achieving GMFCS-ER Level 1 at Last Visit

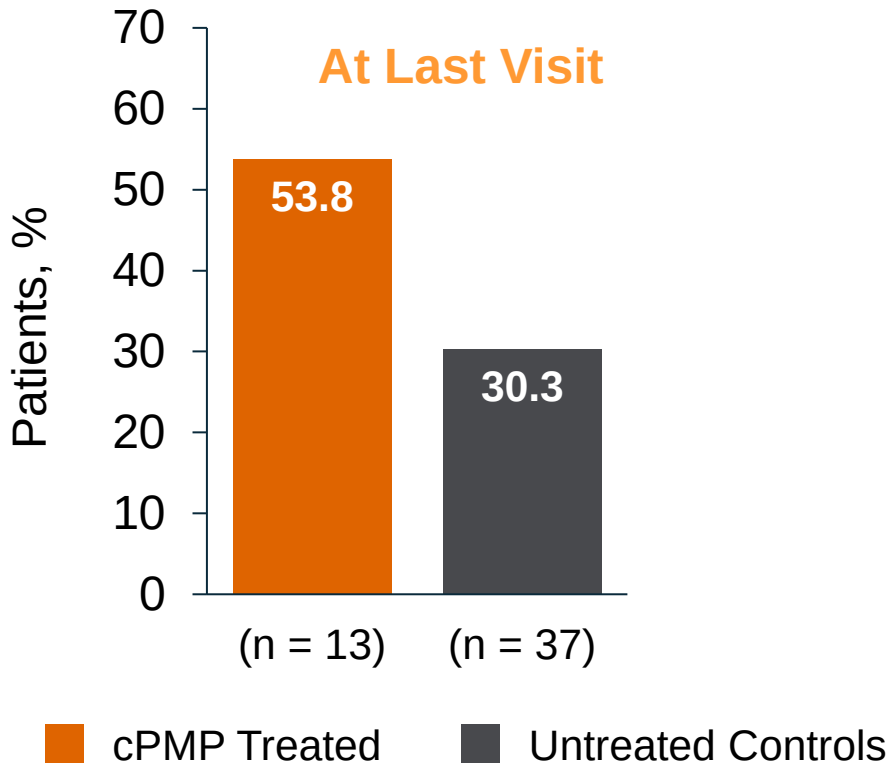


GMFCS-ER Level I represents the highest-rated functioning level on this scale. Children aged 2 and older who are rated as Level I are able to walk independently and, by age 6, can perform higher-level gross motor skills such as running, jumping, and stair climbing.

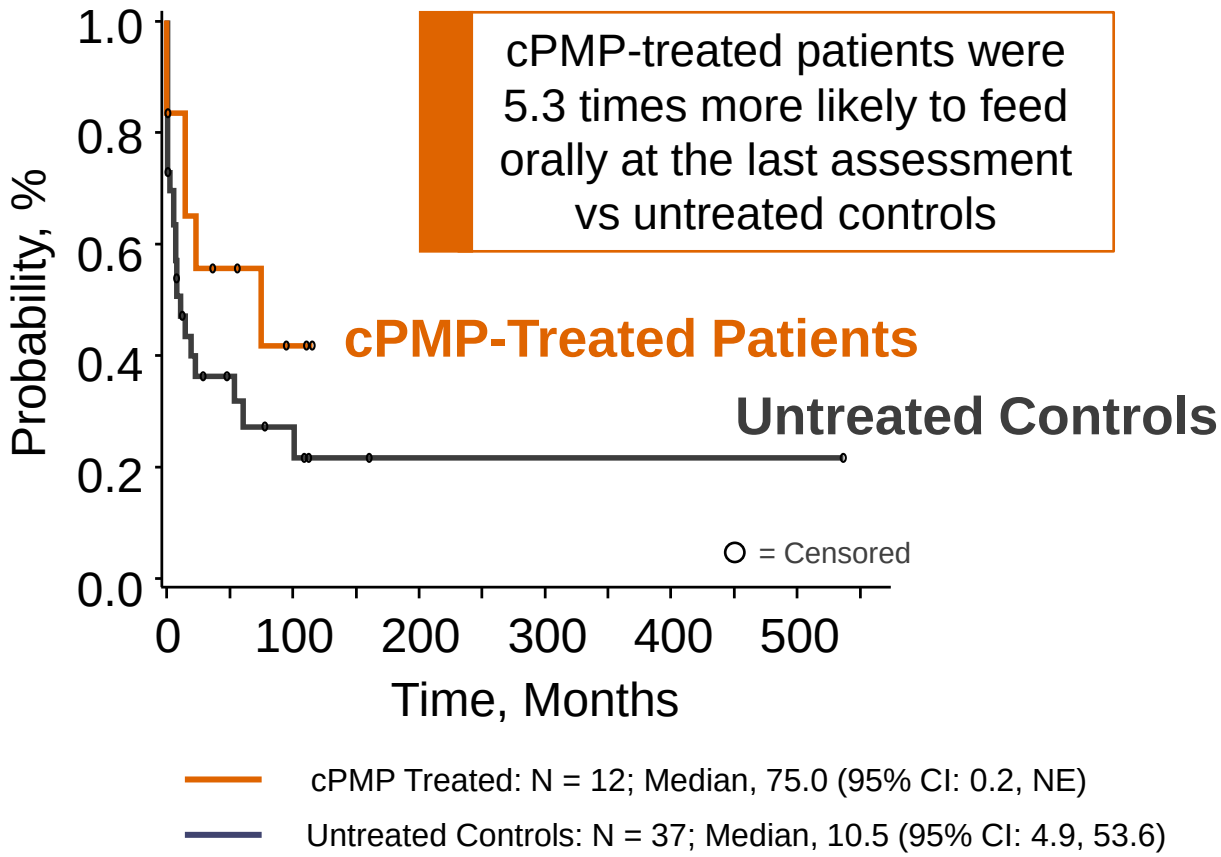
cPMP, cyclic pyranopterin monophosphate; GMFCS-ER, Gross Motor Function Classification System Expanded and Revised.

Oral Feeding in cPMP-Treated Patients vs Controls

Feeding Orally



Time to Sustained Nonoral Feeding[a]



cPMP, cyclic pyranopterin monophosphate; NE = not estimable.

[a]Sustained nonoral feeding was defined as the time at which the patient never subsequently returned to an oral method of feeding

Safety of cPMP

- Most treatment adverse events were mild to moderate, and not related to study drug
  - Most common side effects in fosdenopterin-treated patients were infusion catheter–related complications, pyrexia (fever), viral infection, pneumonia, otitis media (ear infection), vomiting, cough/sneezing, viral upper respiratory infection (common cold/flu-like infection), gastroenteritis (stomach flu-like symptoms), diarrhea, and bacteremia (bacteria in the blood)
  - Side effects for recombinant cPMP-treated patients were similar to the side effects among fosdenopterin-treated patients
- There were no discontinuations or dose modifications due to adverse events
- 2 deaths were noted in the retrospective data
  - 1 patient died due to necrotizing enterocolitis judged as possibly related to study drug
  - 1 patient died due to respiratory syncytial virus pneumonia unrelated to study treatment

Potential for Photosensitivity

- cPMP (fosdenopterin) can make the patient oversensitive to sunlight
- Patients or their caregivers are advised to avoid or minimize patient exposure to sunlight and artificial UV light and adopt precautionary measures when exposed to the sun, including wearing protective clothing and sunglasses, and using broad-spectrum sunscreen with high SPF in patients 6 months of age and older
- If photosensitivity occurs, caregivers/patients are advised to seek medical attention immediately and consider a dermatological evaluation

cPMP, cyclic pyranopterin monophosphate; SPF, sun protection factor; UV, ultraviolet.

Conclusions Leading to the Approval of Fosdenopterin for MoCD Type A

Patients treated with cPMP had **improved overall survival** when compared with untreated historical controls

Patients treated with cPMP **demonstrated decreased urine SSC levels** when compared with untreated historical controls

Additional confirmatory evidence was **provided by the animal model** of MoCD Type A

cPMP (fosdenopterin) was **safe and well-tolerated**

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

Farrell S, et al. *J Inherit Metab Dis*. 2021;44:1085-1087.

Natural History Studies

Provide an opportunity to:

- Characterize ultra-rare and rare disorders
- Develop appropriate disease biomarkers
- Ethically study potentially life-saving treatments
- Facilitate the development of therapeutics in ultra-rare and rare disorders

Thank You

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Case Example: Lumasiran and Nedosiran for Primary Hyperoxaluria

Presenter

John Lieske MD
Mayo Clinic Hospital – Rochester

REAGAN-UDALL FOUNDATION FOR THE FDA

Case Study:
Use of registry data to define the natural history of primary hyperoxaluria

FDA Symposium
May 13, 2024

John C Lieske, MD, FASN

Mayo Clinic Division of Nephrology and Hypertension

RARE KIDNEY STONE CONSORTIUM

Disclosures

Relevant Financial Relationship(s)

Grant funding* and consulting@:

Allena*@

Alnylam*@

BioMarin @

Chinook @

Dicerna/ Novo Nordisc*@

Federation Bio@

Novobiome@

Orfan Bridgebio@

Oxidien @

OxThera*@

Precision Biosciences @

Synlogic*@

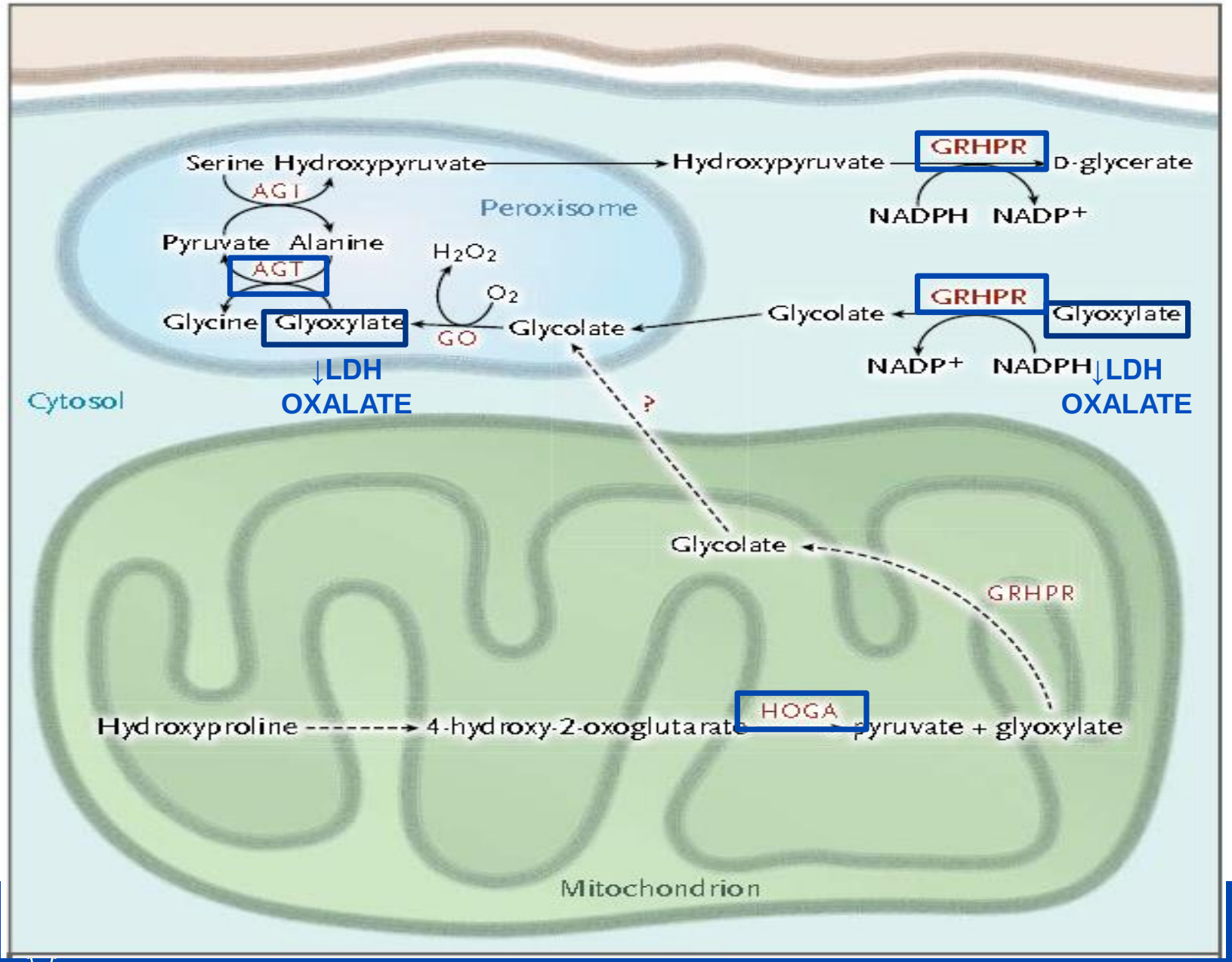
Off Label Usage

None

Outline

- Primary Hyperoxaluria
- Key Role of Patient Advocacy Group (PAG) and ASN to develop registry, disease background, and ultimately engage FDA under the auspices of the Kidney Health Initiative
- Key natural history features that informed treatment efficacy measures
- Ultimate outcome of efforts

Primary Hyperoxaluria: Hepatic oxalate overproduction



Gene mutation

PH type 1 (30%): *AGT*
PH type 2 (10%): *GRHPR*
PH type 3 (60%): *HOGA*

Enzymes implicated

PH 1 and PH2:
Cytosolic LDH
Glyoxalate → Oxalate

PH3: ??

Ancillary tests

PH1: ↑ glycolate
PH2: ↑ glycerate
PH3: ↑ 4-hydroxyglutarate

Hyperoxaluria

High concentrations of oxalate in urine lead to stones, nephrocalcinosis, CKD, and kidney failure, and can result in systemic oxalosis causing multiorgan damage.

Types of Hyperoxaluria

- Primary hyperoxaluria (PH) due to increased hepatic oxalate production caused by any of three known genetic defects in glyoxylate and hydroxyproline metabolism in the liver.

  Rare disease: 1-3 per million population

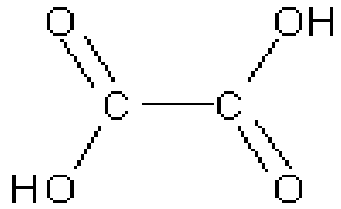
- Enteric hyperoxaluria (EH) caused by fat malabsorption which leads to high absorption of oxalate in small intestine.

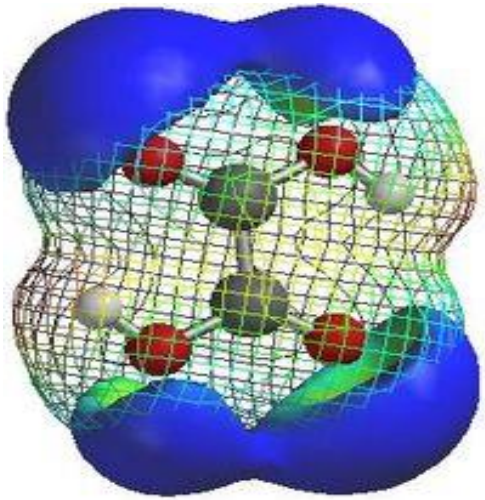
  Estimated to affect ~150,000 patients

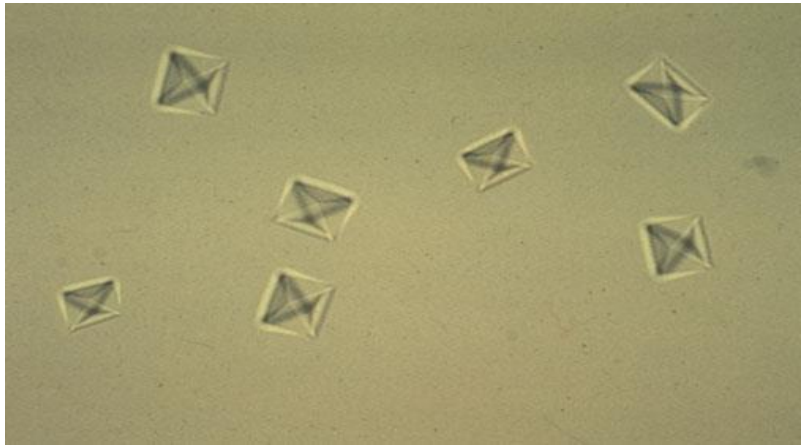
What is oxalate?

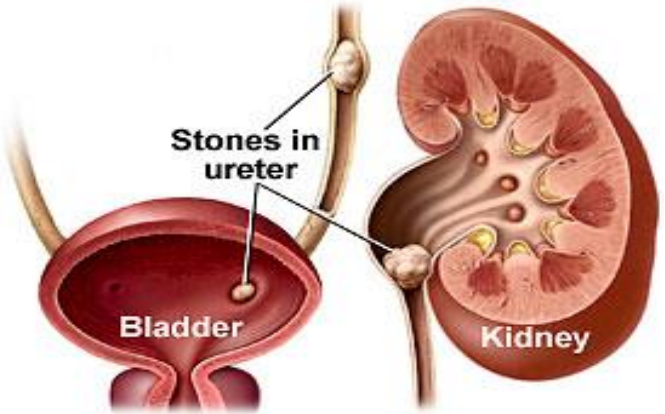
TABLE 3. *Foods with high oxalate content*

Food	Serving size	Oxalate (mg)
Rhubarb	½ cup	720–1032
Spinach	½ cup	570–675
Beetroot	½ cup	573
Swiss chard	½ cup	568
Pokeweed	½ cup	390
Cocoa powder	1 ounce	174
Okra	½ cup	117
Wheat germ	1 ounce	75
Tea (4 min infusion)	1 teaspoon	72
Green gooseberries	½ cup	66
Collards	½ cup	63
Crackers, soybean	1 ounce	58
Pecans	1 ounce	56
Peanuts	1 ounce	52
Grits, white corn	½ cup	50
Sweet potato	½ cup	34
Chocolate	1 ounce	33
Black raspberries	½ cup	32
Leek	½ cup	23
Celery	2 stalks (80 g)	16
Rutabaga	½ cup	16
Eggplant	1 cup	15
Summer squash	½ cup	14
Blackberries	½ cup	13
Green beans	½ cup	11
Blueberries	½ cup	11
Currants, red	½ cup	11
Dewberries	½ cup	10
Black pepper	1 tsp	8
Green pepper	½ cup	8









Time machine travel to 2016

Increasing possibility for clinical trials in oxalate-related diseases

- Alter gastrointestinal oxalate absorption and/or secretion
  - Manipulate the gastrointestinal microbiome
  - Oral oxalate degrading enzymes
- Inhibition or manipulation of hepatic enzyme pathways
  - siRNA
    - Small molecules
    - Chaperones

2016 OHF Annual Scientific Advisory Board meeting

- **Primary and enteric hyperoxaluria are rare diseases**
  - Clinical trials with renal function, CKD, kidney failure, or kidney stones are not feasible
  - The FDA is increasingly receptive to alternatives to these hard clinical endpoints, as long as well-justified
    - Duchenne muscular dystrophy is one example
- Idea of an FDA white paper on oxalate studies discussed with scientific, industry, and patient representatives at a half day meeting.
  - Concept enthusiastically endorsed by all present
  - Despite being an “unfunded mandate” efforts moved forward…

OHF team to DC in Spring 2016

D Milliner

J Lieske

T Lowther

K Hollander

J Bertarelli

Stop 1: ASN

- The mission of KHI is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which the FDA and the greater nephrology community can interact to optimize the evaluation of drugs, devices, biologics, and food products.

https://www.asn-online.org/khi/

Who can join KHI?

- KHI is a collaborative environment for all stakeholders in the kidney community to help foster development of optimum therapies for diseases that affect the kidney. KHI members may include:
  - Patient organizations
  - Health professional organizations
  - Research Institutions
  - Foundations
  - Pharmaceutical and biotechnology companies
  - Device manufacturers
  - Dialysis providers
  - US and international government agencies

Current KHI projects (2016)

- Advancing Technologies to Facilitate Remote Management of Patient Self-Care in Renal Replacement Therapy (RRT)
- Clinical Trial Endpoints for Dialysis Vascular Access
- Data Harmonization in Kidney Transplant
- Data Standards in Diabetic Kidney Disease
- Development of a Roadmap for Innovations in Renal Replacement Therapy (RRT)
- **Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy**
- Overcoming Barriers to Drug Development in Children with CKD
- Pragmatic Trials in Dialysis: Challenges and Opportunities
- Prioritizing Symptoms of ESRD Patients for Developing Therapeutic Interventions
- Regulatory Policies and Positions Affecting Device Approval in the US: Tools to Assess the Process and Foster Device Development for Patients with Kidney Disease
- Workshop to Elucidate Role of Patient Preferences in Support of CDRH Regulatory Actions in Kidney Disease

Stop 2: FDA meeting

- Well attended “1 hr” meeting with ~20 FDA representatives
- In general seemed receptive to our message that large clinical trials with hard endpoints are not feasible
- There is a mechanism to submit paperwork to validate a surrogate endpoint (like oxalate), but was mentioned maybe not be the best approach
- No firm advice r/e next best steps

Kidney Health Initiative (KHI)

- OHF proposal submitted for mid 2016 cycle to help with developing guidance for appropriate endpoints in hyperoxaluria trials
- Well received but ultimately not approved
- Feedback: Not eager to take on “validation of a surrogate endpoint” with all the lab work, etc. that effort might entail
- Plan to reapply for Spring 2017 cycle, and attend stakeholders meeting in May 2017
  - OHF and several officers are now KHI members

OHF SAB meeting 2017

- While waiting to reapply to KHI, we have decided now is the time to seize our momentum and work on a summary document that will:
  - be used when we engage the FDA in further discussion, hopefully culminating in the request from them for us to develop a guidance document
  - form the basis (or starting point) for this comprehensive guidance document

Workgroups

1	Biology of oxalate, including biosynthetic pathways
2	Renal and gastrointestinal oxalate transport
3	Genetics of Primary Hyperoxaluria
4	Pathophysiology of enteric hyperoxaluria
5	Diagnosis of hyperoxaluria, including algorithms and laboratory issues
6	Pathophysiology of calcium oxalate kidney stones and nephrocalcinosis in hyperoxaluric states
7	Treatment strategies for hyperoxaluria- current and future
8	The clinical needs for hyperoxaluria trials from the patients' perspective

Group Leader	Group Members					
T Lowther	B Cellini	J Knight	C Danpure	T McGregor	A Quinn	
M Hatch	Rholmes	D Goldfarb	D Sas	E Lindner		
D Milliner	E Salido	Y Frishberg	M Baum			
J Lieske	A Kausz	J Asplin	D Assimos			
J Asplin	D Milliner	Y Frishberg	M Hatch	J Knight	A Kauz	
D Goldfarb	D Sas	R Holmes	J Lieske	A Kausz	E Lindner	
M Baum	D Assimos	T Lowther	T McGregor	E Salido	B Cellini	A Quinn
J Lawrence	B Kissinger	K Hollander	J Subramanyam	I Aquino		

MAYO CLINIC

Subsequent Timeline

- February 25, 2017
  - Working meeting
- March-April 2017
  - Small group follow-up
- May-June 2017
  - Roll into one document
- July 2017
  - Discussions at OHF workshop

KHI Project

- **May-Sept 2017** Application submitted to KHI and approved
- Initial stakeholders meeting **Feb 22, 2018.**
  - Good representation from industry, academia, patients and families.

Specific Objectives

1. Consensus recommendations for potential surrogate endpoints

- Identify candidate surrogate markers for clinical trials in hyperoxaluria
- Critically assess candidate measures for appropriateness
- Identify gaps in the data and future research needs to fully establish acceptable biochemical marker(s) for clinical trials in hyperoxaluria

2. Develop recommendations for industry guidelines for expedited clinical trials and approvals

- Identify characteristics of patients with differing risks of progression
- Develop a consensus statement of risk tolerance of hyperoxaluric patients/families for clinical trial participation and medication use

Surrogate End Points for Clinical Trials

***Endpoint markers for clinical trials are expected meet the following criteria*:**

- **Biologic plausibility** that the biochemical marker is on the biologic pathway to a hard endpoint such as kidney failure or death
- Epidemiologic or other **data showing consistent association between the biochemical marker and the clinical outcome** of interest
- Any available **data from clinical trials showing that the effects of treatment on the candidate marker largely account for their effects on clinical outcome**
- **An assessment of quantitative effect** on the endpoint marker that is **needed to be clinically significant**

PH Registry Enrollment March-2023

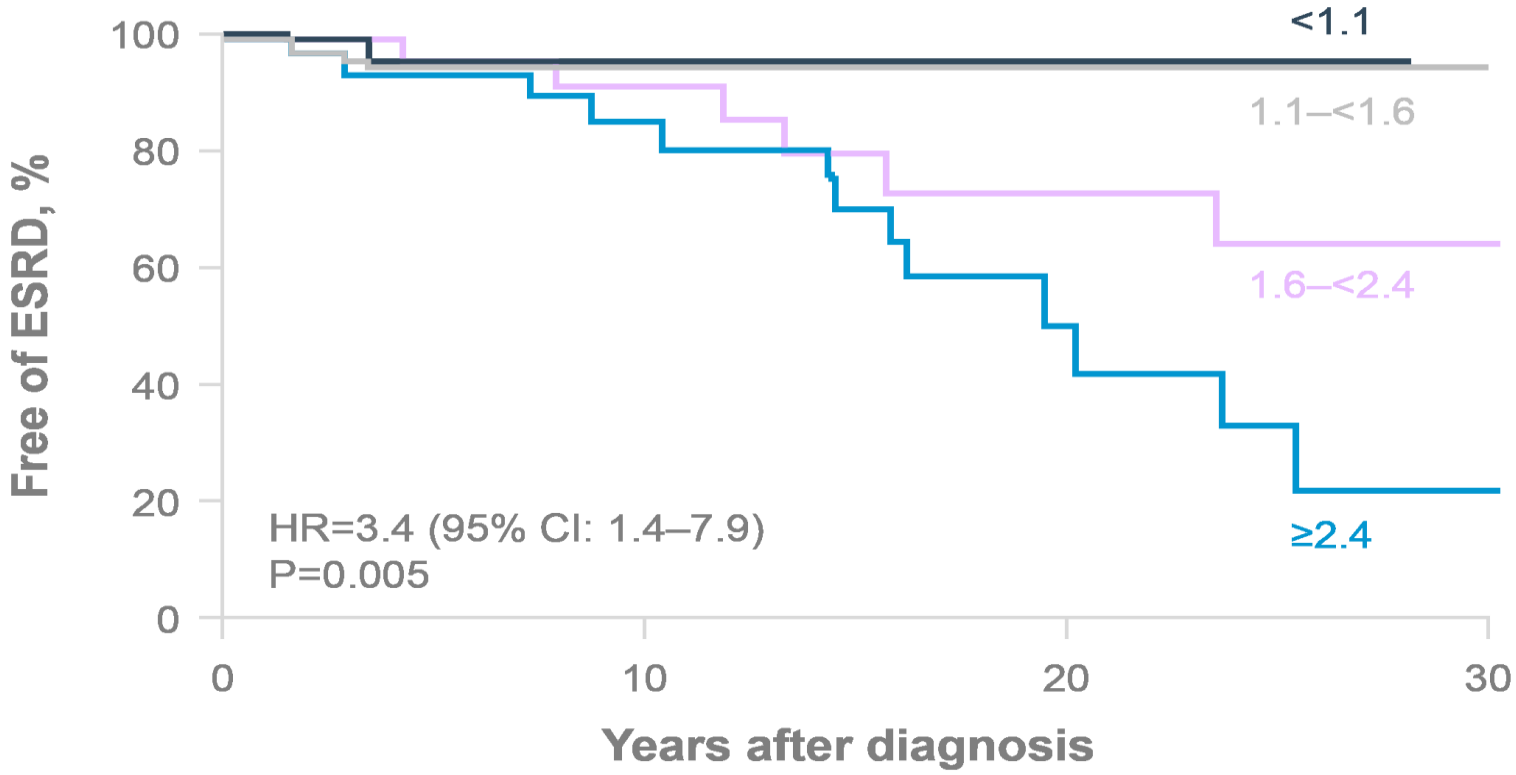
	Total (N=603)
Sex, n (%)	
M	**326 (54.4%)**
F	**273 (45.6%)**
Not Recorded	**4**
Race, n (%)	
Am. Indian	**3 (0.5%)**
Asian	**126 (20.9%)**
African American	**14 (2.3%)**
Hawaiian	**2 (0.3%)**
White	**357 (59.2%)**
Not Disclosed	**101 (16.7%)**
Ethnicity, n (%)	
Hispanic or Latino	**34 (5.6%)**
Non Hispanic or Latino	**339 (56.2%)**
Not Disclosed	**230 (38.1%)**
Deceased, n (%)	
No	**534 (88.6%)**
Yes	**69 (11.4%)**

PH Registry Enrollment March-2023

Renal Failure, n (%)	
No	**349 (57.9%)**
Yes	**254 (42.1%)**
Patients with Serum Labs	
N	**539**
Mean (SD)	**7.5 (7.70)**
Median	**5**
Range	**1.0, 46.0**
Patients with Urine Labs	
N	**490**
Mean (SD)	**6.6 (6.48)**
Median	**4**
Range	**1.0, 30.0**
Year LFU, n (%)	
<=2019	**417 (69.2%)**
2020	**62 (10.3%)**
2021	**45 (7.5%)**
2022	**67 (11.1%)**
2023	**12 (2.0%)**
FU Years	
N	**603**
Mean (SD)	**9.1 (11.59)**
Median	**4.9**
Range	**0.0, 64.1**

Urine oxalate is a key risk factor for kidney failure in PH

RARE KIDNEY STONE CONSORTIUM



UOx quartile mM/day

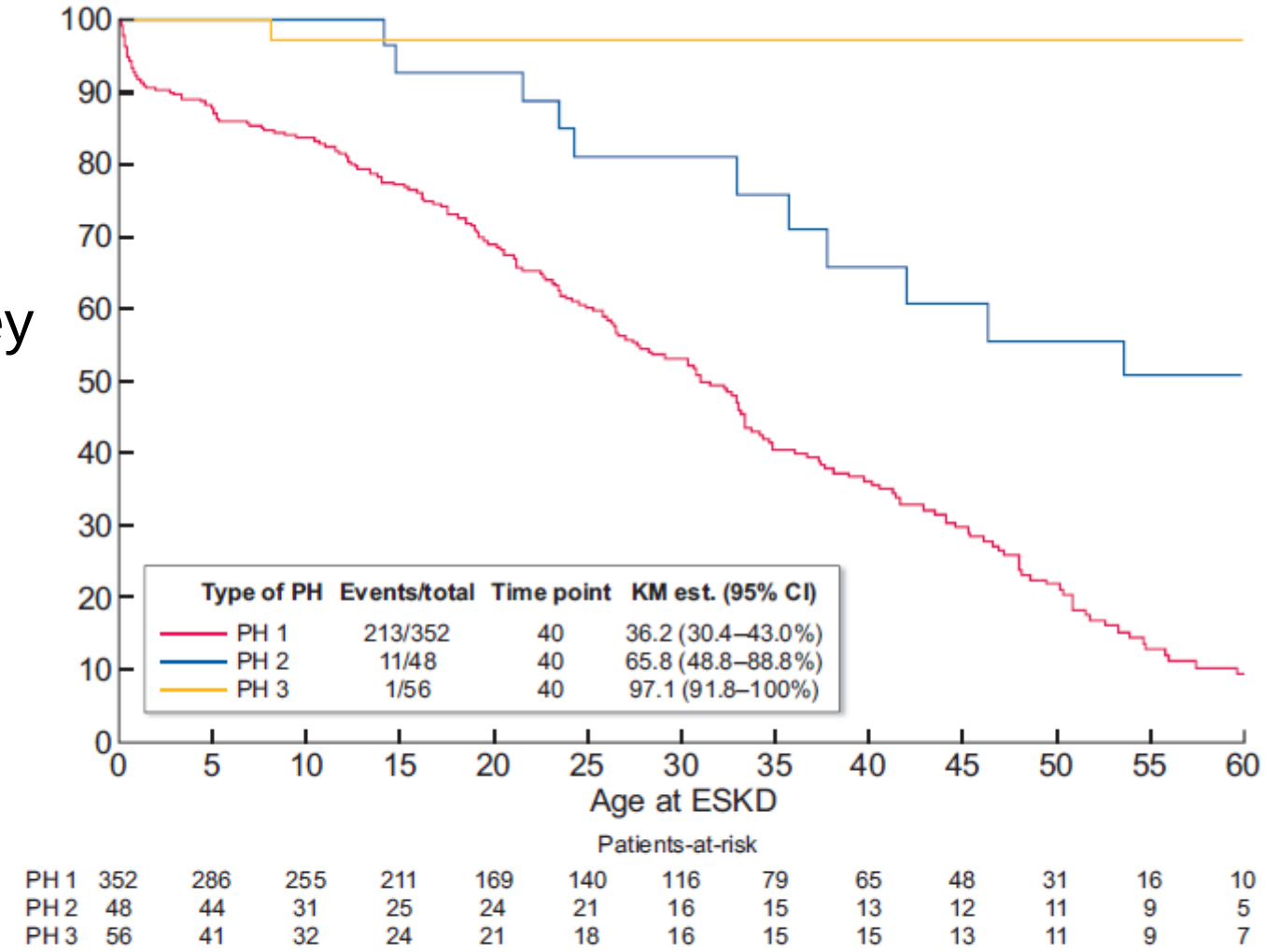
Urine oxalate	Survival estimate, % (number at risk)			
<1.1	100 (42)	96 (7)	96 (1)	–
1.1–<1.6	100 (42)	95 (8)	95 (5)	95 (2)
1.6–<2.4	100 (42)	91 (19)	73 (10)	65 (6)
≥2.4	100 (42)	85 (19)	42 (6)	23 (2)

MAYO CLINIC

Zhao et al Clin J Am Soc Nephrol 11: 119–126, 2016

Kidney failure is common in PH 1 and PH2, especially in PH1

Percent without kidney failure



····· PH3

--- PH2

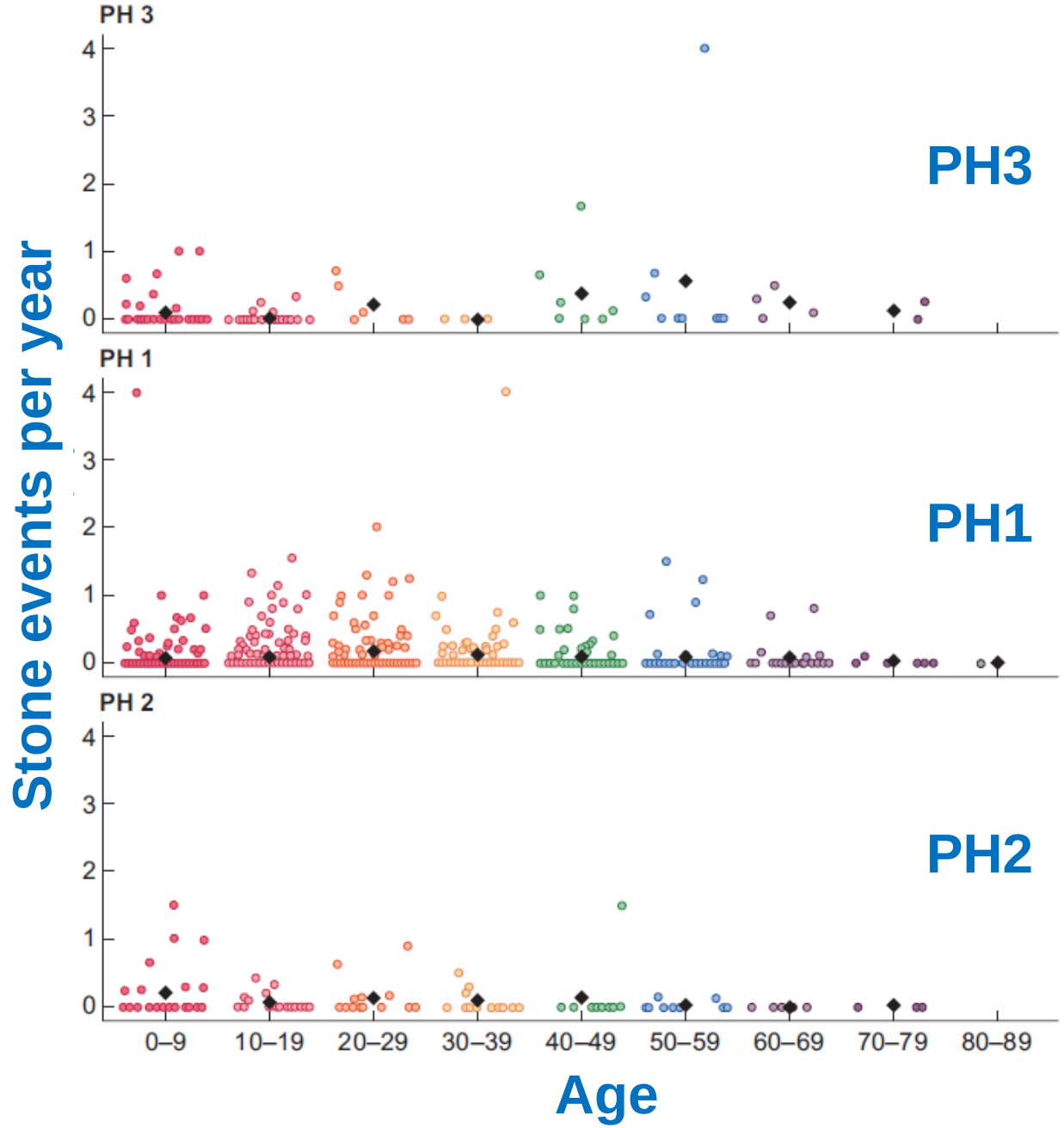
— PH1

RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Zhao et al Clin J Am Soc Nephrol 11: 119–126, 2016

Kidney stones are equally common in all PH types and across the decades

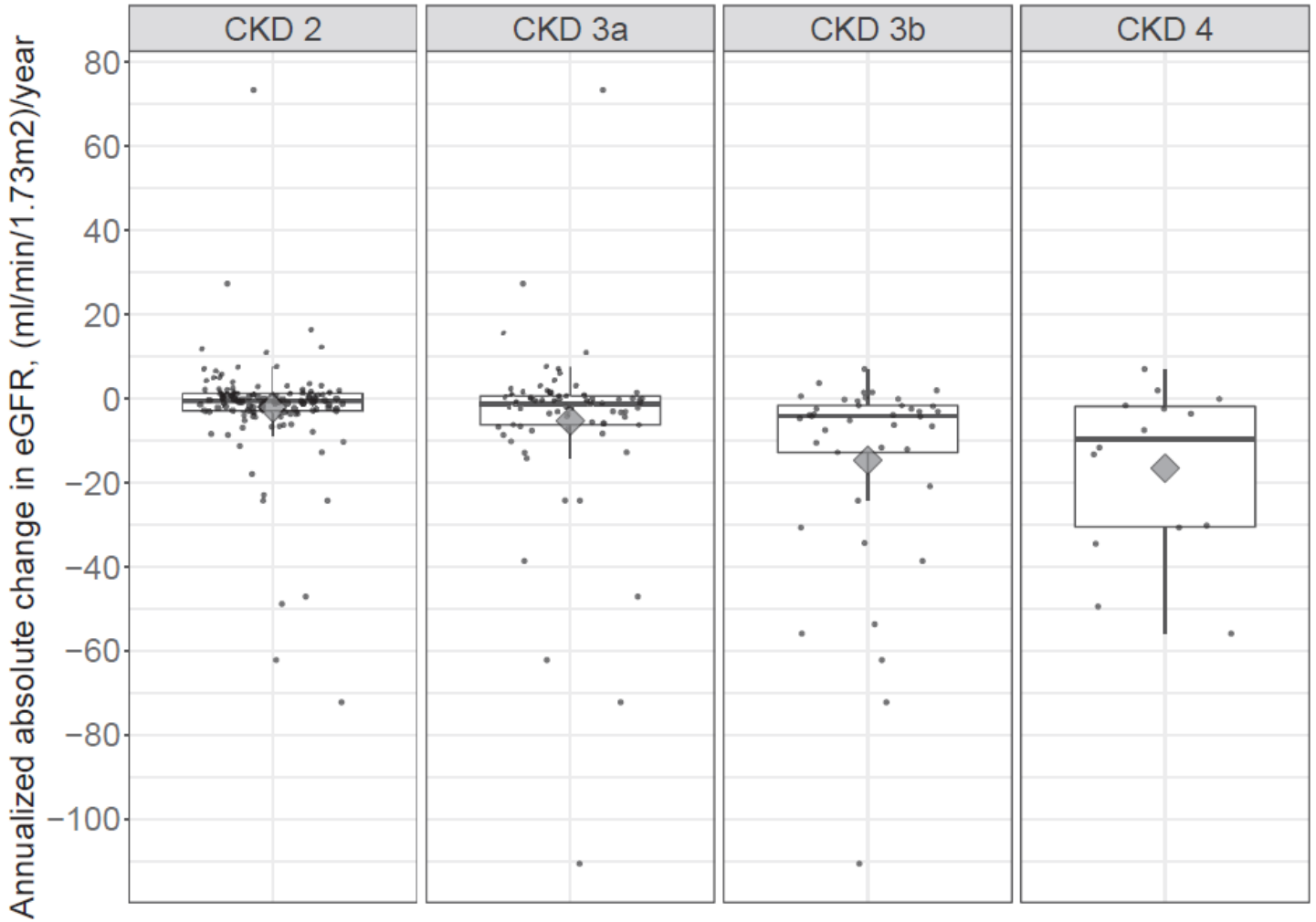


RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Singh P et al Nephrol Dial Transplant. 2022 37(5):869-875.

eGFR declines more dramatically at lower CKD stages

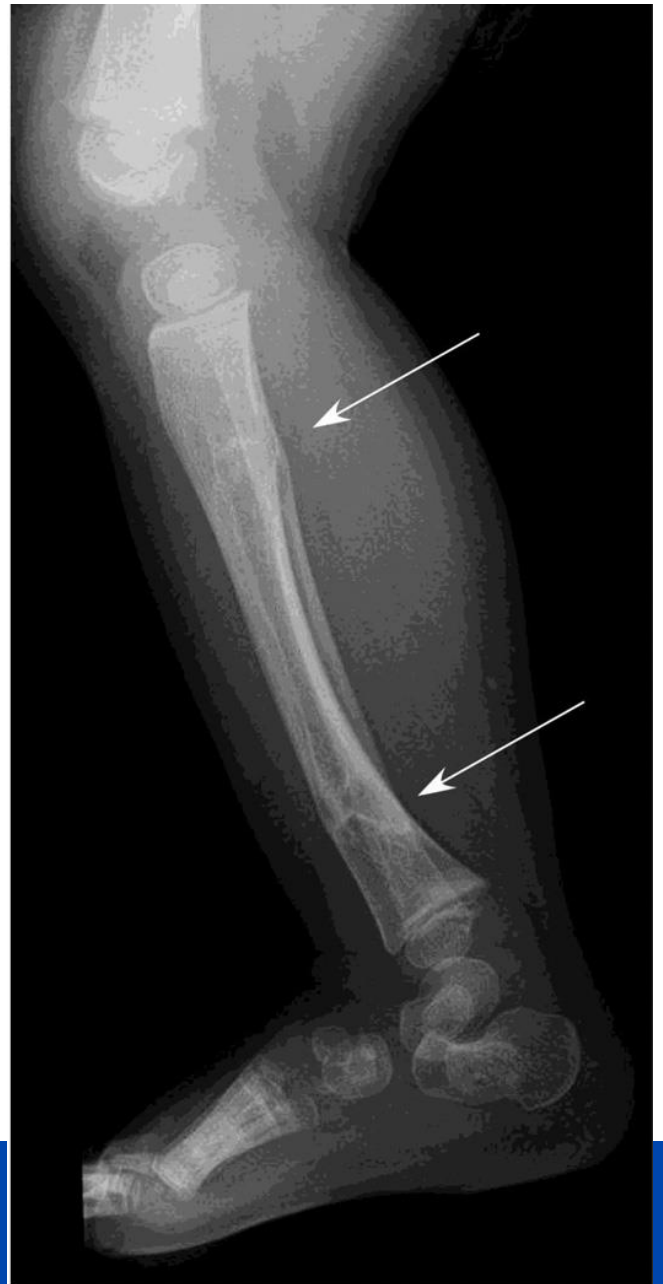


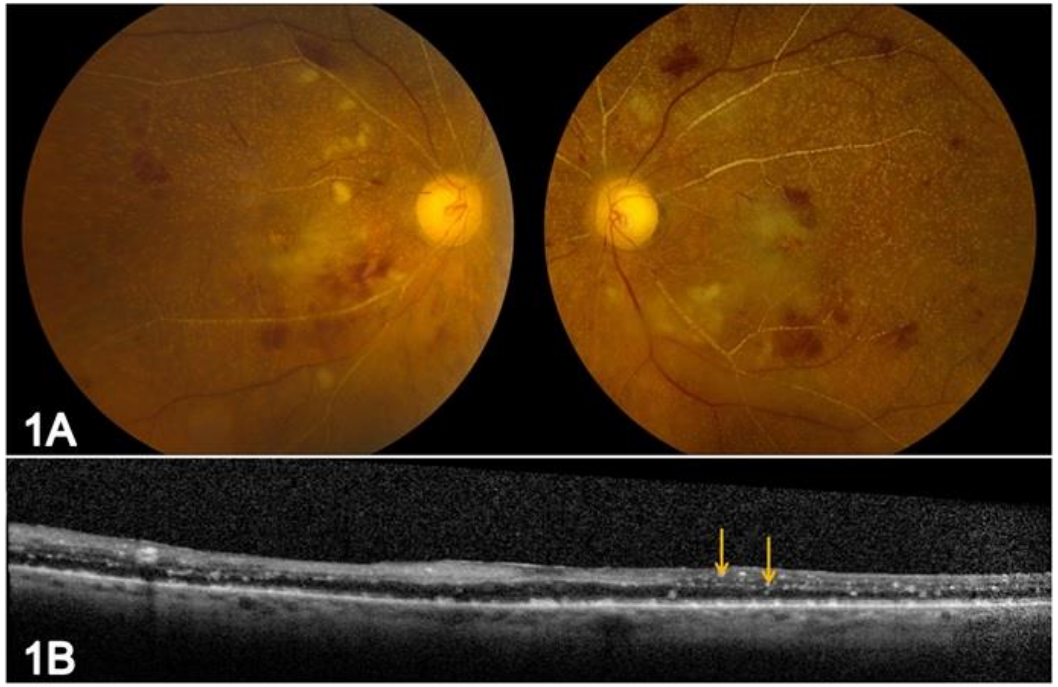
RARE KIDNEY STONE CONSORTIUM

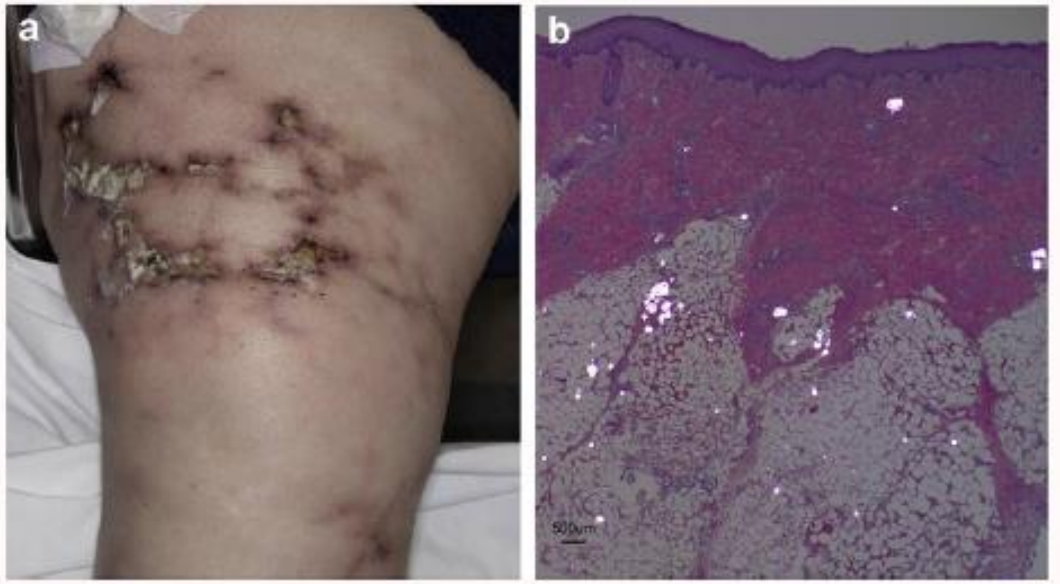
MAYO CLINIC

Singh P, et al: Am J Kidney Dis. 2022; Sep;80(3):373-382

Oxalosis



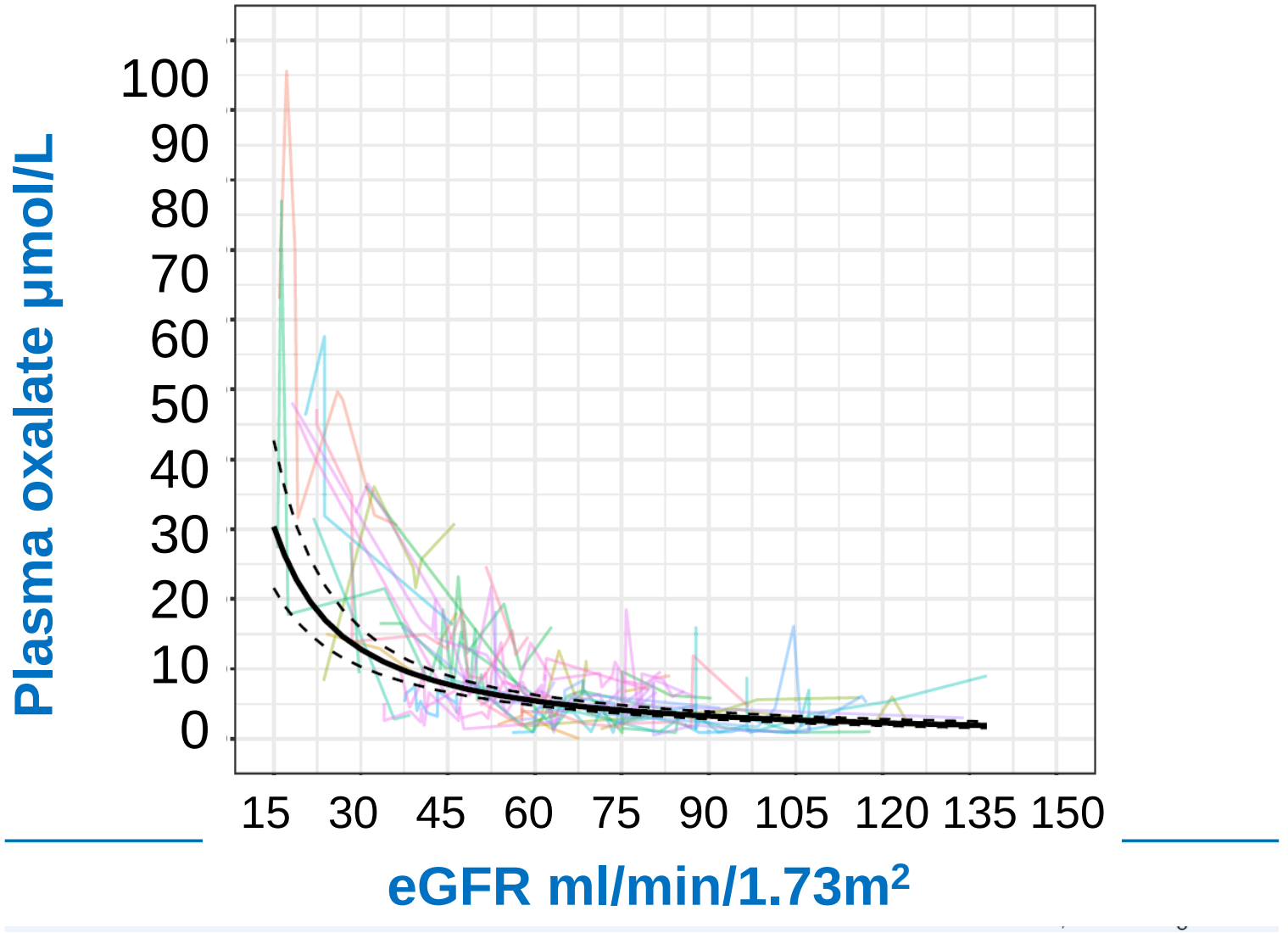




RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Plasma oxalate increases markedly at low eGFR in PH1

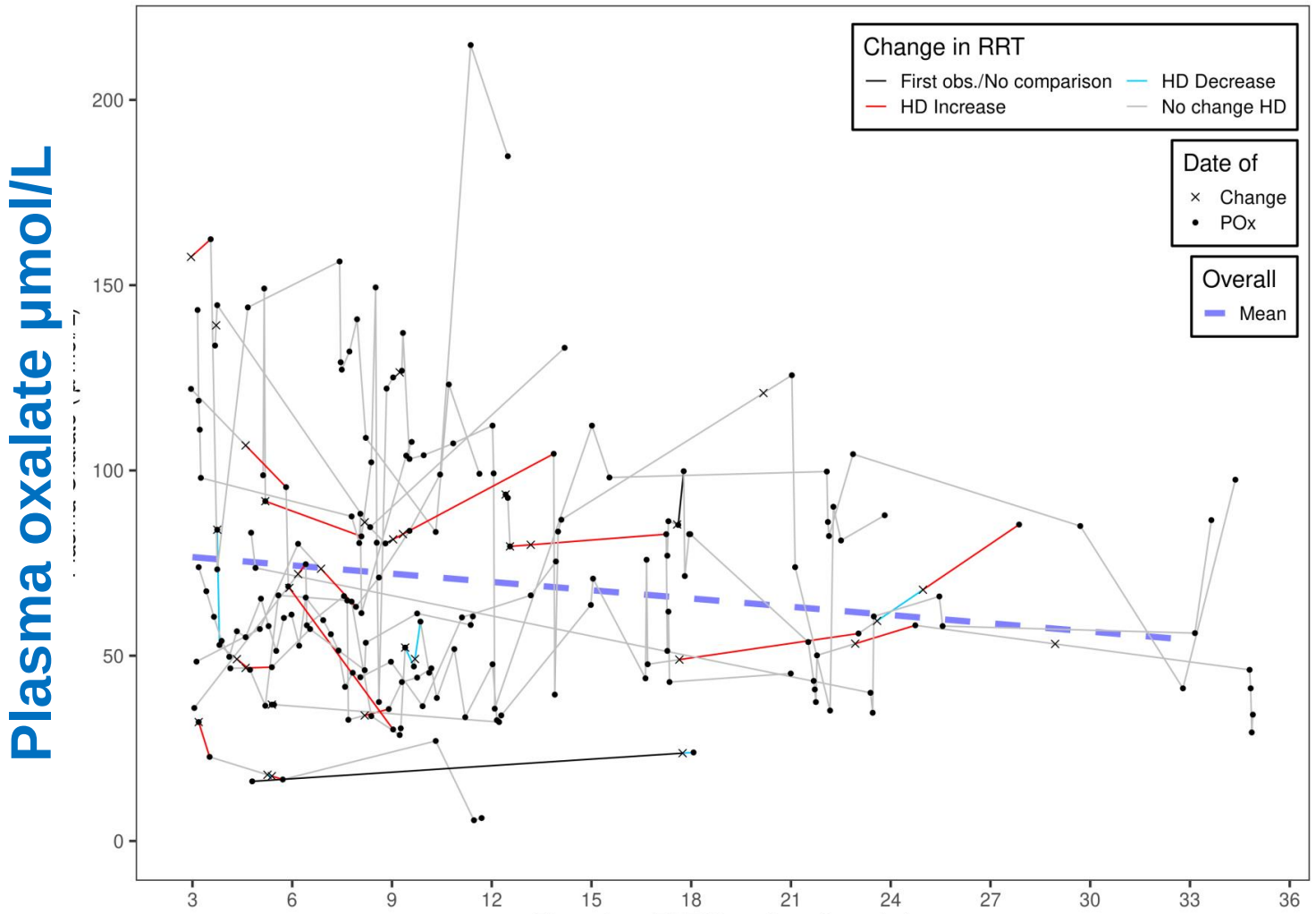


RARE KIDNEY STONE CONSORTIUM

Singh P, et al: Am J Kidney Dis. 2022; Sep;80(3):373-382

MAYO CLINIC

Plasma oxalate over time on dialysis in PH1



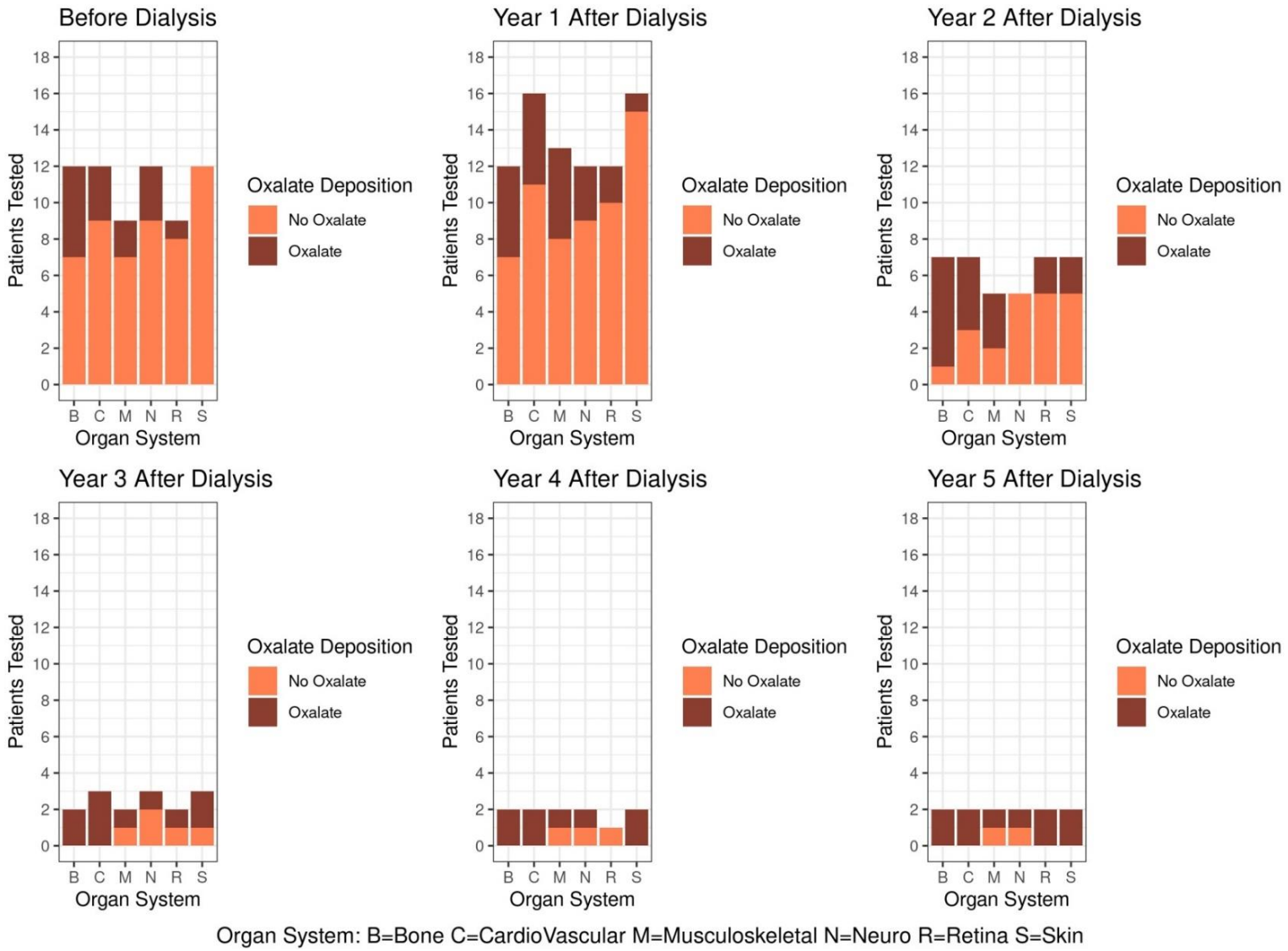
RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Oxalosis over time on dialysis

RARE KIDNEY STONE CONSORTIUM

Bone
Cardiovascular
Musculoskeletal
Neuro
Retina
Skin



Sas DJ et al. Front Med (Lausanne). 2021 Apr 9;8:592357.

KHI Endpoints for Clinical Trials in Hyperoxaluria: Outcomes

- A group of candidate markers compiled for evaluation.
- Promising candidates underwent rigorous examination via detailed literature review
- Biomarkers/endpoints evaluated sequentially on biweekly calls
- **Several remained as viable candidates**
  - **Plasma oxalate**
  - **Urine oxalate**
  - **Change in eGFR**
  - **Stone events**
- Workgroups summarized reviews
- Compiled into a draft report
- Paper draft Back and forth with FDA: published 2020
- PH patient group building on white paper, sought experience of others re: patient/family risk tolerance for clinical trials, new therapies.

Endpoints for Clinical Trials in Hyperoxaluria: KHI PH deliverables

PatientVoice

Feature

End Points for Clinical Trials in Primary Hyperoxaluria

Dawn S. Milliner,[1] Tracy L. McGregor,[2] Aliza Thompson,[3] Bastian Dehmel,[4] John Knight,[5] Ralf Rosskamp,[6] Melanie Blank,[3] Sixun Yang,[7] Sonia Fargue,[5] Gill Rumsby,[8] Jaap Groothoff,[9] Meaghan Allain,[10] Melissa West,[10] Kim Hollander,[11] W. Todd Lowther,[12] and John C. Lieske[1]

Abstract

Patients with primary hyperoxaluria experience kidney stones from a young age and can develop progressive oxalate nephropathy. Progression to kidney failure often develops over a number of years, and is associated with systemic oxalosis, intensive dialysis, and often combined kidney and liver transplantation. There are no therapies approved by the Food and Drug Association. Thus, the Kidney Health Initiative, in partnership with the Oxalosis and Hyperoxaluria Foundation, initiated a project to identify end points for clinical trials. A workgroup of physicians, scientists, patients with primary hyperoxaluria, industry, and United States regulators critically examined the published literature for clinical outcomes and potential surrogate end points that could be used to evaluate new treatments. Kidney stones, change in eGFR, urine oxalate, and plasma oxalate were the strongest candidate end points. Kidney stones affect how patients with primary hyperoxaluria feel and function, but standards for measurement and monitoring are lacking. Primary hyperoxaluria registry data suggest that eGFR decline in most patients is gradual, but can be unpredictable. Epidemiologic data show a strong relationship between urine oxalate and long-term kidney function loss. Urine oxalate is reasonably likely to predict clinical benefit, due to its causal role in stone formation and kidney damage in CKD stages 1–3a, and plasma oxalate is likely associated with risk of systemic oxalosis in CKD 3b–5. Change in slope of eGFR could be considered the equivalent of a clinically meaningful end point in support of traditional approval. A substantial change in urine oxalate as a surrogate end point could support traditional approval in patients with primary hyperoxaluria type 1 and CKD stages 1–3a. A substantial change in markedly elevated plasma oxalate could support accelerated approval in patients with primary hyperoxaluria and CKD stages 3b–5. Primary hyperoxaluria type 1 accounts for the preponderance of available data, thus heavily influences the conclusions. Addressing gaps in data will further facilitate testing of promising new treatments, accelerating improved outcomes for patients with primary hyperoxaluria.

CJASN 15: 1056–1065, 2020. doi: https://doi.org/10.2215/CJN.13821119

Due to the number of contributing authors, the affiliations are listed at the end of this article.

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Primary Hyperoxaluria
The Patient and Caregiver Perspective

Jennifer E. Lawrence and Debra J. Wattenberg

CJASN 15: 909–911, 2020. doi: https://doi.org/10.2215/CJN.13831119

Introduction

Living with primary hyperoxaluria—a rare genetic disease with excess oxalate production leading to frequent kidney stones, kidney impairment, and oxalosis—presents many challenges to patients, caregivers, and their families. Although the progression and severity of primary hyperoxaluria is variable, care for any child or adult with primary hyperoxaluria is an unusual strain to the family due to intensity of required medical care and associated financial hardship. To identify the concerns of the primary hyperoxaluria community, multiple in-person meetings were con-

experience interruptions in school and work, and loss of sleep.

"It is a daily challenge to make sure our son is drinking constantly throughout the day. He visits the school nurse every day who gives him one of his four daily doses of medication through his (gastrostomy) mickey button. As a 12-year-old, he misses sleepovers, sleep away camp, and overnight school trips."

Oxalosis and Hyperoxaluria Foundation, New York, New York

Correspondence: Dr. Jennifer E. Lawrence, Valdosta Specialty Clinic, 2418 North Oak Street, Valdosta, GA 31602. Email: jenlawtidmore@gmail.com

Editorial › Am J Kidney Dis. 2021 Oct 8;S0272-6386(21)00895-7. doi: 10.1053/j.ajkd.2021.09.005.
Online ahead of print.

End Points for Clinical Trials in Hyperoxaluria: Case Study of Patient-Focused Drug Development in a Rare Disease

John C Lieske [1], Meaghan A Malley [2], Melissa West [2], Kim Hollander [3], Dawn S Milliner [4]

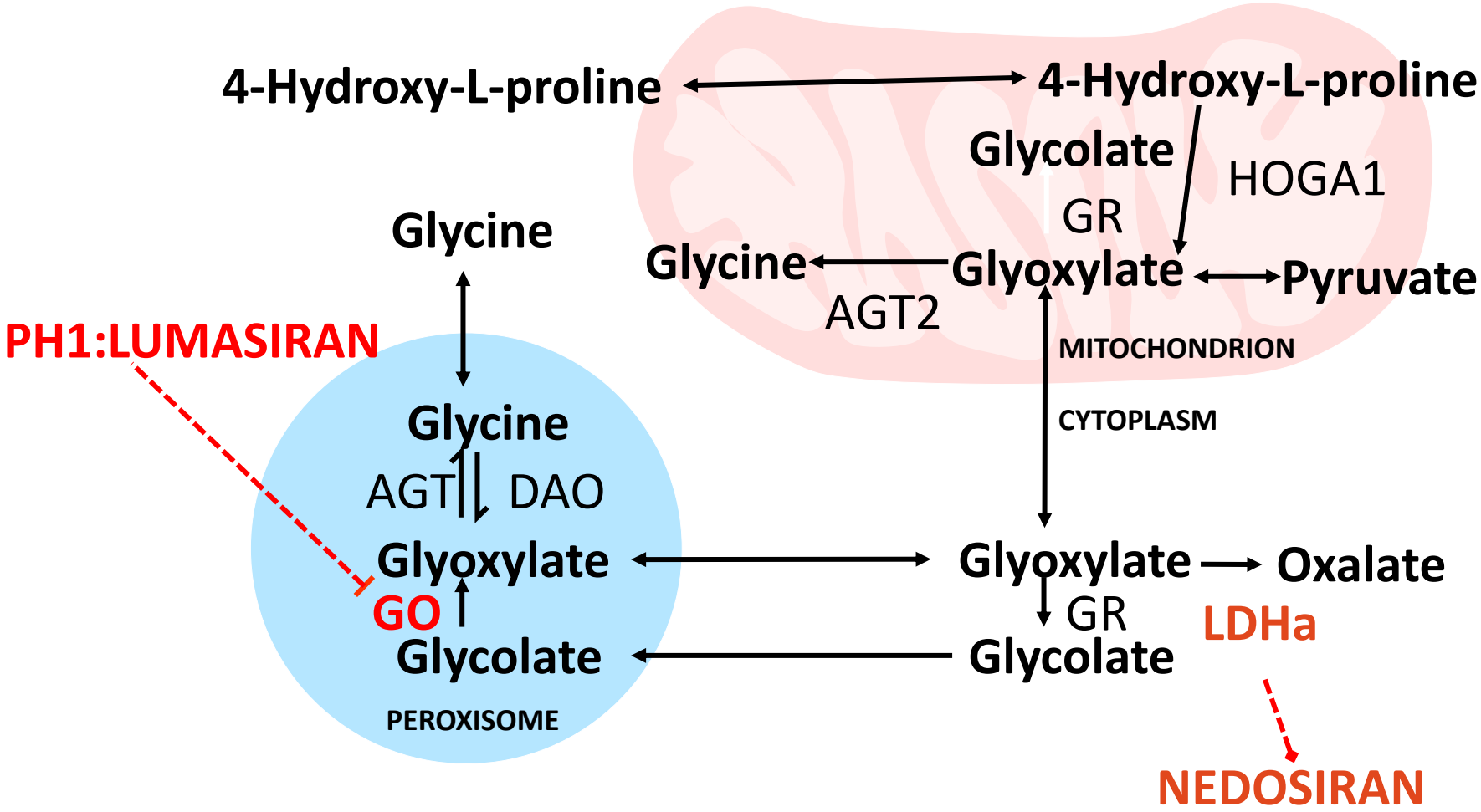
Affiliations + expand

PMID: 34634431 DOI: 10.1053/j.ajkd.2021.09.005

MAYO CLINIC

MAYO CLINIC

siRNA Place in PH1 Therapy



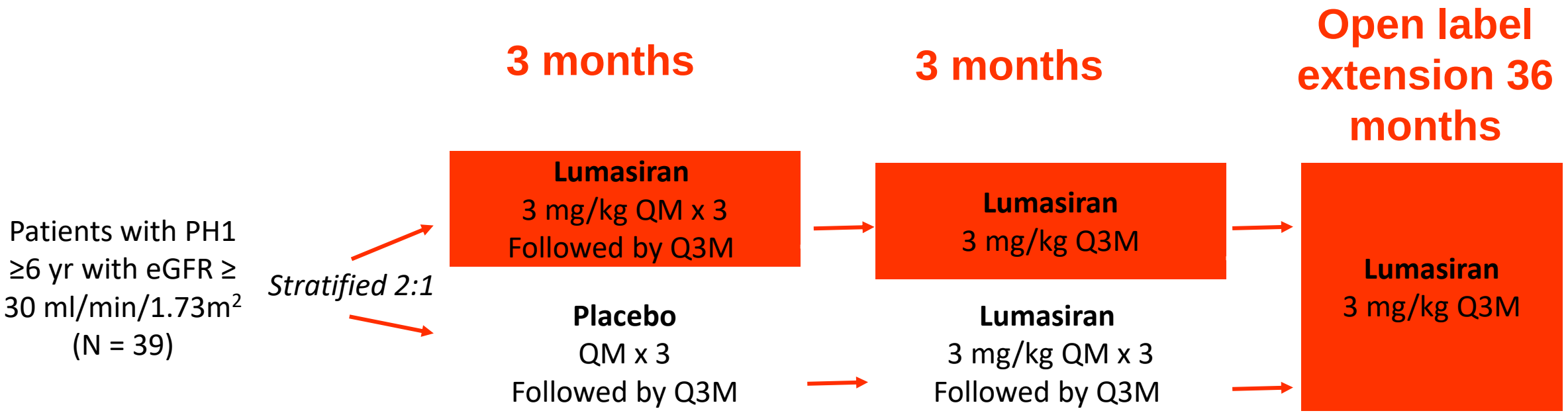
Bacchetta. Clin Kidney J. 2022;15:i17.

PH1, (??? PH2, and PH3):

MAYO CLINIC

ILLUMINATE A

- **Ongoing, phase III trial of subcutaneous lumasiran (small interfering RNA (siRNA silences *HAO1* gene encoding glycolate oxidase)**

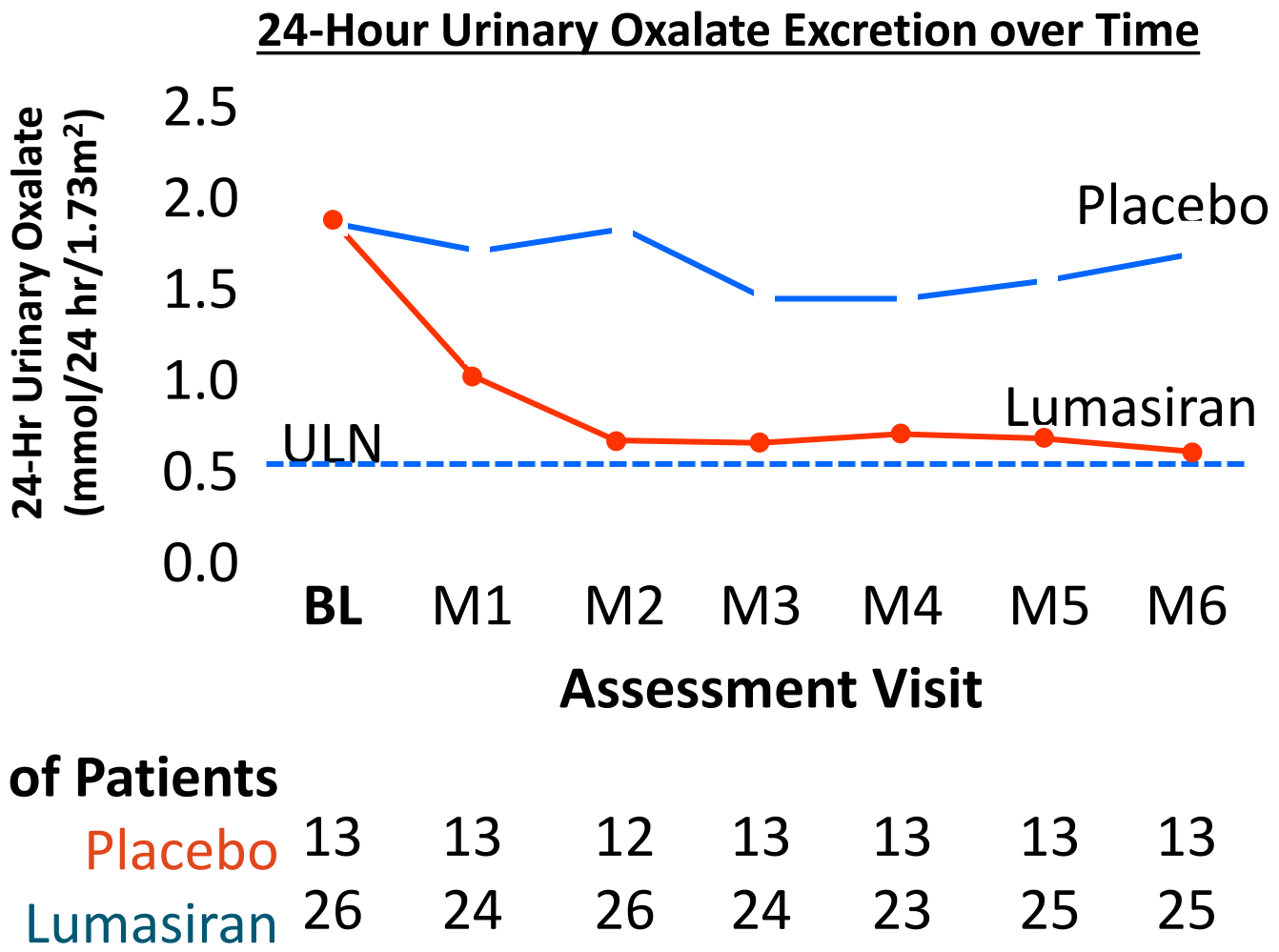


Garrelfs. NEJM. 2021;384:1216

MAYO CLINIC

ILLUMINATE A

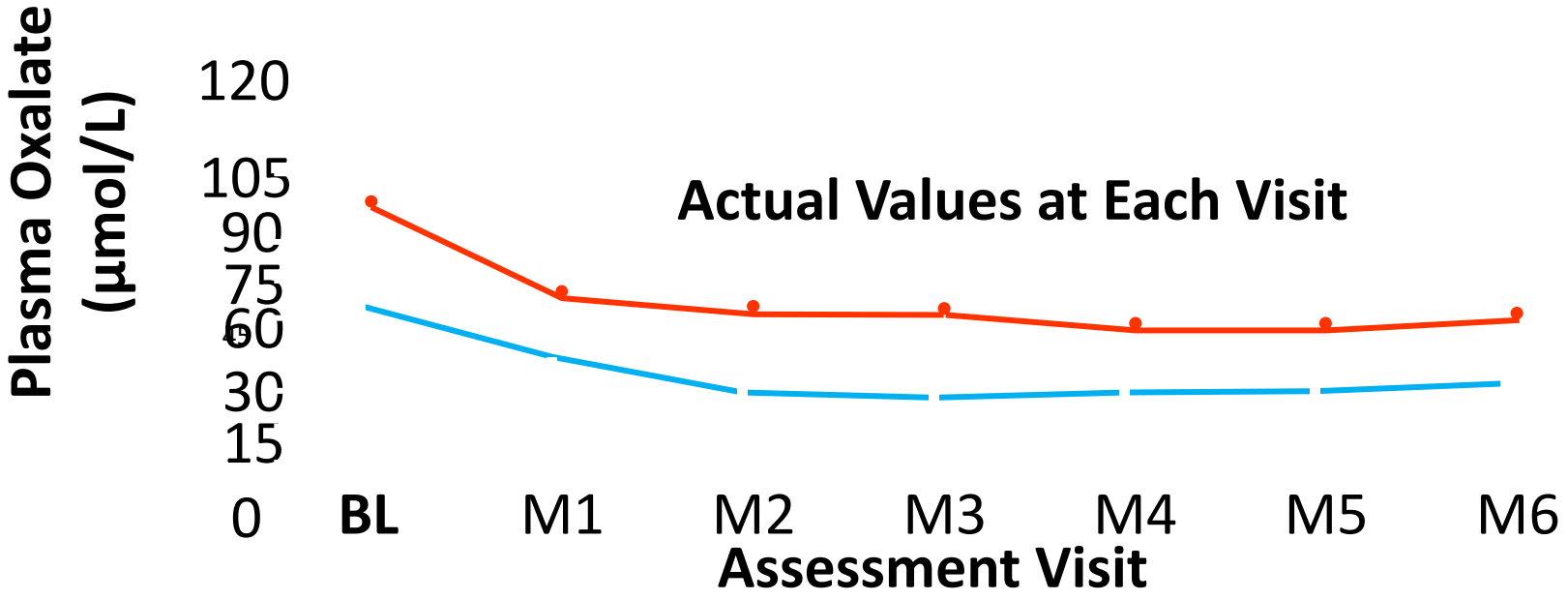
- Mean reduction in urinary oxalate excretion: 65% lumasiran vs 11% placebo (*P* < .001) at 6-mo primary analysis period
- Only transient injection-site reactions reported
- Approved as an Orphan drug 11/2020!



Garrelfs S. N Engl J Med. 2021;384:1216

MAYO CLINIC

ILLUMINATE C (CKD)



No. of Patients	BL	M1	M2	M3	M4	M5	M6
Cohort A	6	6	6	6	6	6	6
Cohort B	15	15	15	15	13	14	15

Cohort B (ESKD; N=15)

Cohort A (CKD4/CKD5; N=6)

Michael M AJKD 2023 81(2):145-15

MAYO CLINIC

Nedosiran

- **Nedosiran: GalNAc-conjugated RNAi treatment that targets hepatic lactate dehydrogenase (LDHa)**
- **RNAi therapy approved for PH; PHYOX program**
  - **PHYOX1 and PHYOX2: completed**
  - **PHYOX3: ongoing; extension trial of PHYOX2 in all types of PH**
  - **PHYOX4: ongoing; phase 1, single dose study in PH3**
  - **PHYOX7: ongoing; safety and efficacy in PH1 or PH2 with severe renal impairment with or without dialysis**
  - **PHYOX8: ongoing; safety, pharmacokinetics, and efficacy in children 0-5 yr with PH and intact kidney function**
  - **PHYOX-OBX: ongoing; natural history in PH3**
- **Approval in US for PH1 in late 2023!**

Goldfarb DS. Urolithiasis. 2023:51:80. Hoppe B. Kidney Int. 2022;101:626. Baum M. Kidney International. 2023;103:207. Coenen M. Abstract Poster1625. Haagensen A. Absract INFO22

MAYO CLINIC

PHYOX2 Results

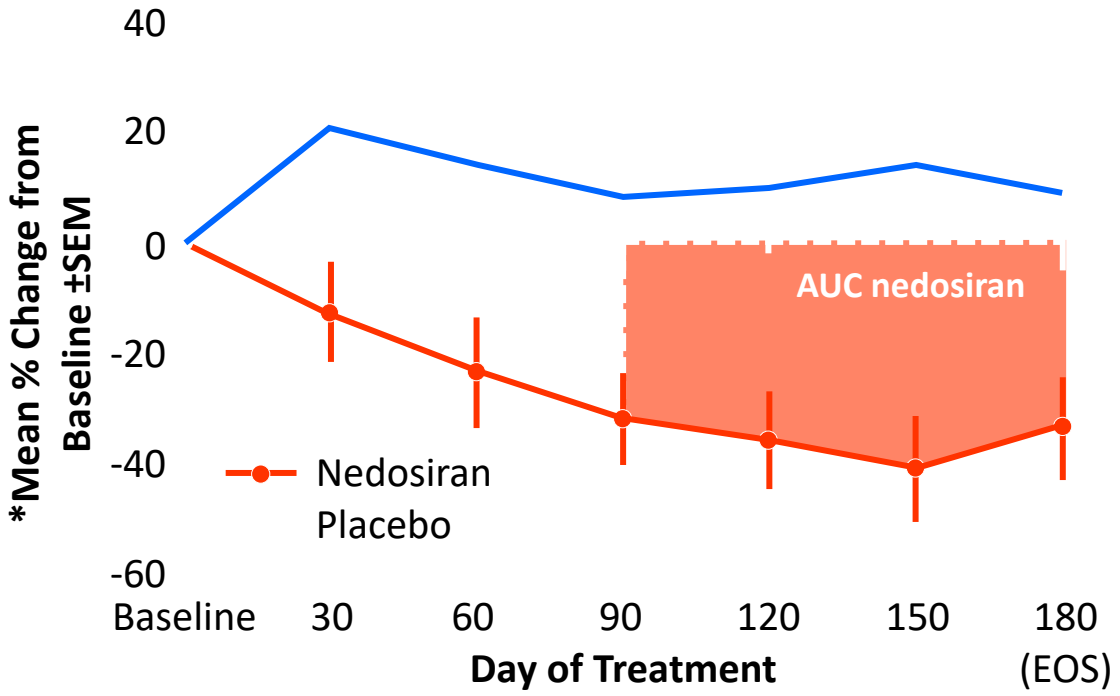
PHYOX2 Met Primary Endpoint Achieving a Significant Reduction in Uox

Mean $AUC_{24\text{-hour Uox}}$ (day 90 to day 180)

Overall mITT Population[1] (PH1 + PH2)

Standardized AUC24-hour Uox from Day 90 to Day	Nedosiran (n = 22)	Placebo (n = 12)
n	22	12
LS Mean (SE)	3507.4 (788.49)	-1664.4 (1189.96)
95% CI for LS Mean	(1961.7, 5053.1)	(-3997.2, 668.4)
LS Mean Difference from Placebo (SE)	5171.7 (1144.07)	
95% CI for Difference from Placebo	(2929.3, 7414.2)	
P-value for Difference from Placebo (2)	**<.0001**	

(1) mITT population = All participants in the ITT population who have at lease one efficacy assessment after the Day 90 dosing visit.
(2) P-value for testing difference from placebo



*LS means from MMRM model using time point estimates
**Multiple imputation (MI) under the missing at random (MAR) assumption was used to handle missing 24-hr Uox data

Baum. Kidney International. 2023;103:207.

MAYO CLINIC

Endpoints for Clinical Trials in Hyperoxaluria: PH Progress to Date

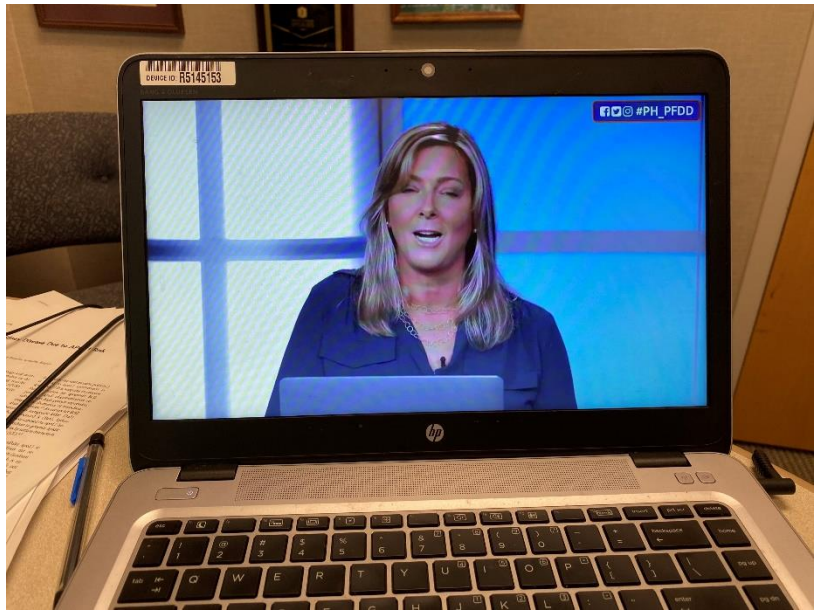
THE VOICE OF THE PATIENT REPORT: PRIMARY HYPEROXALURIA

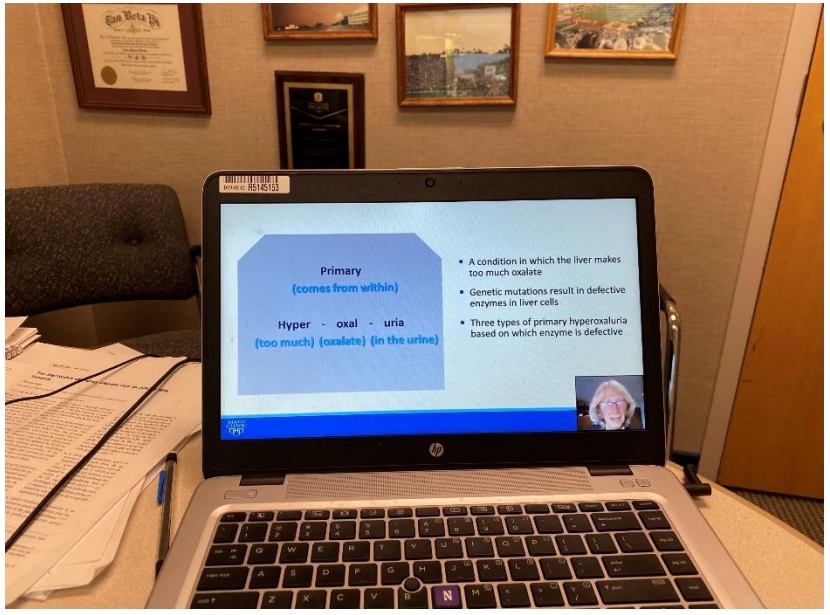
A Report on the Externally Led Patient-Focused Drug Development Meeting Corresponding to FDA's Patient-Focused Drug Development Initiative

Externally Led Public Meeting: October 5, 2020
Report Date:
Hosted by: The Oxalosis & Hyperoxaluria Foundation

Submitted to:
Center for Drug Evaluation and Research (CDER) &
Center for Biologic Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Oxalosis & Hyperoxaluria Foundation
STEPPING STONES TO A CURE





Quality of Life
Collaboration with Dicerna/ Novo Nordisc

- Survey Tools
  - **PH survey** adapted from our Voice of the Patient meeting
  - **The Wisconsin StoneQOL (WisQOL)**
    - The Wisconsin StoneQOL underwent reliability and validity testing in 248 stone formers and demonstrated good internal consistency.
    - This instrument is currently undergoing further testing in a large multicenter trial.
    - Wisconsin StoneQOL scores are expressed on a scale between 0 and 100, with a higher number indicating a better QoL.
  - **Work Productivity and Activity Impairment Questionnaire (WPAI)**
- Administered electronically via REDCAP
- Promoted in OHF sponsored Webinar

Recent PH-related health event

	Living with PH	Parent or caregiver
Kidney stone	14	8
Decreased Kidney function	6	5
Failure to thrive	0	3
Hematuria	3	4
UTI	3	3
Fatigue	5	5
Bone fractures	0	1
Bodily pain	9	7
Nausea or vomiting	2	6
Chills/fever	1	2
Heart or eye problems	0	1
Anxiety or depression	11	8

What outcomes are most meaningful

	Living with PH	Parent or caregiver
Slowing formation of stones	10	7
Stopping formation of stones	14	15
Regaining energy	5	0
Lessening pain	2	0
Improving kidney function	6	5
Decreasing need for superhydration	6	5
Deceasing UTIs	1	0
Stopping disease progression	8	11
Eat what I want	4	1

PH treatment landscape

- **Lumasiran (GO) and Nedosiran (LHDa) seem equally effective for PH1**
  - Unclear why an LDHa approach did not initially work for PH2 or PH3
    - ?Dosing
    - ?pathway nuances
    - ? Genotype: phenotype
- **Other approaches under consideration**
  - Gene therapy
  - Small molecule
  - Multiple targets at once
- **Use of siRNA may allow kidney alone transplant in kidney failure** (without liver transplant)
- **Registries still essential to answer these questions; develop long term outcomes**

Conclusions

- **KHI project has worked as envisioned**
  - Stakeholder identified and engaged
  - ASN staff were instrumental for organizing the group, identifying next steps
  - Robust FDA involvement along the way
- **Project was “ripe” for this process**
  - Strong industry pipeline
  - Pressing need for consensus regarding trial designs for this rare disease population since standard double blind trials with hard endpoints may not be feasible or timely
- **Pooling data in retrospective registries was crucial to understand this monogenic disease**
  - define natural history and disease surrogates
  - Attract industry and technology
  - Support regulatory approval
- **In 2024 there are 2 approved therapies for the devastating disease PH1!**

Hard work towards newer treatments

Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE

RARE KIDNEY STONE CONSORTIUM

rarekidneystones@mayo.edu
www.rarekidneystones.org
1-800-270-4637

Questions?
Lieske.John@mayo.edu

Case Example Reactor Panel

Reactor Panel

Catherine Lerro, PhD, MPH, Oncology Center of Excellence, FDA
Kirtida Mistry, MBBCh, DCH, MRCPCH, Center for Drug Evaluation and Research, FDA
Jill Morris, PhD, National Institute of Neurological Disorders and Stroke, NIH
Catherine Pilgrim-Grayson, MD,MPH, Center for Drug Evaluation and Research, FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

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Thank You!

Meeting materials will be posted on:
www.reaganudall.org

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FOR THE FDA

Leveraging Natural History Data for Rare Disease Drug Development and Approval:

Demonstrated Increased Survival in MoCD Type A Patients Treated With Fosdenopterin

Ronen Spiegel, MD

Clinical Associate Professor, Director of Pediatric B Department,
and Head of Center for Rare Diseases, Emek Medical Center, Afula, Israel

Liza Squires, MD

Former Chief Medical Officer, Origin Biosciences
Sentynl Therapeutics, Inc.

SENTYNL THERAPEUTICS, INC.

Molybdenum Cofactor Deficiency (MoCD) Type A

- Rare, autosomal-recessive in-born error of metabolism caused by pathogenic variants in the *MOCS1* gene[1,2]
- Rapidly progressive, irreversible neurologic damage due to loss of the MoCo-dependent enzyme sulfite oxidase, resulting in neurotoxic sulfite accumulation[1,3]
- Patients rarely survive beyond the first few years of life[1]
- Early diagnosis is crucial[4]
- Biomarkers[1,4]
  - Decreasing, low, or undetectable plasma or urinary uric acid
  - Increased plasma and urine xanthine/hypoxanthine
  - Increased urinary sulfites
  - Increased SSC in the plasma and urine

Signs and symptoms often present in the first hours to weeks of life[1]

Intractable Seizures

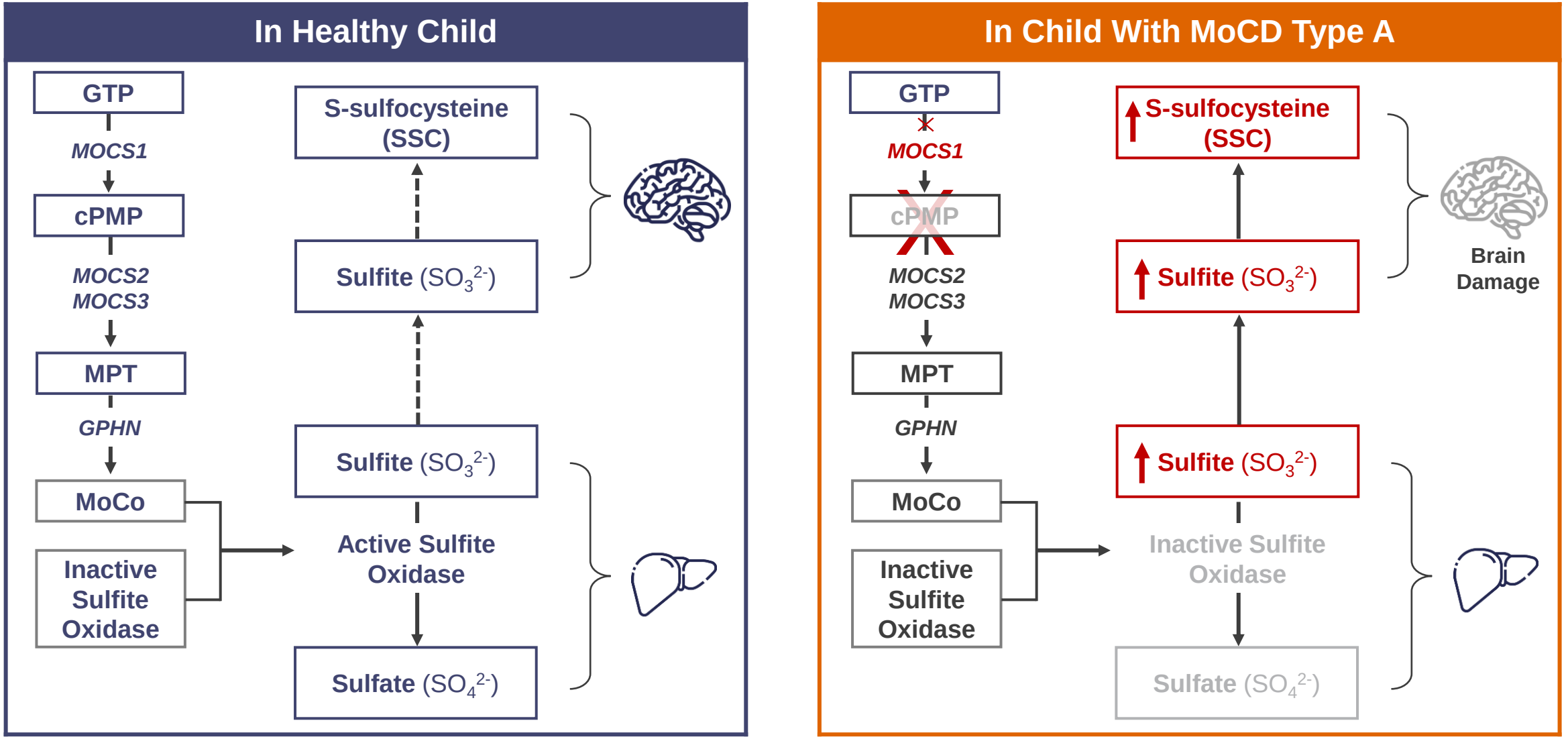
Feeding Difficulties

Abnormal Neuro Examination

MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; *MOCS1*, molybdenum cofactor synthesis 1; SSC, S-sulfocysteine.

1. Atwal PS, et al. *Mol Genet Metab*. 2016;117:1-4; 2. Reiss J, et al. *Hum Mutat*. 2011;32:10-18; 3. Mechler K, et al. *Genet Med*. 2015;17:965-970; 4. Kumar A, et al. *J Clin Invest*. 2017;127:4365-4378

Biochemical Pathology of MoCD[1-3]



cPMP, cyclic pyranopterin monophosphate; *GPHN*, gephyrin; GTP, guanosine triphosphate; MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; *MOCS1/2/3*, molybdenum cofactor synthesis 1/2/3; MPT, molybdopterin.

1. Reiss J, et al. *Hum Mutat*. 2011;32:10-18; 2. Atwal PS, et al. *Mol Genet Metab*. 2016;117:1-4; 3. Kumar A, et al. *J Clin Invest*. 2017;127:4365-4378.

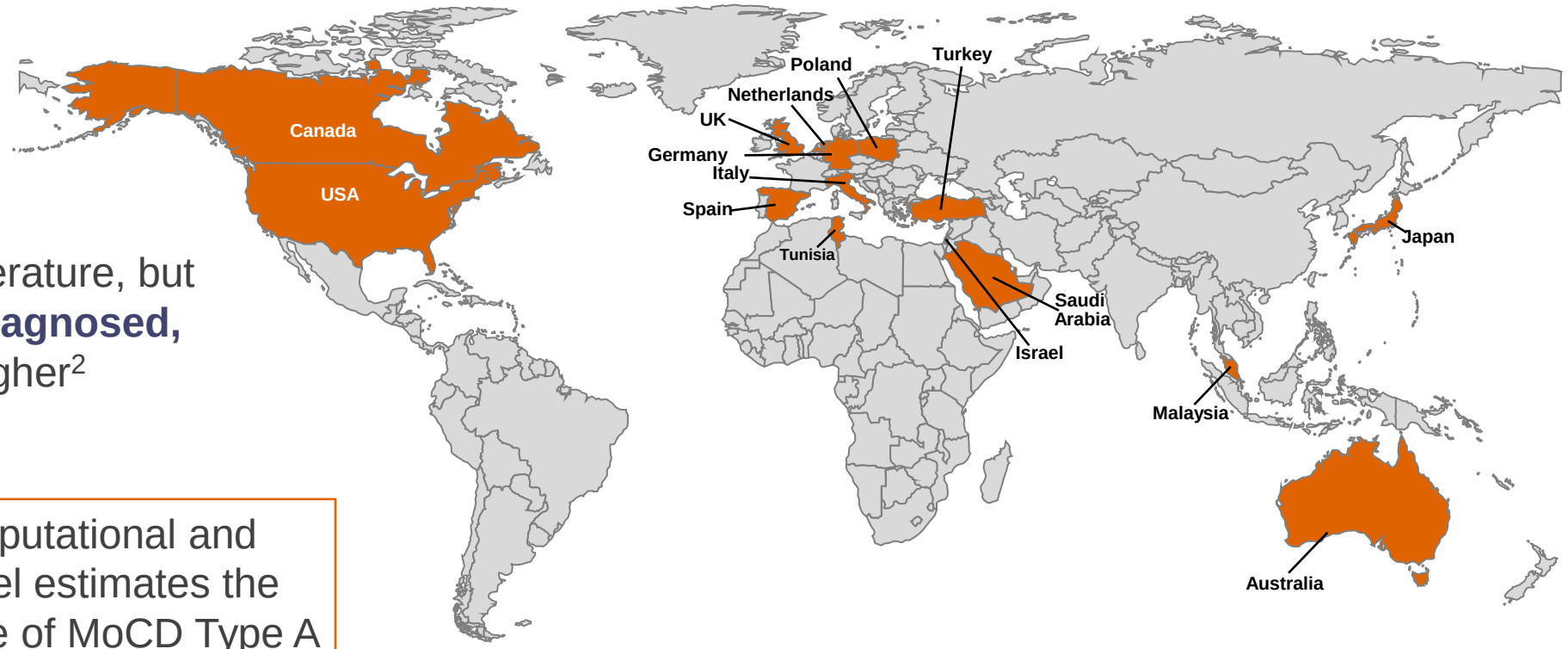
Epidemiology of MoCD: An Ultra-Rare Disease

MoCD Occurs Worldwide, With "Hot Spots" in Multiple Countries[1]

MoCD is an **ultra-rare, pan-ethnic** disease

>100

cases reported in the literature, but **MoCD is likely underdiagnosed,** and numbers may be higher[2]



An iterative computational and biochemical model estimates the worldwide incidence of MoCD Type A is **1:342,000 to 411,000** births[3]

MoCD, molybdenum cofactor deficiency.

1. Spiegel R, et al. A natural history study of molybdenum cofactor and isolated sulfite oxidase deficiencies. Presented at the 2019 SSIEM meeting; September 3-6, 2019; Rotterdam, The Netherlands; 2. NIH. https://ghr.nlm.nih.gov/condition/molybdenum-cofactor-deficiency. Accessed April 25, 2024; 3. Mayr SJ, et al. Forecasting the incidence of rare diseases: an iterative computational and biochemical approach in molybdenum cofactor deficiency type A. Presented at the 2019 SSIEM meeting; September 3-6, 2019; Rotterdam, The Netherlands.

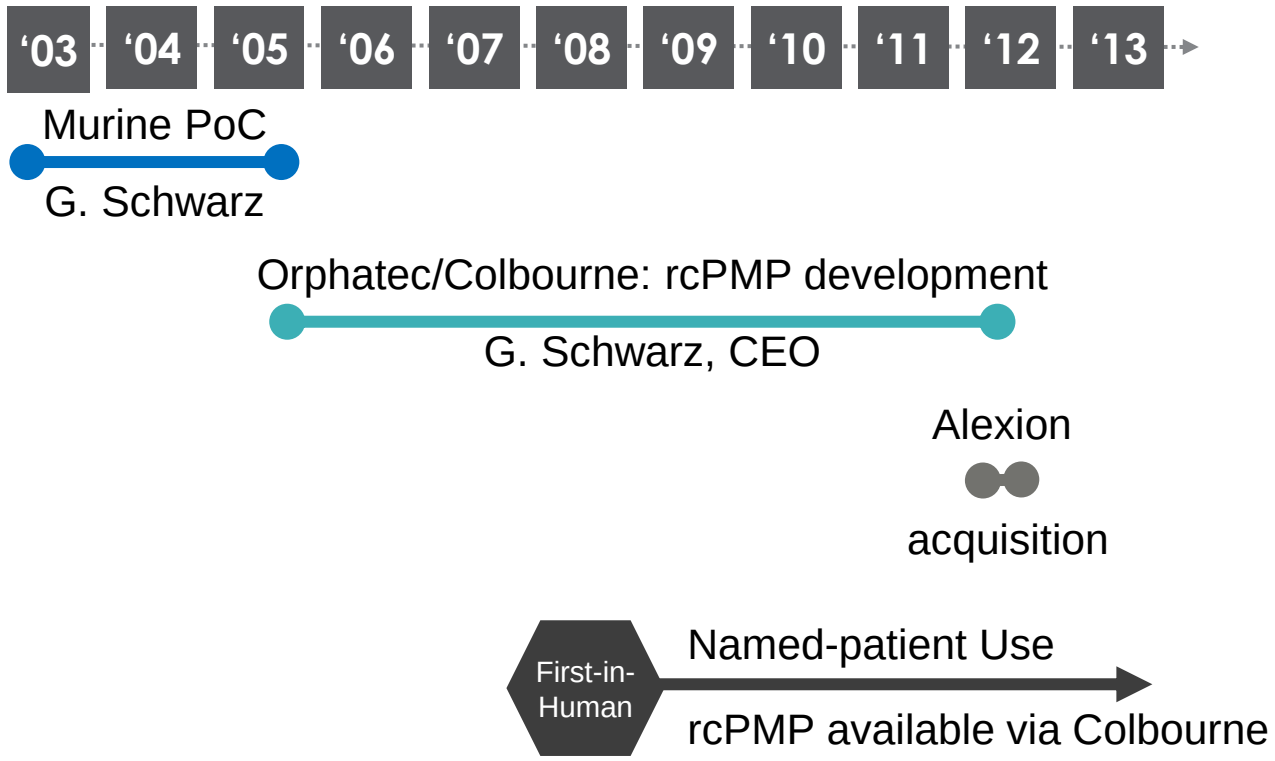
cPMP Replacement Therapy | First-in-Human Experience

- Prof Guenter Schwarz in Cologne, Germany, discovers that **cPMP is produced as a natural chemical byproduct** by *Escherichia coli*
- Selects for **strains of *Escherichia coli*** to manufacture **recombinant form of cPMP**
- Dr Schwarz's lab **tests cPMP in *MOCS1*-knockout mouse model**, showing its potential as replacement therapy
- **First baby is treated** with recombinant cPMP and **shows rapid biochemical response in 2008**
- Colbourne Pharmaceuticals **begins named-patient program** with recombinant cPMP

Dr Guenter Schwarz

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; *MOCS1*, molybdenum cofactor synthesis 1.

First 10 Years of Recombinant cPMP Therapy



- **No approved treatments**; supportive care only
- **No patient advocacy group**
- 10 patients with MoCD Type A **treated with recombinant cPMP** gave consent for retrospective data
- Named-patient use, with **each dose prepared by fermentation** in the lab
- **Unethical to initiate a randomized, placebo-controlled trial** in patients with an ultra-rare and fatal disease

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant cyclic pyranopterin monophosphate.

Natural History Study Design (MCD-502)

Multinational, multicenter, retrospective, and prospective study in patients with MoCD or isolated SOX deficiency

Primary Objective

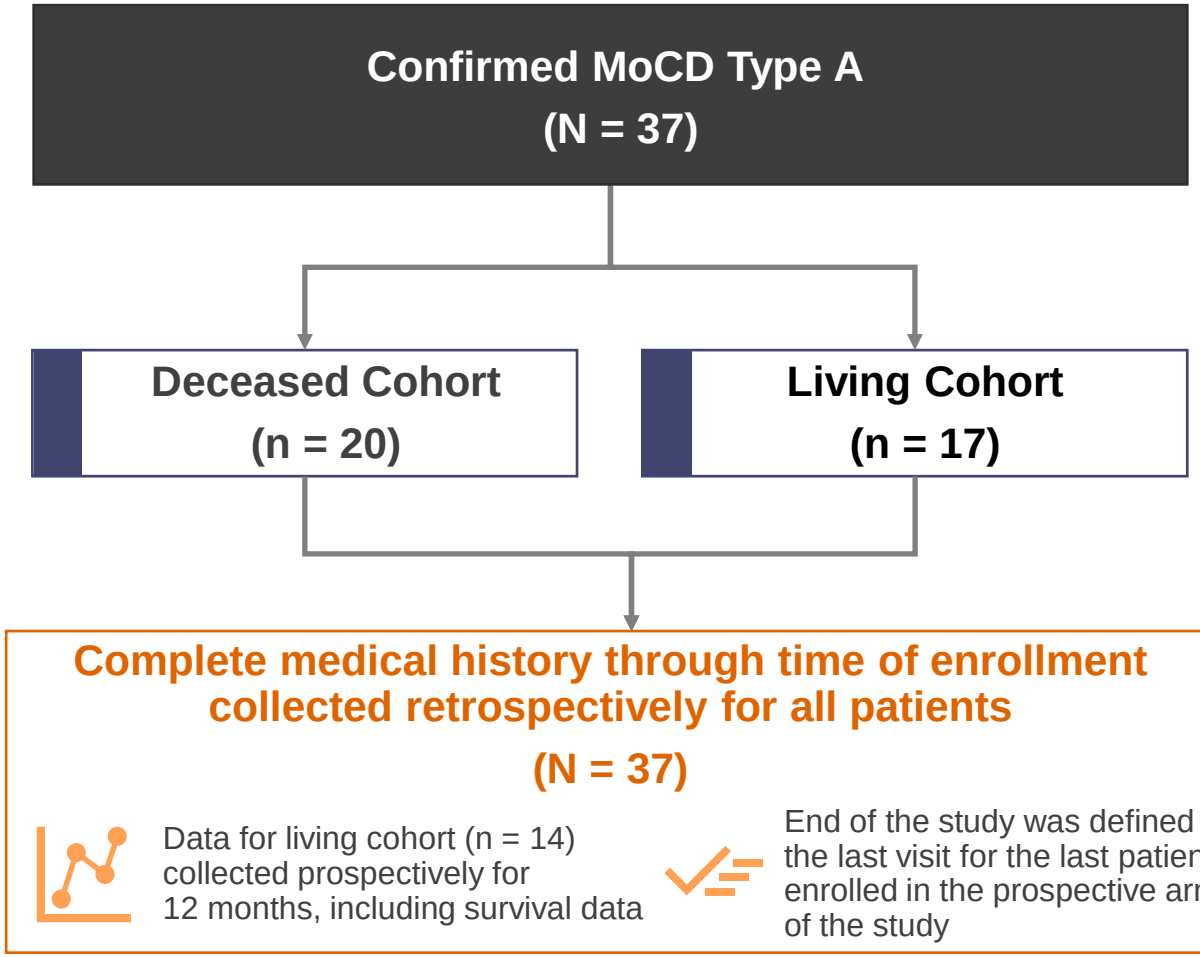
- ✓ To characterize the natural history of patients with MoCD by
  - Documenting the natural progression of the disease
  - Developing a more complete understanding of the phenotype
  - Describing the clinical and biochemical variability of the condition

Inclusion Criteria

- ✓ MoCD or isolated SOX deficiency
  - Clinical and biochemical diagnosis
    - Elevated SSC levels in urine, serum, or plasma
    - Positive urine sulfite dipstick

OR

- ✓ Genetic diagnosis



MoCD, molybdenum cofactor deficiency; SOX, sulfite oxidase.

Natural History Data as a Surrogate Placebo Group

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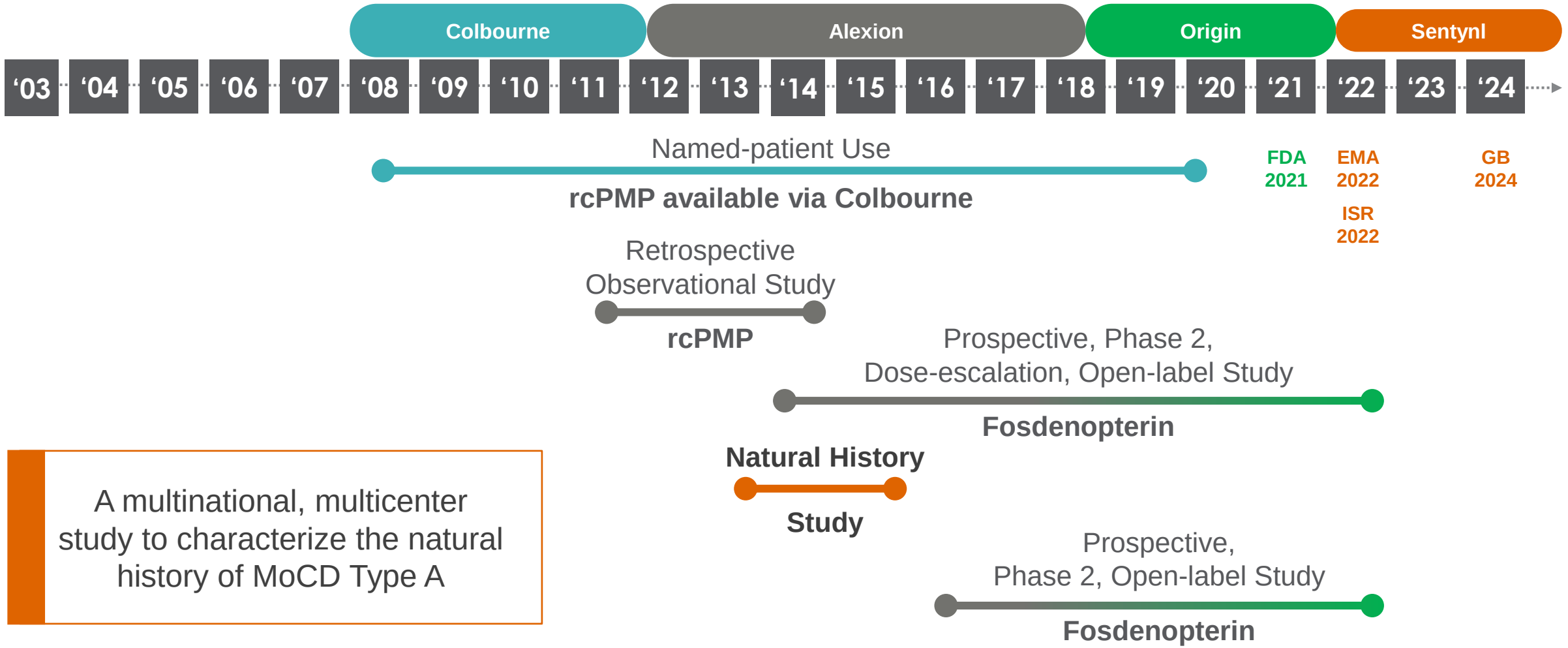
Developed and approved for use in the US only.

Clinical Development of Fosdenopterin (cPMP)



A multinational, multicenter study to characterize the natural history of MoCD Type A

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant cyclic pyranopterin monophosphate.

cPMP Clinical Development Program: Using Natural History Data

Objectives

- Summarize clinical efficacy of cPMP (inclusive of both recombinant cPMP and fosdenopterin)
  - Retrospective, observational study (MCD-501)
  - Phase 2, open-label, dose-escalation study (MCD-201)
  - Phase 2/3 open-label study (MCD-202)
- Interpret the response to cPMP in patients with MoCD Type A
- Compare the survival rate of children with MoCD Type A treated with cPMP replacement therapy with the survival rate of untreated patients with MoCD Type A from a natural history study

Key Variables Assessed in the Clinical Studies

- Baseline characteristics
- Growth parameters
- Overall survival
- GMFCS-ER
- Biomarkers
- Seizures
- Feeding patterns
- Neurologic examinations
- Developmental assessments

cPMP, cyclic pyranopterin monophosphate; GMFCS, Gross Motor Function Classification System-Expanded and Revised; MoCD, molybdenum cofactor deficiency.

Full Analysis Set

Patients with MoCD Type A treated with cPMP replacement therapy (recombinant cPMP and/or fosdenopterin) from 1 retrospective, observational study and 2 prospective, open-label, single-arm studies (N = 13)

VS

Patients with MoCD Type A who were enrolled in a multinational, multicenter, retrospective/prospective natural history study (N = 37)

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

Patient Demographics

Characteristics, n (%)	cPMP-Treated Patients (N = 13)	Untreated Controls (N = 37)
Male	7 (53.8)	28 (75.7)
Female	6 (46.2)	9 (24.3)
Region of birth		
North America	2 (15.4)	3 (8.1)
Europe	6 (46.2)	14 (37.8)
Rest of world	5 (38.5)	20 (54.1)
Age of first MoCD symptom category		
≤ 28 days	13 (100)	33 (89.2)
> 28 days	0	4 (10.8)

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

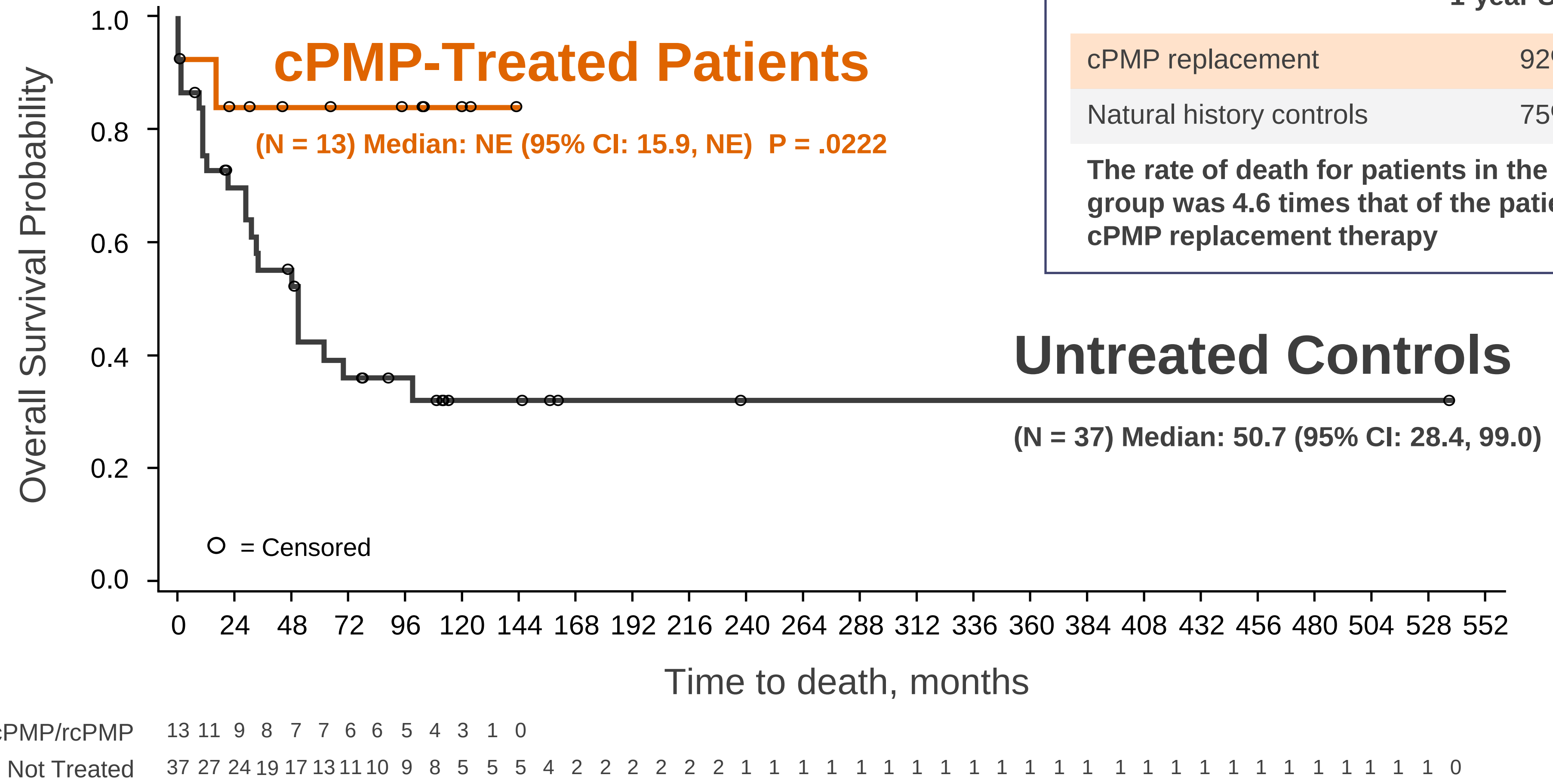
MoCD Presenting Signs and Symptoms

Parameters, n (%)	cPMP-Treated Patients (N = 13)	Untreated Controls (N = 37)
Seizures	9 (69.2)	34 (91.9)
Feeding difficulties	8 (61.5)	31 (83.8)
High-pitched cry	7 (53.8)	16 (43.2)
Exaggerated startle response	5 (38.5)	12 (32.4)
Number of reported other symptoms[a]	21	20

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

[a]Other signs and symptoms included but were not limited to metabolic acidosis, hypertonia, hypotonia, encephalopathy, intracranial hemorrhage.

cPMP Replacement Therapy Improves Overall Survival

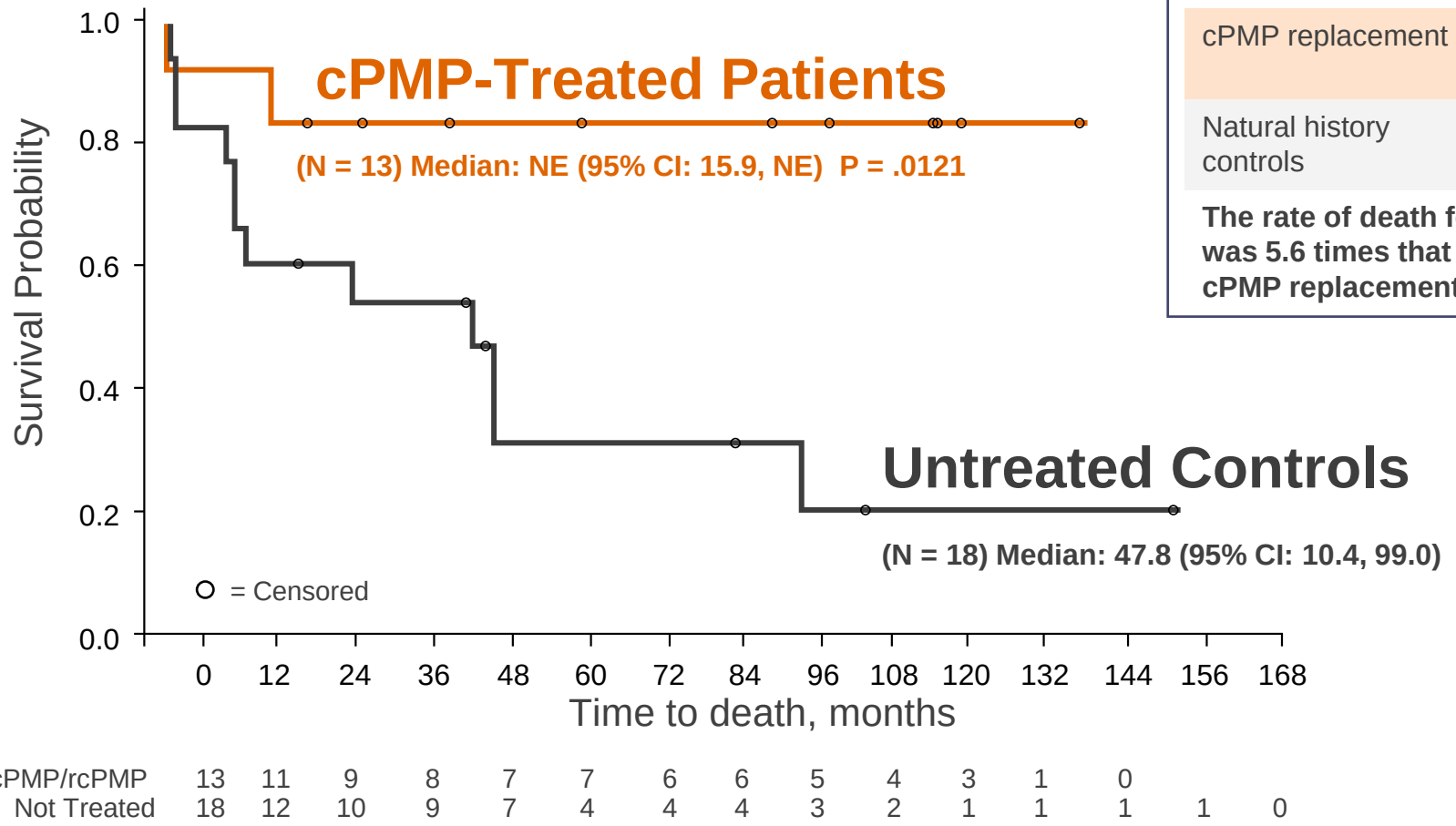


	1-year Survival	2-year Survival
cPMP replacement	92%	84%
Natural history controls	75%	70%

The rate of death for patients in the untreated control group was 4.6 times that of the patients who received cPMP replacement therapy

cPMP, cyclic pyranopterin monophosphate; NE, not evaluable; rcPMP, recombinant cyclic pyranopterin monophosphate.

cPMP Replacement Therapy Improved Overall Survival: Genotype-Matched Controls



	1-year Survival	2-year Survival	3-year Survival
cPMP replacement	92%	84%	84%
Natural history controls	67%	61%	55%

The rate of death for patients in the untreated control group was 5.6 times that of the patients who received cPMP replacement therapy

cPMP, cyclic pyranopterin monophosphate; NE, not evaluable; rcPMP, recombinant cyclic pyranopterin monophosphate.

Urine SSC Levels in cPMP-treated Patients vs Controls

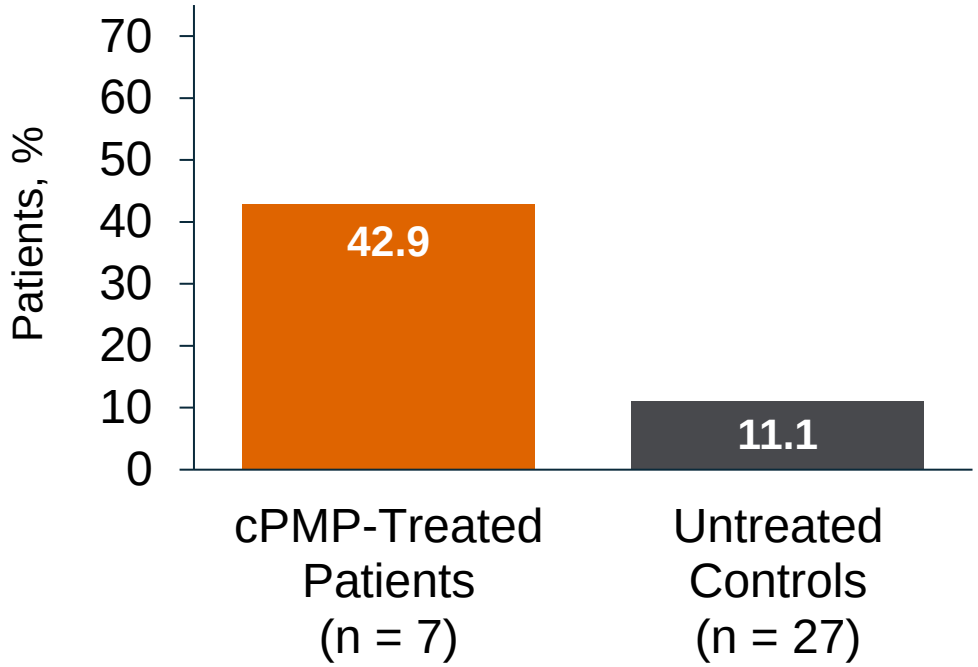
S-sulfocysteine/creatinine, µmol/mmol	cPMP-Treated Patients (N = 12)	Untreated Controls (N = 37)
Baseline, first value, n	12	22
Mean (SD)	181.1 (282.53)	136.3 (87.21)
Last visit, n	12	22
Mean (SD)	11.4 (6.87)	156.6 (100.70)
Change to last visit, n	12	18
Mean (SD)	−169.6 (282.44)	24.8 (104.61)

Pathological values of S-sulfocysteine are > 50 µmol/mmol creatinine

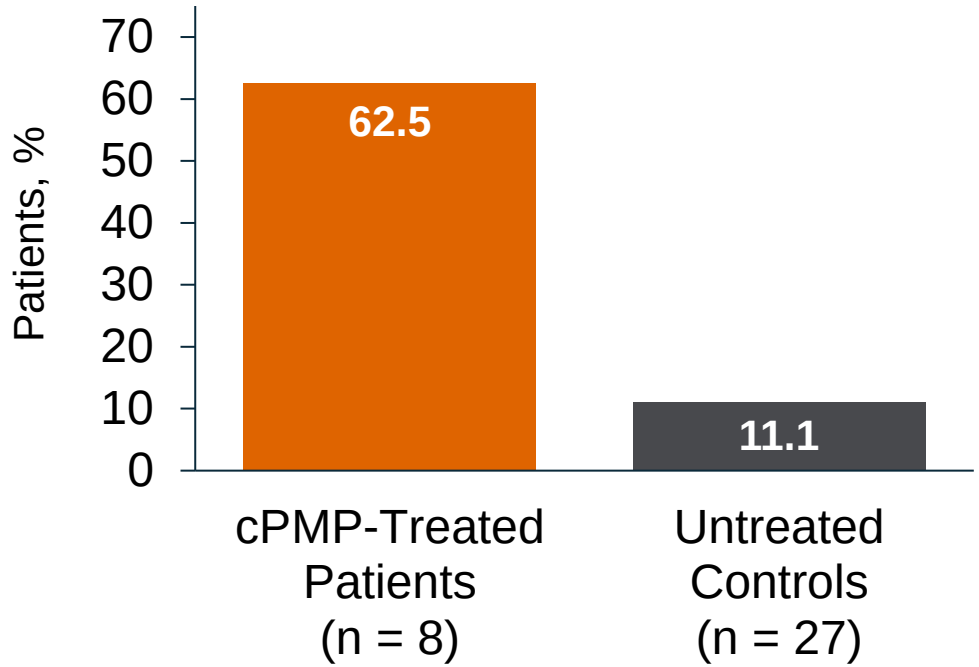
cPMP, cyclic pyranopterin monophosphate.

Sitting Unassisted in cPMP-Treated Patients vs Controls

Unassisted Sitting by 12 Months[a]



Unassisted Sitting at Any Time[a]

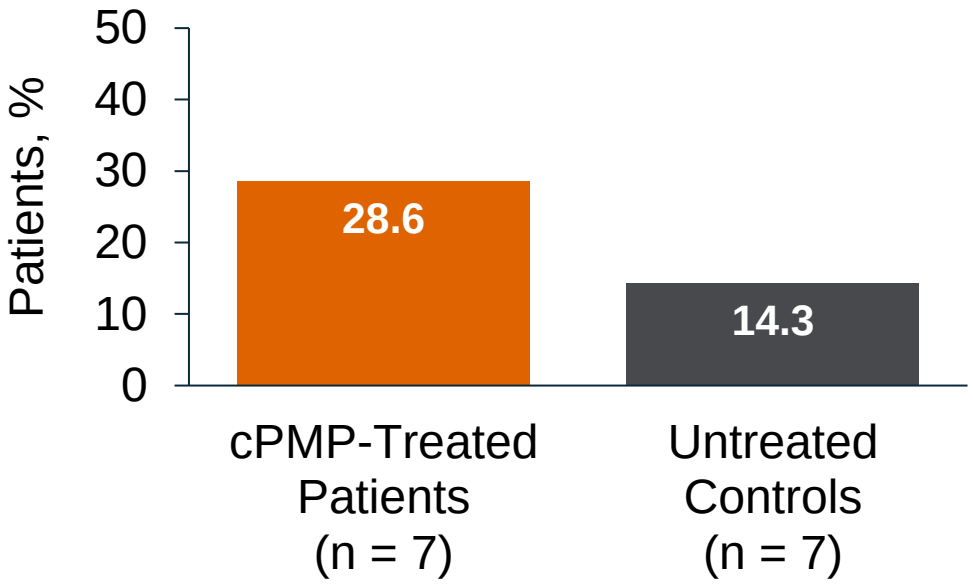


cPMP, cyclic pyranopterin monophosphate.

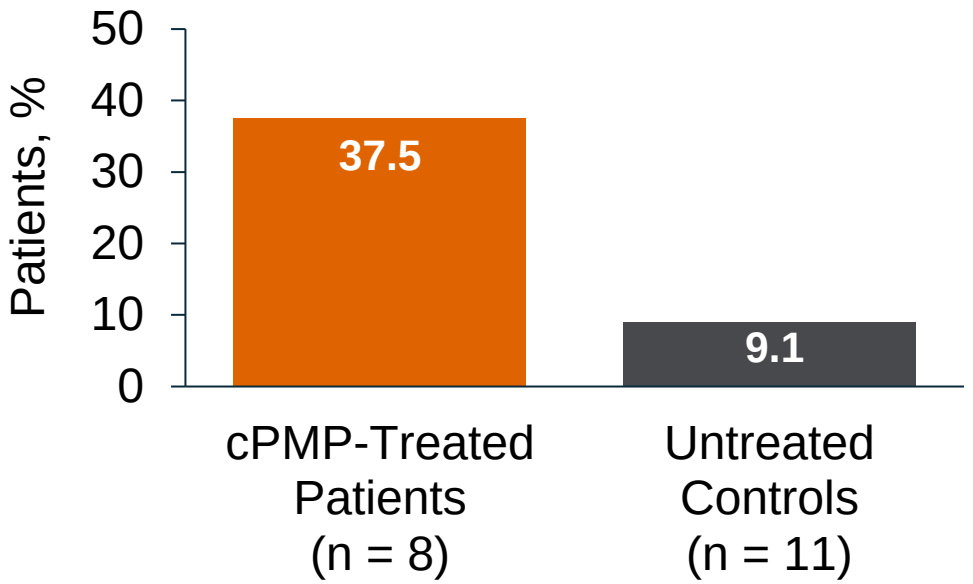
[a]Unassisted sitting was measured as ability to sit independently for 30 seconds.

Achievement of GMFCS Level 1 in cPMP-Treated Patients vs Controls

Achieving GMFCS-ER Level 1 at Month 12



Achieving GMFCS-ER Level 1 at Last Visit

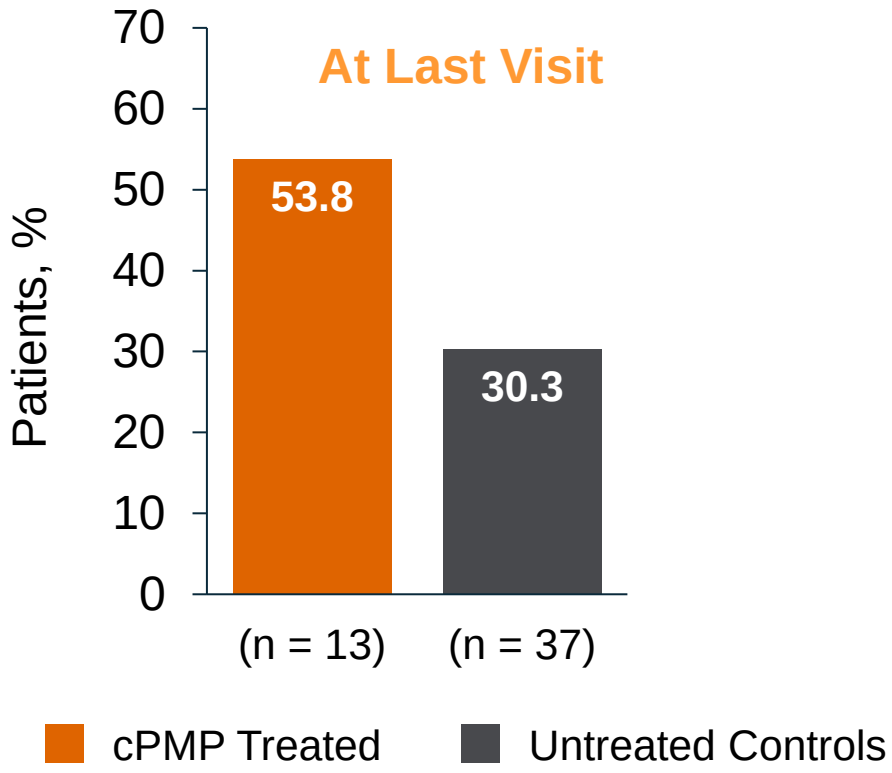


GMFCS-ER Level I represents the highest-rated functioning level on this scale. Children aged 2 and older who are rated as Level I are able to walk independently and, by age 6, can perform higher-level gross motor skills such as running, jumping, and stair climbing.

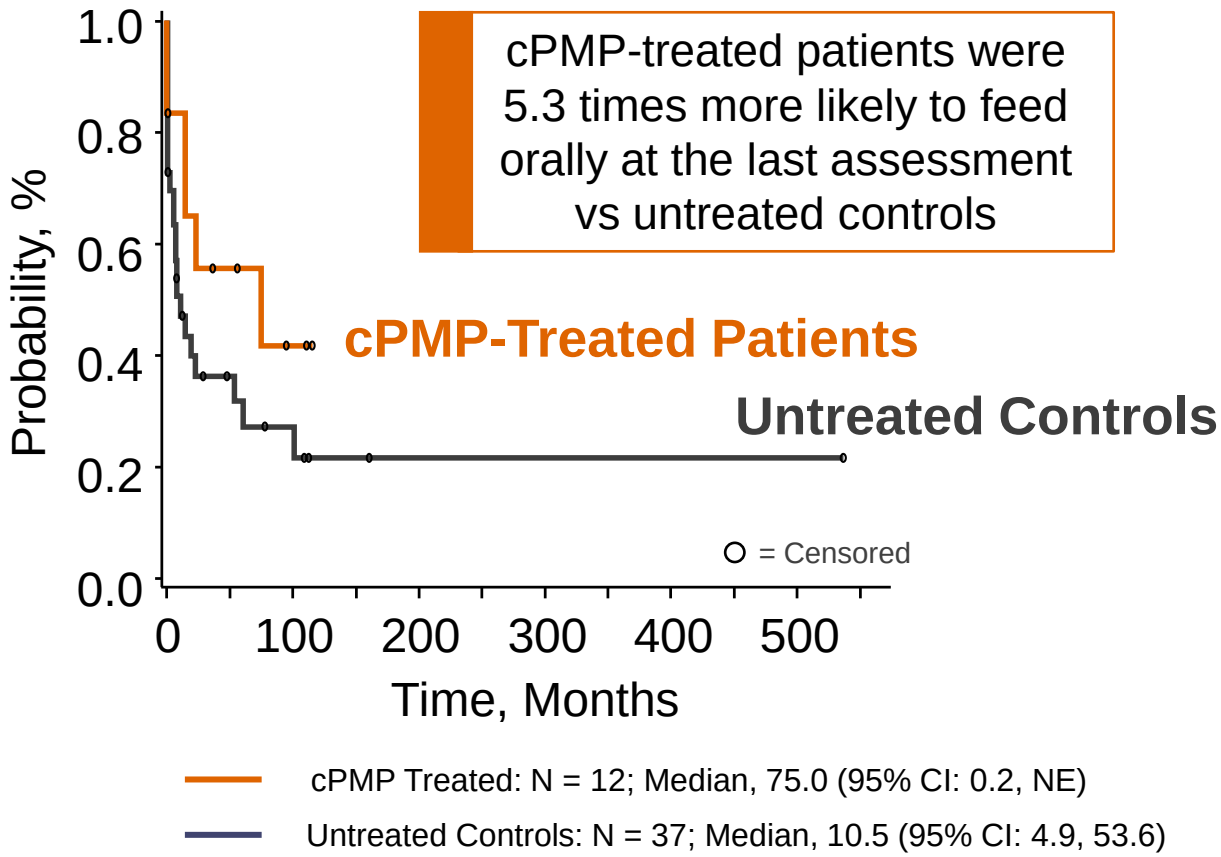
cPMP, cyclic pyranopterin monophosphate; GMFCS-ER, Gross Motor Function Classification System Expanded and Revised.

Oral Feeding in cPMP-Treated Patients vs Controls

Feeding Orally



Time to Sustained Nonoral Feeding[a]



cPMP, cyclic pyranopterin monophosphate; NE = not estimable.

[a]Sustained nonoral feeding was defined as the time at which the patient never subsequently returned to an oral method of feeding

Safety of cPMP

- Most treatment adverse events were mild to moderate, and not related to study drug
  - Most common side effects in fosdenopterin-treated patients were infusion catheter–related complications, pyrexia (fever), viral infection, pneumonia, otitis media (ear infection), vomiting, cough/sneezing, viral upper respiratory infection (common cold/flu-like infection), gastroenteritis (stomach flu-like symptoms), diarrhea, and bacteremia (bacteria in the blood)
  - Side effects for recombinant cPMP-treated patients were similar to the side effects among fosdenopterin-treated patients
- There were no discontinuations or dose modifications due to adverse events
- 2 deaths were noted in the retrospective data
  - 1 patient died due to necrotizing enterocolitis judged as possibly related to study drug
  - 1 patient died due to respiratory syncytial virus pneumonia unrelated to study treatment

Potential for Photosensitivity

- cPMP (fosdenopterin) can make the patient oversensitive to sunlight
- Patients or their caregivers are advised to avoid or minimize patient exposure to sunlight and artificial UV light and adopt precautionary measures when exposed to the sun, including wearing protective clothing and sunglasses, and using broad-spectrum sunscreen with high SPF in patients 6 months of age and older
- If photosensitivity occurs, caregivers/patients are advised to seek medical attention immediately and consider a dermatological evaluation

cPMP, cyclic pyranopterin monophosphate; SPF, sun protection factor; UV, ultraviolet.

Conclusions Leading to the Approval of Fosdenopterin for MoCD Type A

Patients treated with cPMP had **improved overall survival** when compared with untreated historical controls

Patients treated with cPMP **demonstrated decreased urine SSC levels** when compared with untreated historical controls

Additional confirmatory evidence was **provided by the animal model** of MoCD Type A

cPMP (fosdenopterin) was **safe and well-tolerated**

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

Farrell S, et al. *J Inherit Metab Dis*. 2021;44:1085-1087.

Natural History Studies

Provide an opportunity to:

- Characterize ultra-rare and rare disorders
- Develop appropriate disease biomarkers
- Ethically study potentially life-saving treatments
- Facilitate the development of therapeutics in ultra-rare and rare disorders

Thank You

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Case Example: Lumasiran and Nedosiran for Primary Hyperoxaluria

Presenter

John Lieske MD
Mayo Clinic Hospital – Rochester

REAGAN-UDALL FOUNDATION FOR THE FDA

Case Study:
Use of registry data to define the natural history of primary hyperoxaluria

FDA Symposium
May 13, 2024

John C Lieske, MD, FASN

Mayo Clinic Division of Nephrology and Hypertension

RARE KIDNEY STONE CONSORTIUM

Disclosures

Relevant Financial Relationship(s)

Grant funding* and consulting@:

Allena*@

Alnylam*@

BioMarin @

Chinook @

Dicerna/ Novo Nordisc*@

Federation Bio@

Novobiome@

Orfan Bridgebio@

Oxidien @

OxThera*@

Precision Biosciences @

Synlogic*@

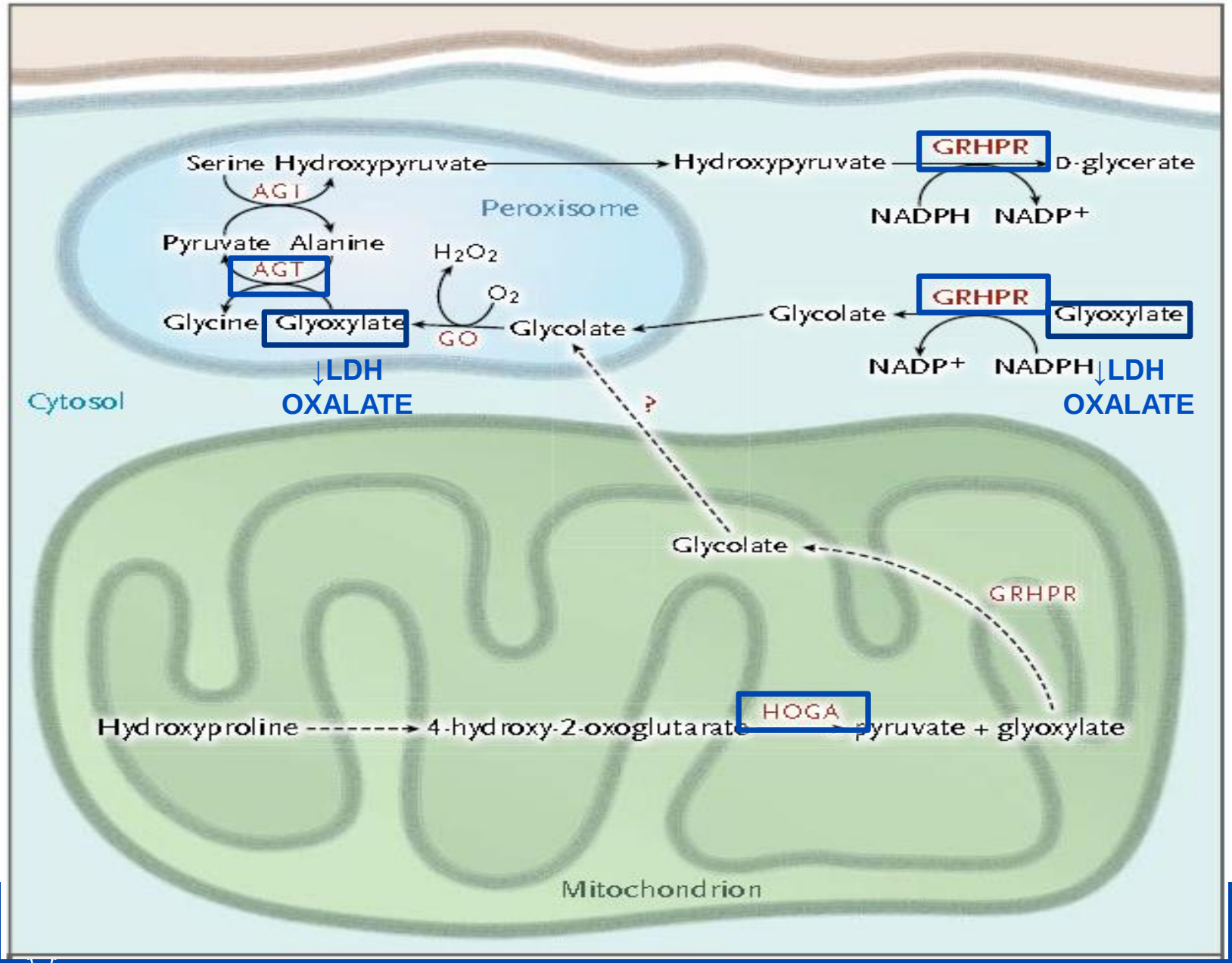
Off Label Usage

None

Outline

- Primary Hyperoxaluria
- Key Role of Patient Advocacy Group (PAG) and ASN to develop registry, disease background, and ultimately engage FDA under the auspices of the Kidney Health Initiative
- Key natural history features that informed treatment efficacy measures
- Ultimate outcome of efforts

Primary Hyperoxaluria: Hepatic oxalate overproduction



Gene mutation

PH type 1 (30%): *AGT*
PH type 2 (10%): *GRHPR*
PH type 3 (60%): *HOGA*

Enzymes implicated

PH 1 and PH2:
Cytosolic LDH
Glyoxalate → Oxalate

PH3: ??

Ancillary tests

PH1: ↑ glycolate
PH2: ↑ glycerate
PH3: ↑ 4-hydroxyglutarate

Hyperoxaluria

High concentrations of oxalate in urine lead to stones, nephrocalcinosis, CKD, and kidney failure, and can result in systemic oxalosis causing multiorgan damage.

Types of Hyperoxaluria

- Primary hyperoxaluria (PH) due to increased hepatic oxalate production caused by any of three known genetic defects in glyoxylate and hydroxyproline metabolism in the liver.

  Rare disease: 1-3 per million population

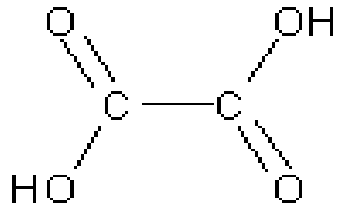
- Enteric hyperoxaluria (EH) caused by fat malabsorption which leads to high absorption of oxalate in small intestine.

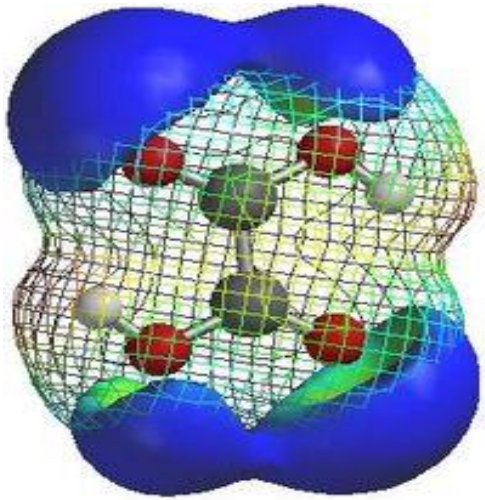
  Estimated to affect ~150,000 patients

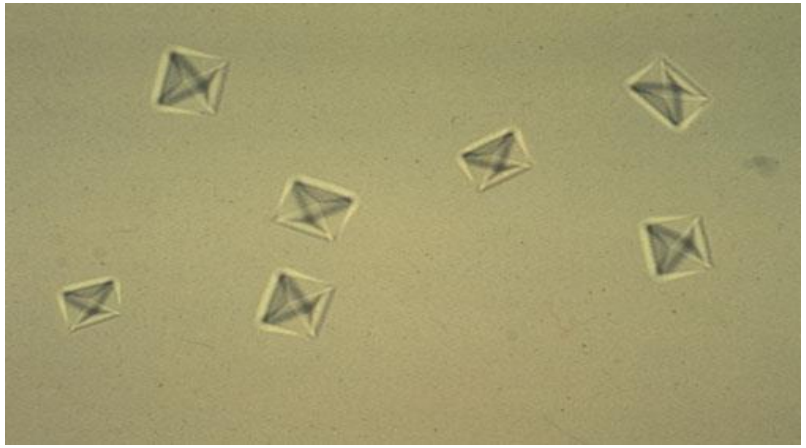
What is oxalate?

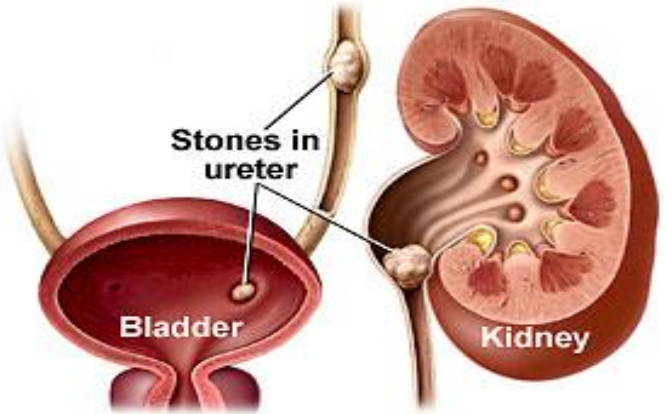
TABLE 3. *Foods with high oxalate content*

Food	Serving size	Oxalate (mg)
Rhubarb	½ cup	720–1032
Spinach	½ cup	570–675
Beetroot	½ cup	573
Swiss chard	½ cup	568
Pokeweed	½ cup	390
Cocoa powder	1 ounce	174
Okra	½ cup	117
Wheat germ	1 ounce	75
Tea (4 min infusion)	1 teaspoon	72
Green gooseberries	½ cup	66
Collards	½ cup	63
Crackers, soybean	1 ounce	58
Pecans	1 ounce	56
Peanuts	1 ounce	52
Grits, white corn	½ cup	50
Sweet potato	½ cup	34
Chocolate	1 ounce	33
Black raspberries	½ cup	32
Leek	½ cup	23
Celery	2 stalks (80 g)	16
Rutabaga	½ cup	16
Eggplant	1 cup	15
Summer squash	½ cup	14
Blackberries	½ cup	13
Green beans	½ cup	11
Blueberries	½ cup	11
Currants, red	½ cup	11
Dewberries	½ cup	10
Black pepper	1 tsp	8
Green pepper	½ cup	8









Time machine travel to 2016

Increasing possibility for clinical trials in oxalate-related diseases

- Alter gastrointestinal oxalate absorption and/or secretion
  - Manipulate the gastrointestinal microbiome
  - Oral oxalate degrading enzymes
- Inhibition or manipulation of hepatic enzyme pathways
  - siRNA
    - Small molecules
    - Chaperones

2016 OHF Annual Scientific Advisory Board meeting

- **Primary and enteric hyperoxaluria are rare diseases**
  - Clinical trials with renal function, CKD, kidney failure, or kidney stones are not feasible
  - The FDA is increasingly receptive to alternatives to these hard clinical endpoints, as long as well-justified
    - Duchenne muscular dystrophy is one example
- Idea of an FDA white paper on oxalate studies discussed with scientific, industry, and patient representatives at a half day meeting.
  - Concept enthusiastically endorsed by all present
  - Despite being an “unfunded mandate” efforts moved forward…

OHF team to DC in Spring 2016

D Milliner

J Lieske

T Lowther

K Hollander

J Bertarelli

Stop 1: ASN

- The mission of KHI is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which the FDA and the greater nephrology community can interact to optimize the evaluation of drugs, devices, biologics, and food products.

https://www.asn-online.org/khi/

Who can join KHI?

- KHI is a collaborative environment for all stakeholders in the kidney community to help foster development of optimum therapies for diseases that affect the kidney. KHI members may include:
  - Patient organizations
  - Health professional organizations
  - Research Institutions
  - Foundations
  - Pharmaceutical and biotechnology companies
  - Device manufacturers
  - Dialysis providers
  - US and international government agencies

Current KHI projects (2016)

- Advancing Technologies to Facilitate Remote Management of Patient Self-Care in Renal Replacement Therapy (RRT)
- Clinical Trial Endpoints for Dialysis Vascular Access
- Data Harmonization in Kidney Transplant
- Data Standards in Diabetic Kidney Disease
- Development of a Roadmap for Innovations in Renal Replacement Therapy (RRT)
- **Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy**
- Overcoming Barriers to Drug Development in Children with CKD
- Pragmatic Trials in Dialysis: Challenges and Opportunities
- Prioritizing Symptoms of ESRD Patients for Developing Therapeutic Interventions
- Regulatory Policies and Positions Affecting Device Approval in the US: Tools to Assess the Process and Foster Device Development for Patients with Kidney Disease
- Workshop to Elucidate Role of Patient Preferences in Support of CDRH Regulatory Actions in Kidney Disease

Stop 2: FDA meeting

- Well attended “1 hr” meeting with ~20 FDA representatives
- In general seemed receptive to our message that large clinical trials with hard endpoints are not feasible
- There is a mechanism to submit paperwork to validate a surrogate endpoint (like oxalate), but was mentioned maybe not be the best approach
- No firm advice r/e next best steps

Kidney Health Initiative (KHI)

- OHF proposal submitted for mid 2016 cycle to help with developing guidance for appropriate endpoints in hyperoxaluria trials
- Well received but ultimately not approved
- Feedback: Not eager to take on “validation of a surrogate endpoint” with all the lab work, etc. that effort might entail
- Plan to reapply for Spring 2017 cycle, and attend stakeholders meeting in May 2017
  - OHF and several officers are now KHI members

OHF SAB meeting 2017

- While waiting to reapply to KHI, we have decided now is the time to seize our momentum and work on a summary document that will:
  - be used when we engage the FDA in further discussion, hopefully culminating in the request from them for us to develop a guidance document
  - form the basis (or starting point) for this comprehensive guidance document

Workgroups

1	Biology of oxalate, including biosynthetic pathways
2	Renal and gastrointestinal oxalate transport
3	Genetics of Primary Hyperoxaluria
4	Pathophysiology of enteric hyperoxaluria
5	Diagnosis of hyperoxaluria, including algorithms and laboratory issues
6	Pathophysiology of calcium oxalate kidney stones and nephrocalcinosis in hyperoxaluric states
7	Treatment strategies for hyperoxaluria- current and future
8	The clinical needs for hyperoxaluria trials from the patients' perspective

Group Leader	Group Members					
T Lowther	B Cellini	J Knight	C Danpure	T McGregor	A Quinn	
M Hatch	Rholmes	D Goldfarb	D Sas	E Lindner		
D Milliner	E Salido	Y Frishberg	M Baum			
J Lieske	A Kausz	J Asplin	D Assimos			
J Asplin	D Milliner	Y Frishberg	M Hatch	J Knight	A Kauz	
D Goldfarb	D Sas	R Holmes	J Lieske	A Kausz	E Lindner	
M Baum	D Assimos	T Lowther	T McGregor	E Salido	B Cellini	A Quinn
J Lawrence	B Kissinger	K Hollander	J Subramanyam	I Aquino		

MAYO CLINIC

Subsequent Timeline

- February 25, 2017
  - Working meeting
- March-April 2017
  - Small group follow-up
- May-June 2017
  - Roll into one document
- July 2017
  - Discussions at OHF workshop

KHI Project

- **May-Sept 2017** Application submitted to KHI and approved
- Initial stakeholders meeting **Feb 22, 2018.**
  - Good representation from industry, academia, patients and families.

Specific Objectives

1. Consensus recommendations for potential surrogate endpoints

- Identify candidate surrogate markers for clinical trials in hyperoxaluria
- Critically assess candidate measures for appropriateness
- Identify gaps in the data and future research needs to fully establish acceptable biochemical marker(s) for clinical trials in hyperoxaluria

2. Develop recommendations for industry guidelines for expedited clinical trials and approvals

- Identify characteristics of patients with differing risks of progression
- Develop a consensus statement of risk tolerance of hyperoxaluric patients/families for clinical trial participation and medication use

Surrogate End Points for Clinical Trials

***Endpoint markers for clinical trials are expected meet the following criteria*:**

- **Biologic plausibility** that the biochemical marker is on the biologic pathway to a hard endpoint such as kidney failure or death
- Epidemiologic or other **data showing consistent association between the biochemical marker and the clinical outcome** of interest
- Any available **data from clinical trials showing that the effects of treatment on the candidate marker largely account for their effects on clinical outcome**
- **An assessment of quantitative effect** on the endpoint marker that is **needed to be clinically significant**

PH Registry Enrollment March-2023

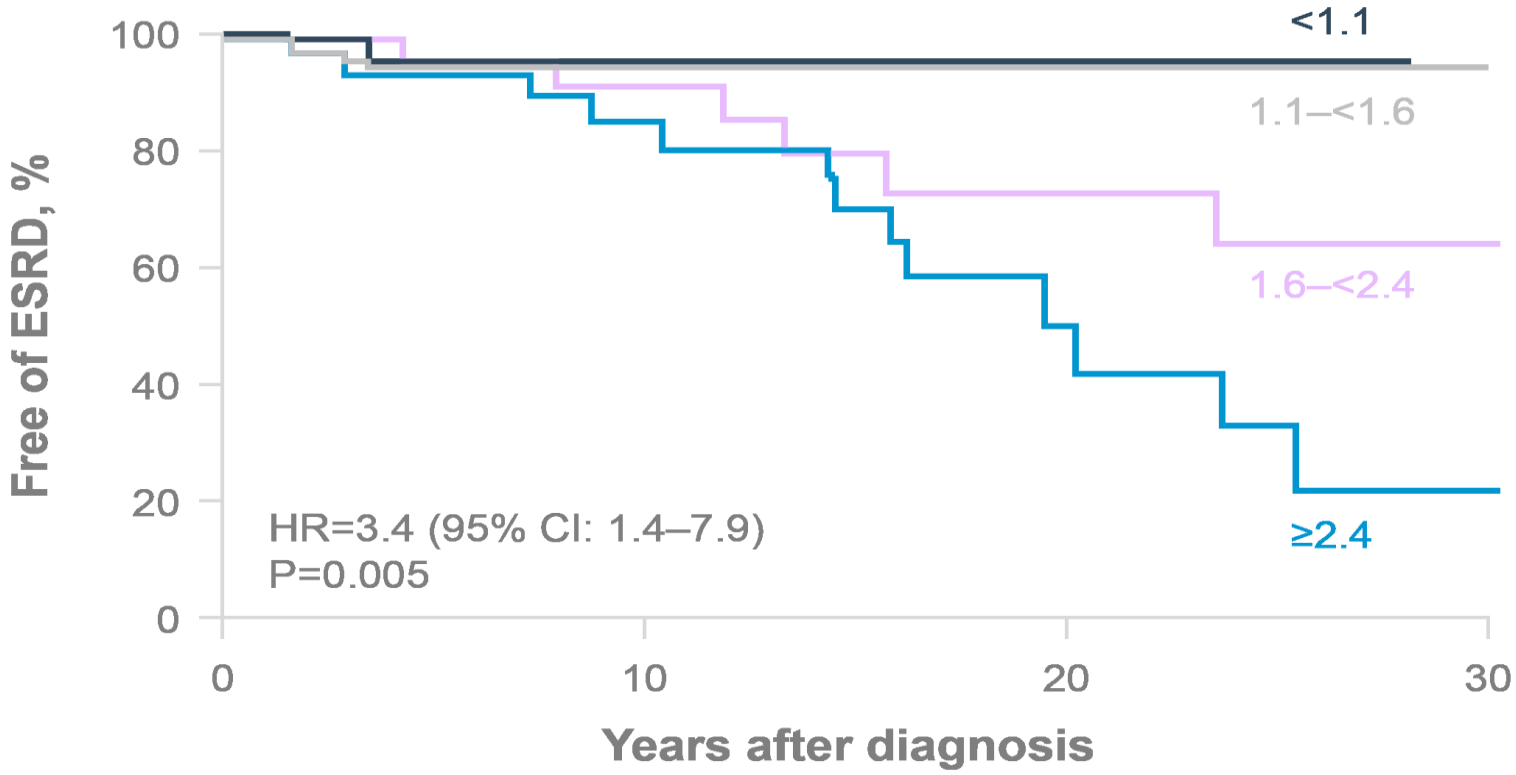
	Total (N=603)
Sex, n (%)	
M	**326 (54.4%)**
F	**273 (45.6%)**
Not Recorded	**4**
Race, n (%)	
Am. Indian	**3 (0.5%)**
Asian	**126 (20.9%)**
African American	**14 (2.3%)**
Hawaiian	**2 (0.3%)**
White	**357 (59.2%)**
Not Disclosed	**101 (16.7%)**
Ethnicity, n (%)	
Hispanic or Latino	**34 (5.6%)**
Non Hispanic or Latino	**339 (56.2%)**
Not Disclosed	**230 (38.1%)**
Deceased, n (%)	
No	**534 (88.6%)**
Yes	**69 (11.4%)**

PH Registry Enrollment March-2023

Renal Failure, n (%)	
No	**349 (57.9%)**
Yes	**254 (42.1%)**
Patients with Serum Labs	
N	**539**
Mean (SD)	**7.5 (7.70)**
Median	**5**
Range	**1.0, 46.0**
Patients with Urine Labs	
N	**490**
Mean (SD)	**6.6 (6.48)**
Median	**4**
Range	**1.0, 30.0**
Year LFU, n (%)	
<=2019	**417 (69.2%)**
2020	**62 (10.3%)**
2021	**45 (7.5%)**
2022	**67 (11.1%)**
2023	**12 (2.0%)**
FU Years	
N	**603**
Mean (SD)	**9.1 (11.59)**
Median	**4.9**
Range	**0.0, 64.1**

Urine oxalate is a key risk factor for kidney failure in PH

RARE KIDNEY STONE CONSORTIUM



UOx quartile mM/day

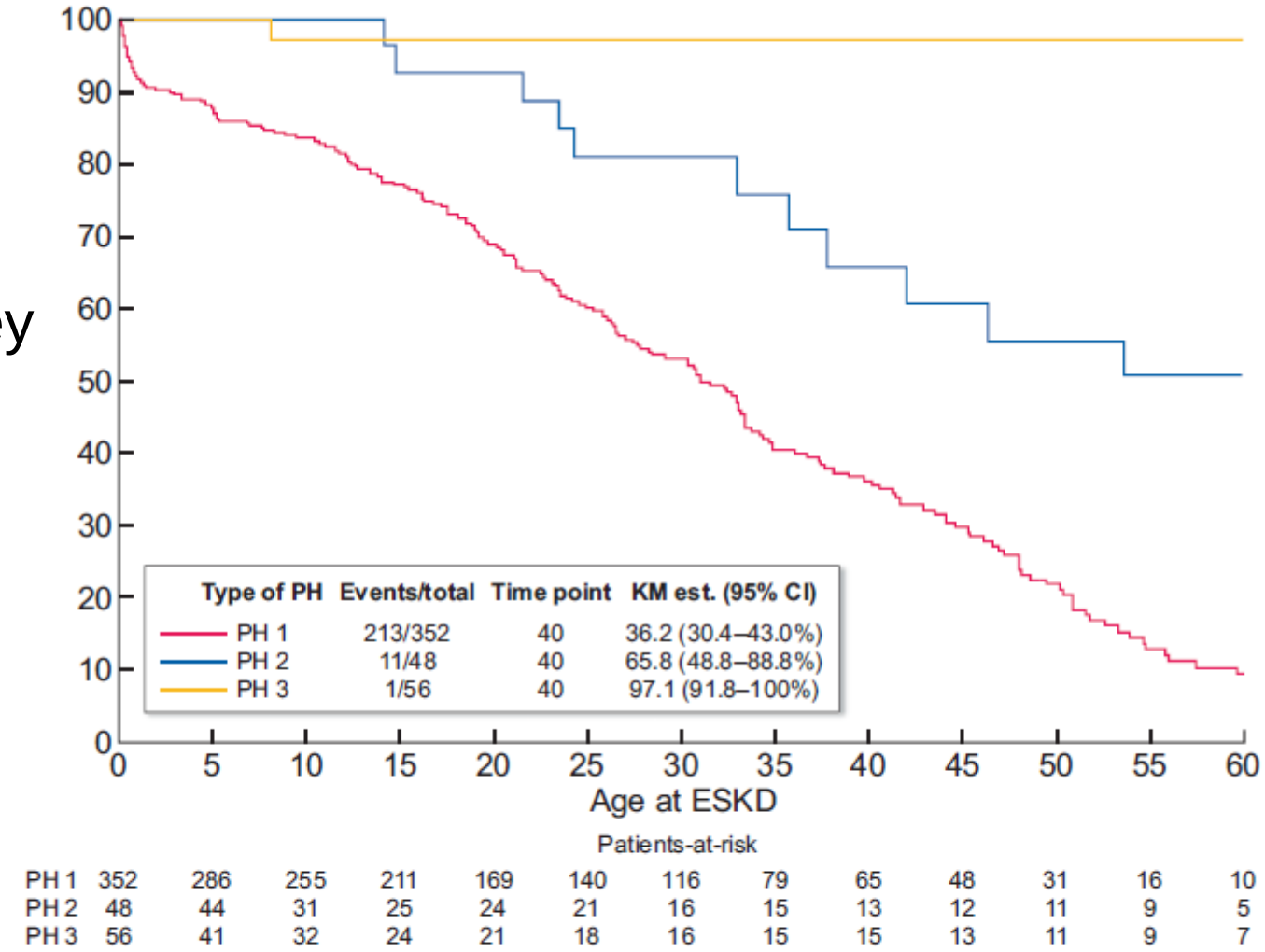
Urine oxalate	Survival estimate, % (number at risk)			
<1.1	100 (42)	96 (7)	96 (1)	–
1.1–<1.6	100 (42)	95 (8)	95 (5)	95 (2)
1.6–<2.4	100 (42)	91 (19)	73 (10)	65 (6)
≥2.4	100 (42)	85 (19)	42 (6)	23 (2)

MAYO CLINIC

Zhao et al Clin J Am Soc Nephrol 11: 119–126, 2016

Kidney failure is common in PH 1 and PH2, especially in PH1

Percent without kidney failure



····· PH3

--- PH2

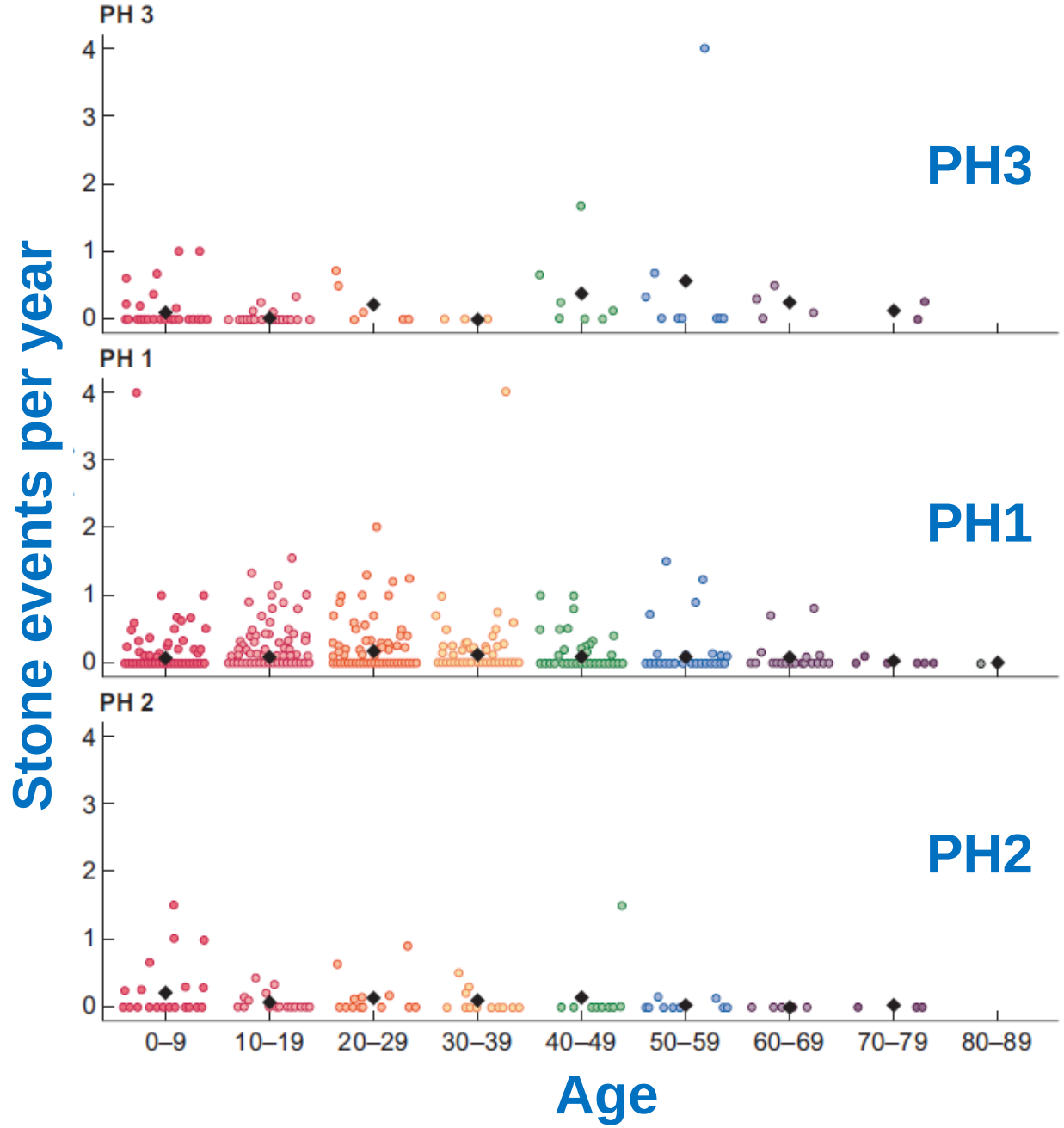
— PH1

RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Zhao et al Clin J Am Soc Nephrol 11: 119–126, 2016

Kidney stones are equally common in all PH types and across the decades

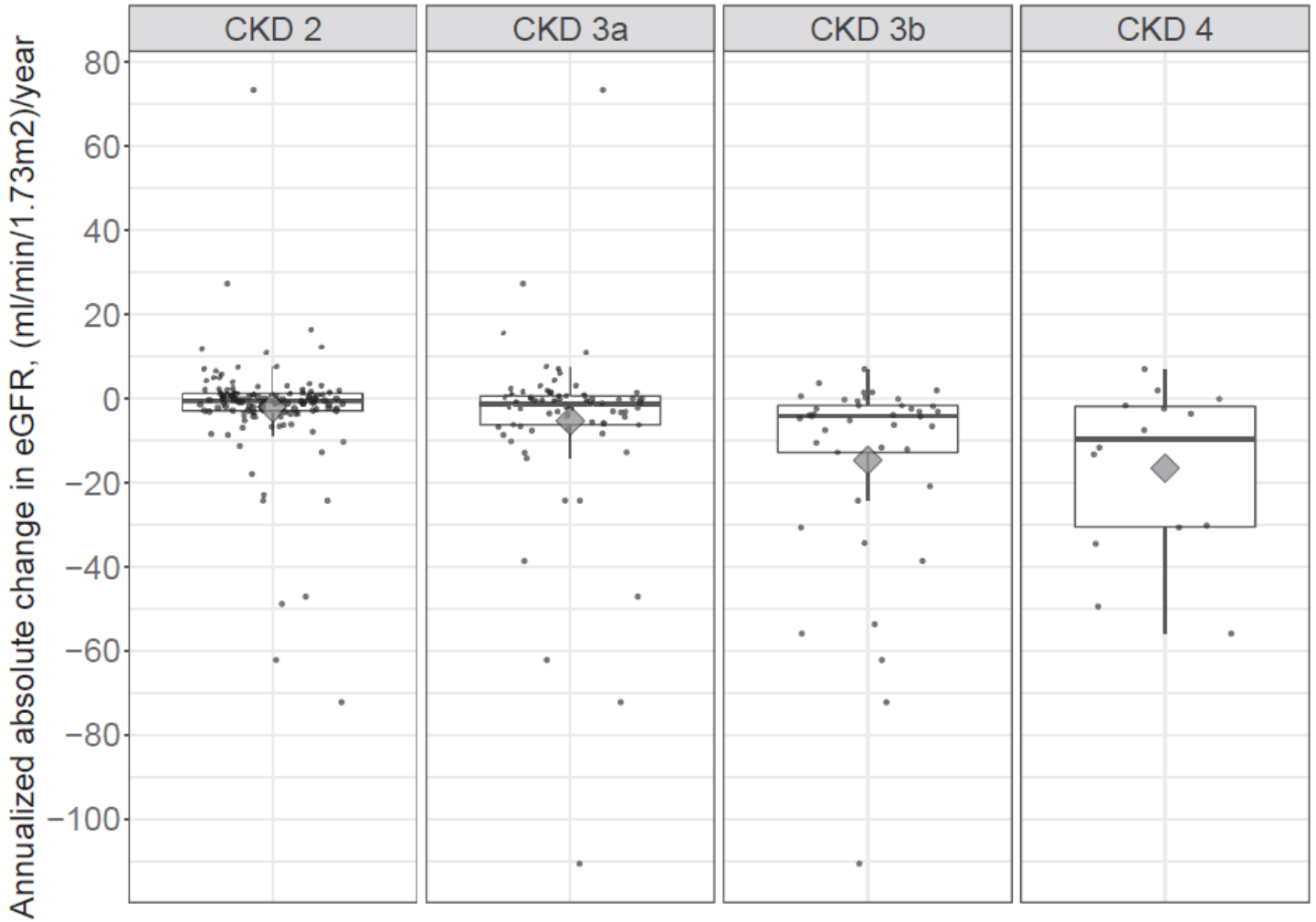


RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Singh P et al Nephrol Dial Transplant. 2022 37(5):869-875.

eGFR declines more dramatically at lower CKD stages

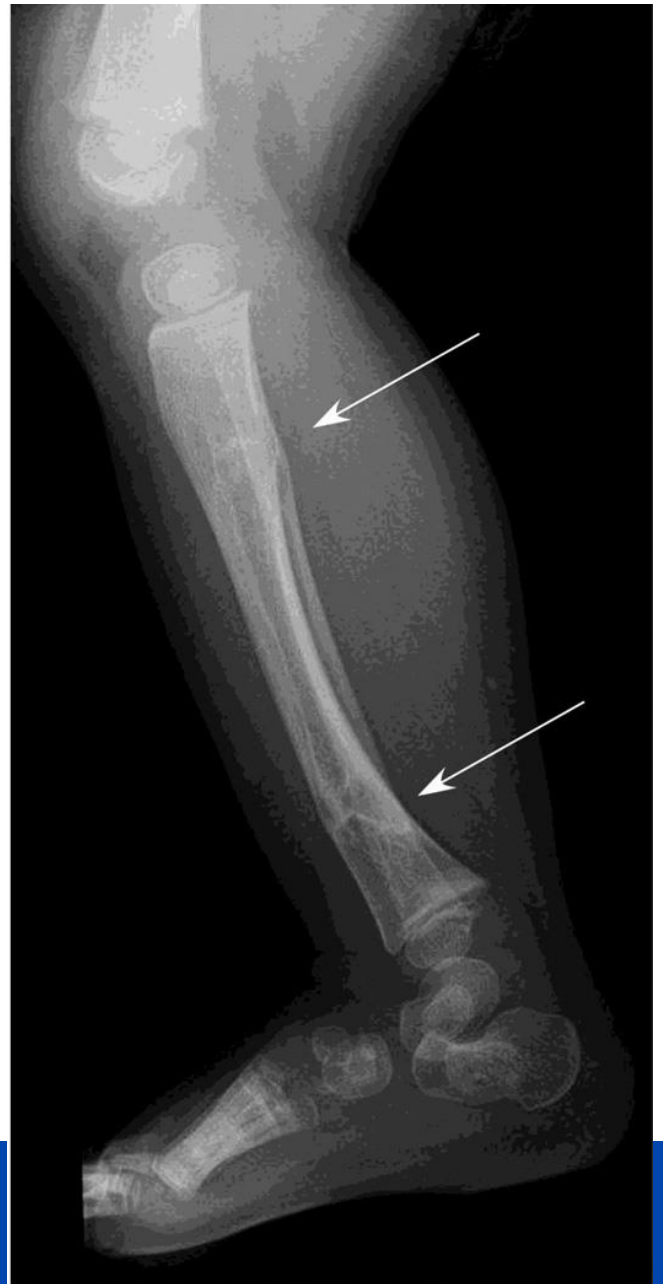


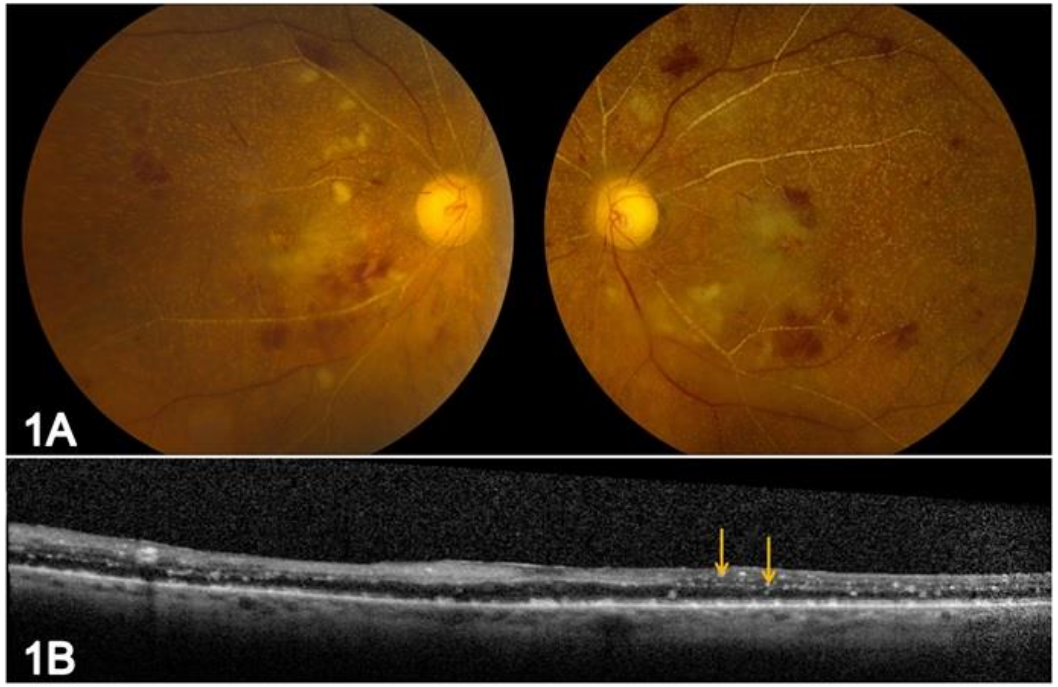
RARE KIDNEY STONE CONSORTIUM

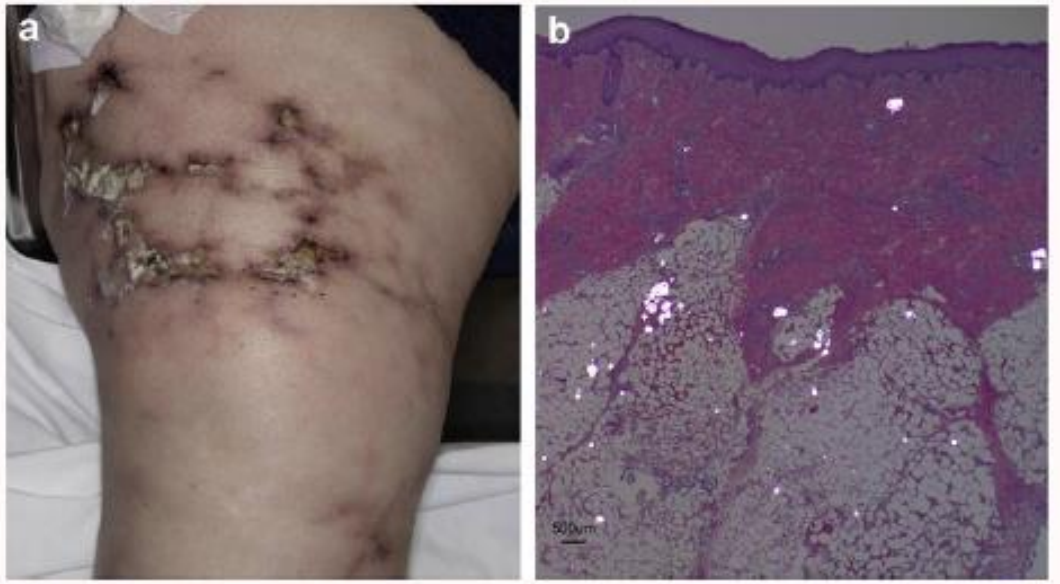
MAYO CLINIC

Singh P, et al: Am J Kidney Dis. 2022; Sep;80(3):373-382

Oxalosis

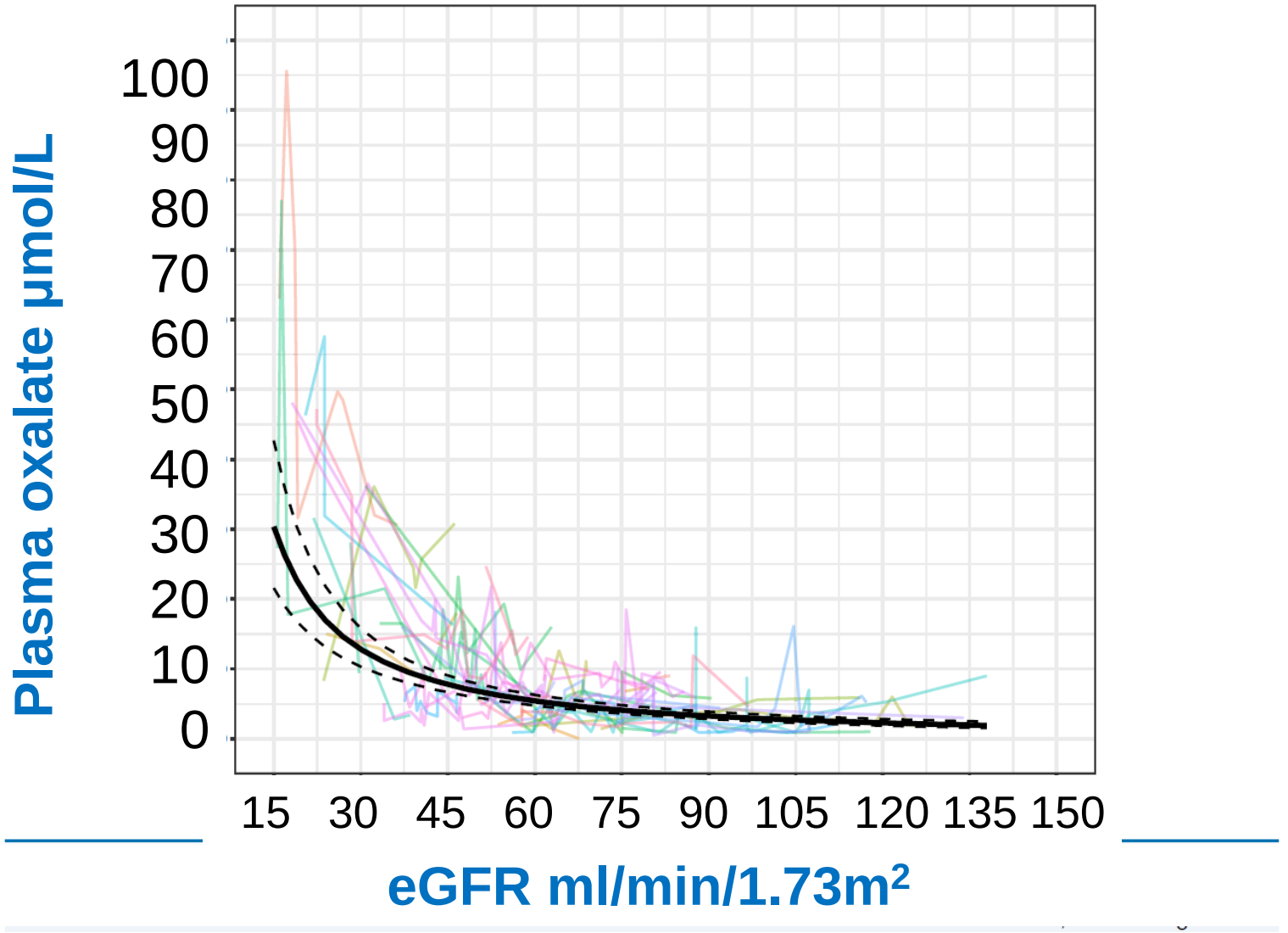






RARE KIDNEY STONE CONSORTIUM

Plasma oxalate increases markedly at low eGFR in PH1

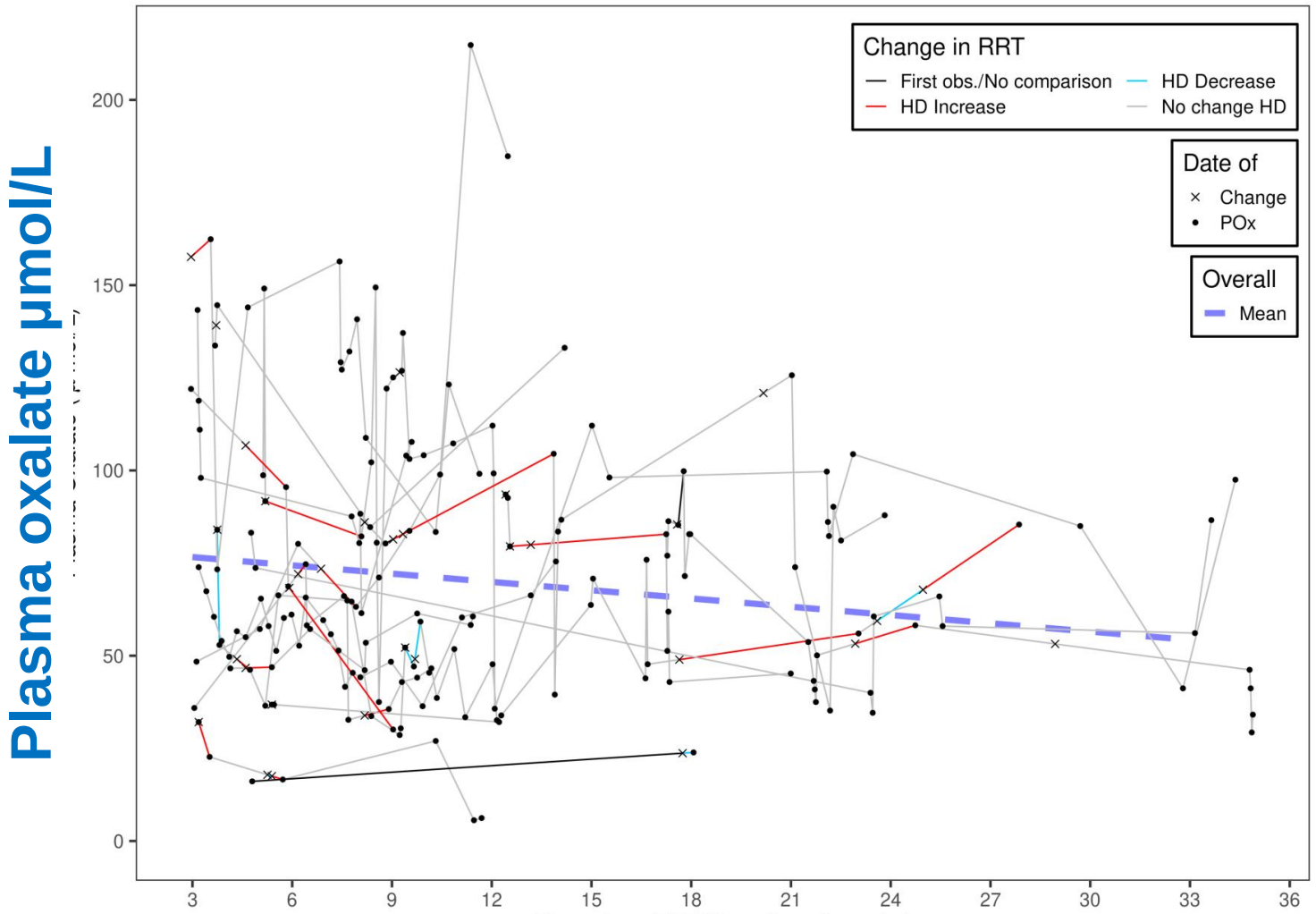


RARE KIDNEY STONE CONSORTIUM

Singh P, et al: Am J Kidney Dis. 2022; Sep;80(3):373-382

MAYO CLINIC

Plasma oxalate over time on dialysis in PH1



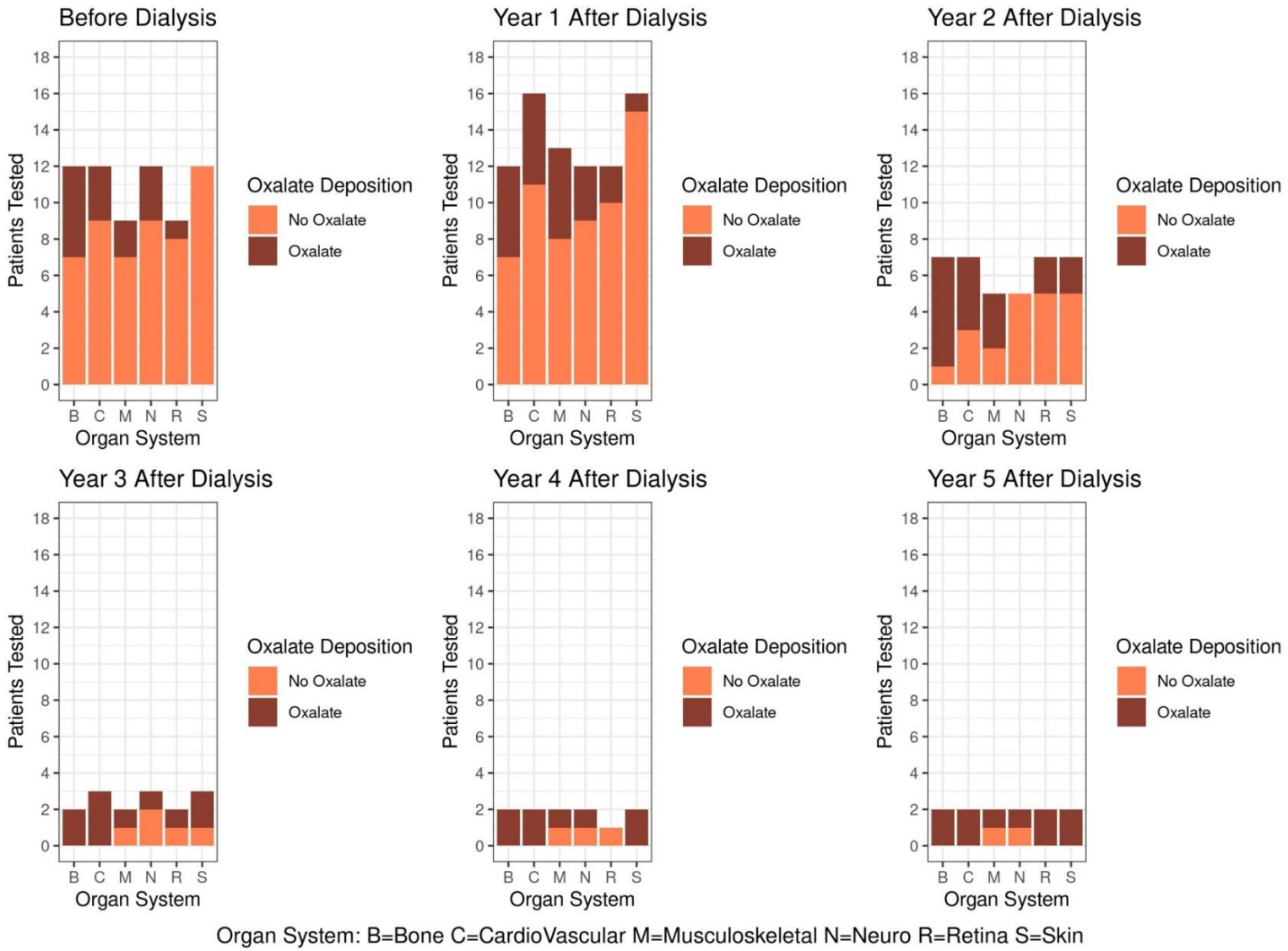
RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Oxalosis over time on dialysis

RARE KIDNEY STONE CONSORTIUM

Bone
Cardiovascular
Musculoskeletal
Neuro
Retina
Skin



Sas DJ et al. Front Med (Lausanne). 2021 Apr 9;8:592357.

KHI Endpoints for Clinical Trials in Hyperoxaluria: Outcomes

- A group of candidate markers compiled for evaluation.
- Promising candidates underwent rigorous examination via detailed literature review
- Biomarkers/endpoints evaluated sequentially on biweekly calls
- **Several remained as viable candidates**
  - **Plasma oxalate**
  - **Urine oxalate**
  - **Change in eGFR**
  - **Stone events**
- Workgroups summarized reviews
- Compiled into a draft report
- Paper draft Back and forth with FDA: published 2020
- PH patient group building on white paper, sought experience of others re: patient/family risk tolerance for clinical trials, new therapies.

Endpoints for Clinical Trials in Hyperoxaluria: KHI PH deliverables

PatientVoice

Feature

End Points for Clinical Trials in Primary Hyperoxaluria

Dawn S. Milliner,[1] Tracy L. McGregor,[2] Aliza Thompson,[3] Bastian Dehmel,[4] John Knight,[5] Ralf Rosskamp,[6] Melanie Blank,[3] Sixun Yang,[7] Sonia Fargue,[5] Gill Rumsby,[8] Jaap Groothoff,[9] Meaghan Allain,[10] Melissa West,[10] Kim Hollander,[11] W. Todd Lowther,[12] and John C. Lieske[1]

Abstract

Patients with primary hyperoxaluria experience kidney stones from a young age and can develop progressive oxalate nephropathy. Progression to kidney failure often develops over a number of years, and is associated with systemic oxalosis, intensive dialysis, and often combined kidney and liver transplantation. There are no therapies approved by the Food and Drug Association. Thus, the Kidney Health Initiative, in partnership with the Oxalosis and Hyperoxaluria Foundation, initiated a project to identify end points for clinical trials. A workgroup of physicians, scientists, patients with primary hyperoxaluria, industry, and United States regulators critically examined the published literature for clinical outcomes and potential surrogate end points that could be used to evaluate new treatments. Kidney stones, change in eGFR, urine oxalate, and plasma oxalate were the strongest candidate end points. Kidney stones affect how patients with primary hyperoxaluria feel and function, but standards for measurement and monitoring are lacking. Primary hyperoxaluria registry data suggest that eGFR decline in most patients is gradual, but can be unpredictable. Epidemiologic data show a strong relationship between urine oxalate and long-term kidney function loss. Urine oxalate is reasonably likely to predict clinical benefit, due to its causal role in stone formation and kidney damage in CKD stages 1–3a, and plasma oxalate is likely associated with risk of systemic oxalosis in CKD 3b–5. Change in slope of eGFR could be considered the equivalent of a clinically meaningful end point in support of traditional approval. A substantial change in urine oxalate as a surrogate end point could support traditional approval in patients with primary hyperoxaluria type 1 and CKD stages 1–3a. A substantial change in markedly elevated plasma oxalate could support accelerated approval in patients with primary hyperoxaluria and CKD stages 3b–5. Primary hyperoxaluria type 1 accounts for the preponderance of available data, thus heavily influences the conclusions. Addressing gaps in data will further facilitate testing of promising new treatments, accelerating improved outcomes for patients with primary hyperoxaluria.

CJASN 15: 1056–1065, 2020. doi: https://doi.org/10.2215/CJN.13821119

Due to the number of contributing authors, the affiliations are listed at the end of this article.

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Primary Hyperoxaluria
The Patient and Caregiver Perspective

Jennifer E. Lawrence and Debra J. Wattenberg

CJASN 15: 909–911, 2020. doi: https://doi.org/10.2215/CJN.13831119

Introduction

Living with primary hyperoxaluria—a rare genetic disease with excess oxalate production leading to frequent kidney stones, kidney impairment, and oxalosis—presents many challenges to patients, caregivers, and their families. Although the progression and severity of primary hyperoxaluria is variable, care for any child or adult with primary hyperoxaluria is an unusual strain to the family due to intensity of required medical care and associated financial hardship. To identify the concerns of the primary hyperoxaluria community, multiple in-person meetings were con-

experience interruptions in school and work, and loss of sleep.

"It is a daily challenge to make sure our son is drinking constantly throughout the day. He visits the school nurse every day who gives him one of his four daily doses of medication through his (gastrostomy) mickey button. As a 12-year-old, he misses sleepovers, sleep away camp, and overnight school trips."

Oxalosis and Hyperoxaluria Foundation, New York, New York

Correspondence: Dr. Jennifer E. Lawrence, Valdosta Specialty Clinic, 2418 North Oak Street, Valdosta, GA 31602. Email: jenlawtidmore@gmail.com

Editorial › Am J Kidney Dis. 2021 Oct 8;S0272-6386(21)00895-7. doi: 10.1053/j.ajkd.2021.09.005. Online ahead of print.

End Points for Clinical Trials in Hyperoxaluria: Case Study of Patient-Focused Drug Development in a Rare Disease

John C Lieske [1], Meaghan A Malley [2], Melissa West [2], Kim Hollander [3], Dawn S Milliner [4]

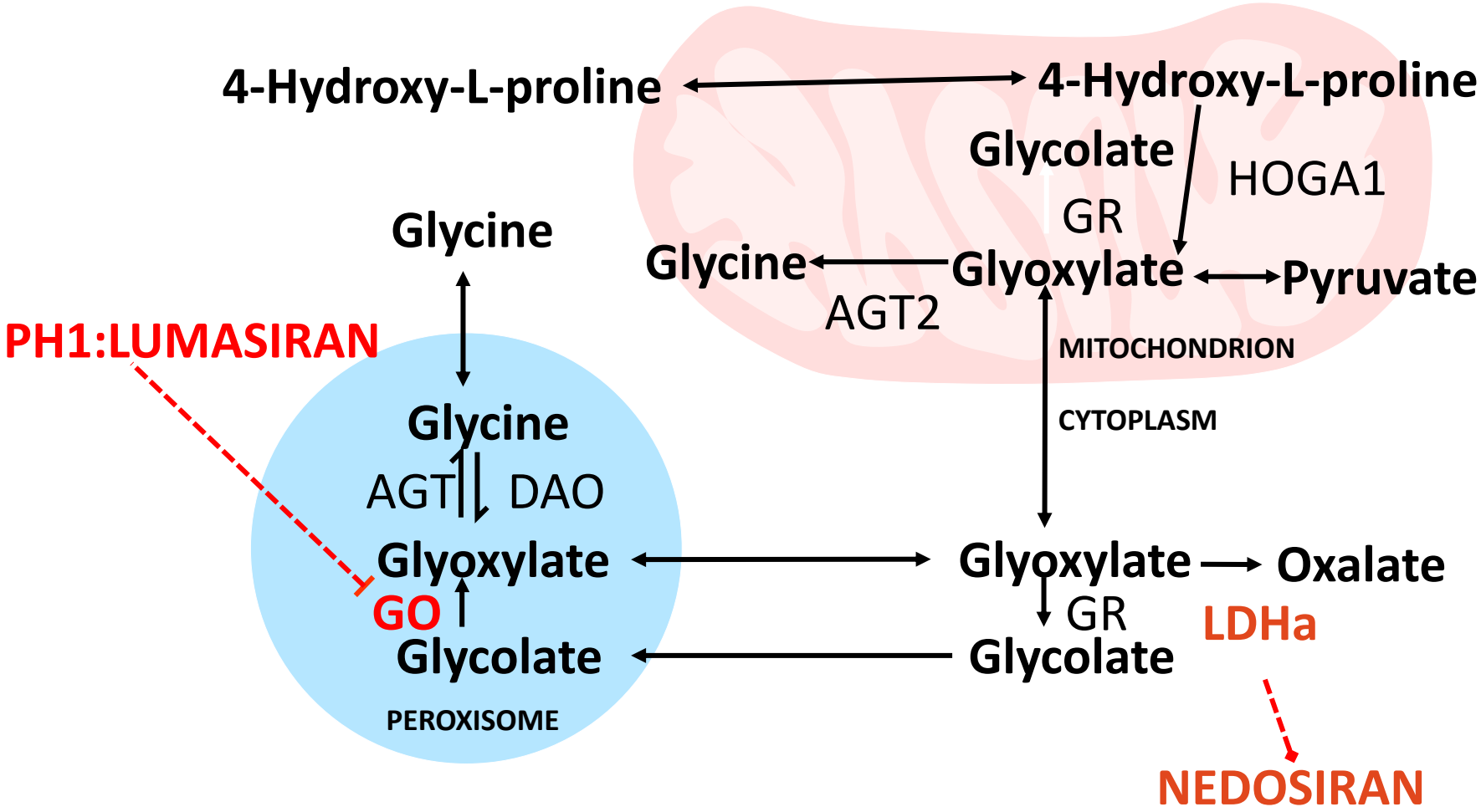
Affiliations + expand

PMID: 34634431 DOI: 10.1053/j.ajkd.2021.09.005

MAYO CLINIC

MAYO CLINIC

siRNA Place in PH1 Therapy



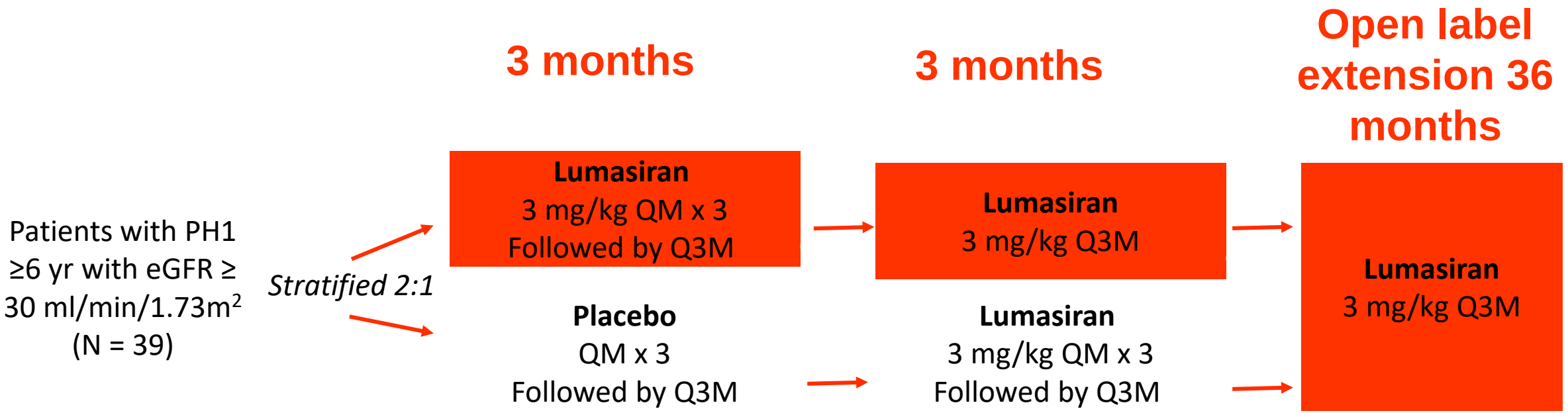
Bacchetta. Clin Kidney J. 2022;15:i17.

PH1, (??? PH2, and PH3):

MAYO CLINIC

ILLUMINATE A

- **Ongoing, phase III trial of subcutaneous lumasiran (small interfering RNA (siRNA silences *HAO1* gene encoding glycolate oxidase)**

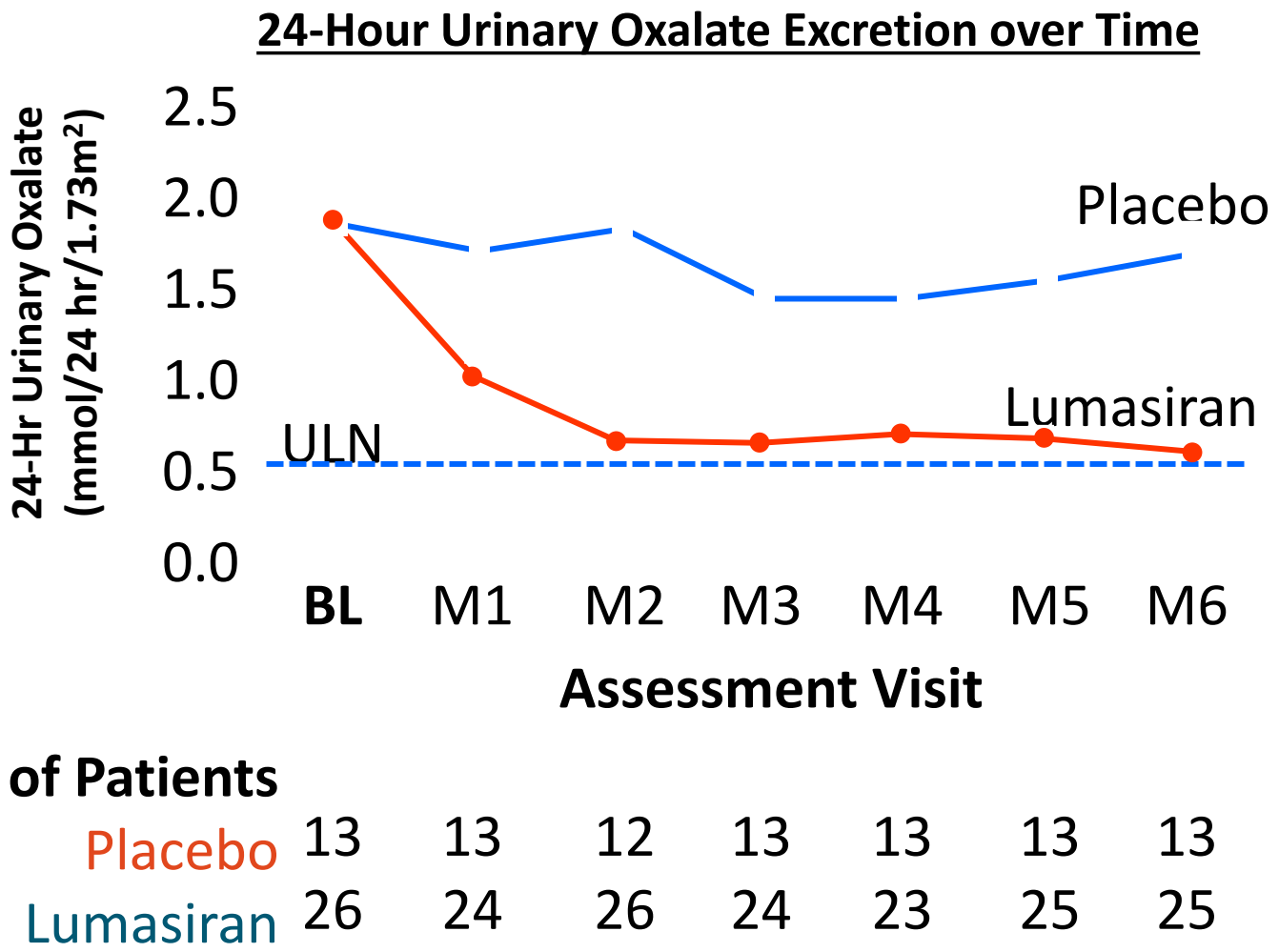


Garrelfs. NEJM. 2021;384:1216

MAYO CLINIC

ILLUMINATE A

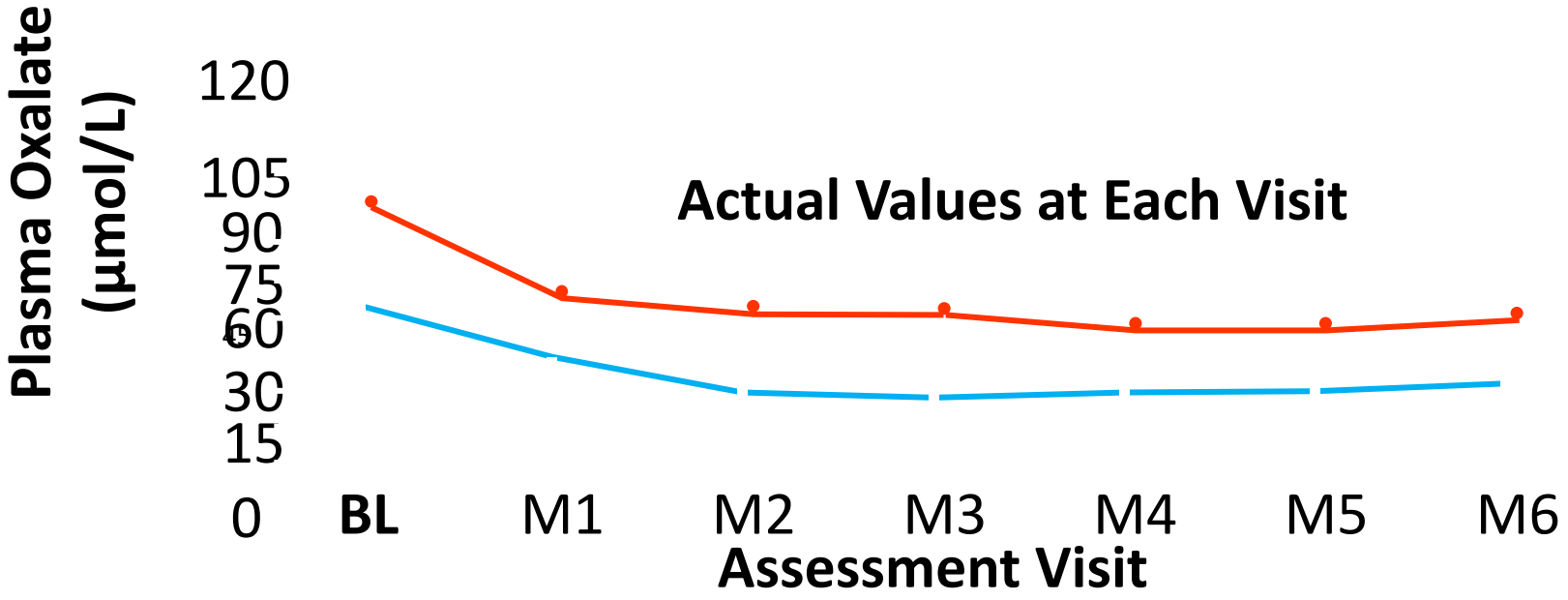
- Mean reduction in urinary oxalate excretion: 65% lumasiran vs 11% placebo (*P* < .001) at 6-mo primary analysis period
- Only transient injection-site reactions reported
- Approved as an Orphan drug 11/2020!



Garrelfs S. N Engl J Med. 2021;384:1216

MAYO CLINIC

ILLUMINATE C (CKD)



No. of Patients	BL	M1	M2	M3	M4	M5	M6
Cohort A	6	6	6	6	6	6	6
Cohort B	15	15	15	15	13	14	15

Cohort B (ESKD; N=15)

Cohort A (CKD4/CKD5; N=6)

Michael M AJKD 2023 81(2):145-15

MAYO CLINIC

Nedosiran

- **Nedosiran: GalNAc-conjugated RNAi treatment that targets hepatic lactate dehydrogenase (LDHa)**
- **RNAi therapy approved for PH; PHYOX program**
  - **PHYOX1 and PHYOX2: completed**
  - **PHYOX3: ongoing; extension trial of PHYOX2 in all types of PH**
  - **PHYOX4: ongoing; phase 1, single dose study in PH3**
  - **PHYOX7: ongoing; safety and efficacy in PH1 or PH2 with severe renal impairment with or without dialysis**
  - **PHYOX8: ongoing; safety, pharmacokinetics, and efficacy in children 0-5 yr with PH and intact kidney function**
  - **PHYOX-OBX: ongoing; natural history in PH3**
- **Approval in US for PH1 in late 2023!**

Goldfarb DS. Urolithiasis. 2023:51:80. Hoppe B. Kidney Int. 2022;101:626. Baum M. Kidney International. 2023;103:207. Coenen M. Abstract Poster1625. Haagensen A. Absract INFO22

MAYO CLINIC

PHYOX2 Results

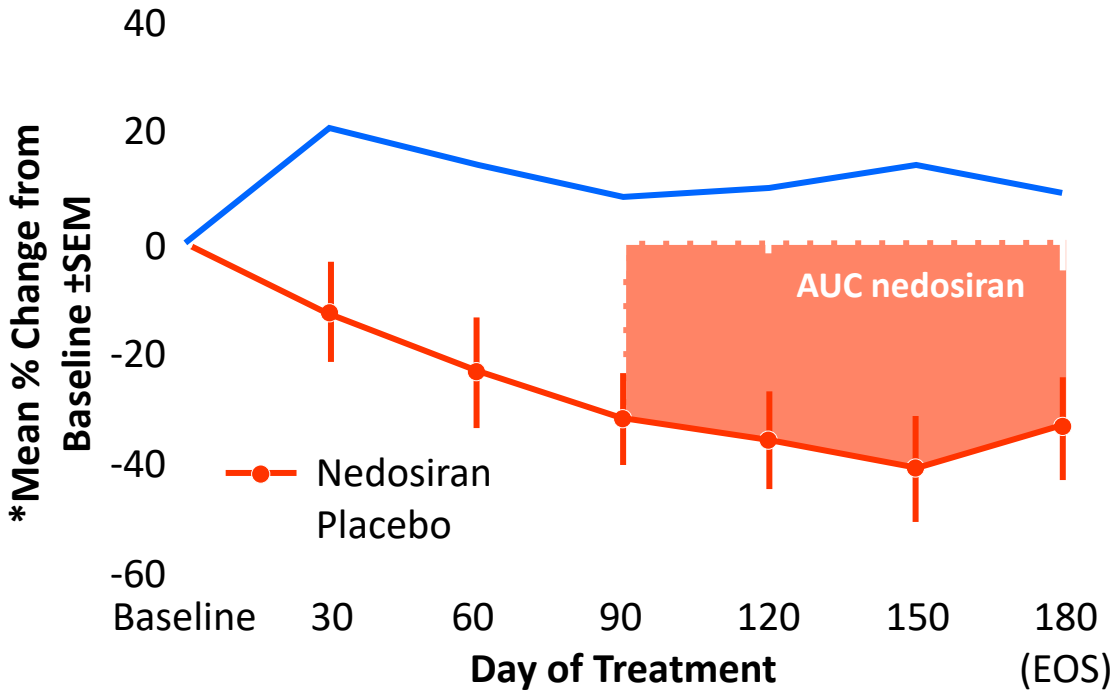
PHYOX2 Met Primary Endpoint Achieving a Significant Reduction in Uox

Mean $AUC_{24\text{-hour Uox}}$ (day 90 to day 180)

Overall mITT Population[1] (PH1 + PH2)

Standardized AUC24-hour Uox from Day 90 to Day	Nedosiran (n = 22)	Placebo (n = 12)
n	22	12
LS Mean (SE)	3507.4 (788.49)	-1664.4 (1189.96)
95% CI for LS Mean	(1961.7, 5053.1)	(-3997.2, 668.4)
LS Mean Difference from Placebo (SE)	5171.7 (1144.07)	
95% CI for Difference from Placebo	(2929.3, 7414.2)	
P-value for Difference from Placebo (2)	**<.0001**	

(1) mITT population = All participants in the ITT population who have at lease one efficacy assessment after the Day 90 dosing visit.
(2) P-value for testing difference from placebo



*LS means from MMRM model using time point estimates
**Multiple imputation (MI) under the missing at random (MAR) assumption was used to handle missing 24-hr Uox data

Baum. Kidney International. 2023;103:207.

MAYO CLINIC

Endpoints for Clinical Trials in Hyperoxaluria: PH Progress to Date

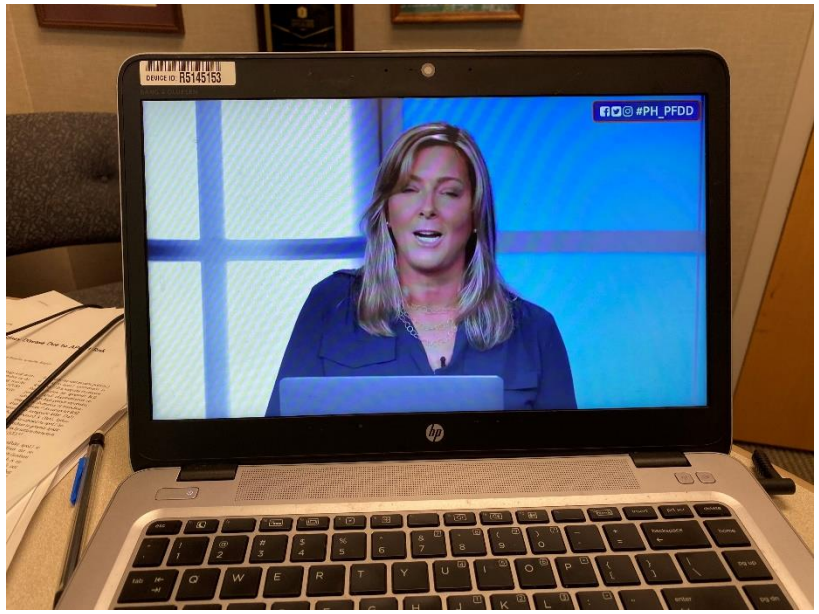
THE VOICE OF THE PATIENT REPORT: PRIMARY HYPEROXALURIA

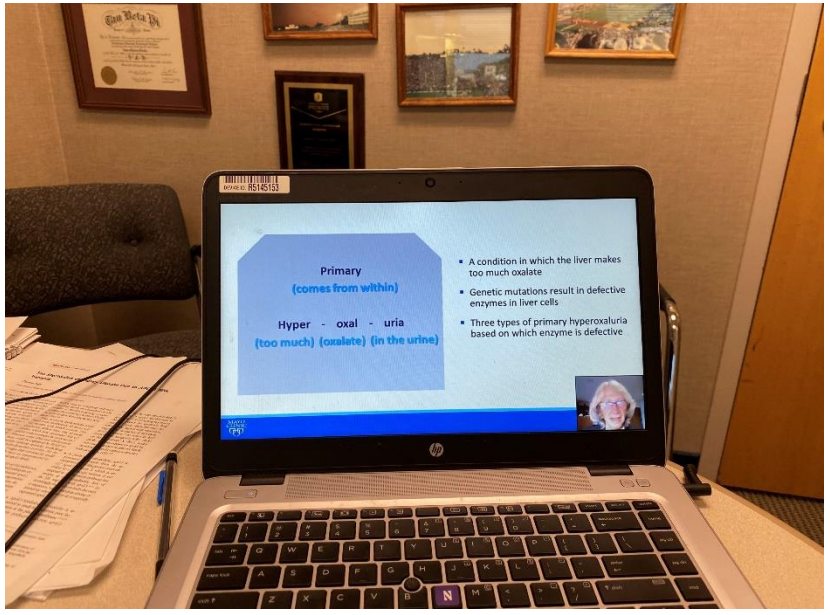
A Report on the Externally Led Patient-Focused Drug Development Meeting Corresponding to FDA's Patient-Focused Drug Development Initiative

Externally Led Public Meeting: October 5, 2020
Report Date:
Hosted by: The Oxalosis & Hyperoxaluria Foundation

Submitted to:
Center for Drug Evaluation and Research (CDER) &
Center for Biologic Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Oxalosis & Hyperoxaluria Foundation
STEPPING STONES TO A CURE





Quality of Life
Collaboration with Dicerna/ Novo Nordisc

- Survey Tools
  - **PH survey** adapted from our Voice of the Patient meeting
  - **The Wisconsin StoneQOL (WisQOL)**
    - The Wisconsin StoneQOL underwent reliability and validity testing in 248 stone formers and demonstrated good internal consistency.
    - This instrument is currently undergoing further testing in a large multicenter trial.
    - Wisconsin StoneQOL scores are expressed on a scale between 0 and 100, with a higher number indicating a better QoL.
  - **Work Productivity and Activity Impairment Questionnaire (WPAI)**
- Administered electronically via REDCAP
- Promoted in OHF sponsored Webinar

Recent PH-related health event

	Living with PH	Parent or caregiver
Kidney stone	14	8
Decreased Kidney function	6	5
Failure to thrive	0	3
Hematuria	3	4
UTI	3	3
Fatigue	5	5
Bone fractures	0	1
Bodily pain	9	7
Nausea or vomiting	2	6
Chills/fever	1	2
Heart or eye problems	0	1
Anxiety or depression	11	8

What outcomes are most meaningful

	Living with PH	Parent or caregiver
Slowing formation of stones	10	7
Stopping formation of stones	14	15
Regaining energy	5	0
Lessening pain	2	0
Improving kidney function	6	5
Decreasing need for superhydration	6	5
Deceasing UTIs	1	0
Stopping disease progression	8	11
Eat what I want	4	1

PH treatment landscape

- **Lumasiran (GO) and Nedosiran (LHDa) seem equally effective for PH1**
  - Unclear why an LDHa approach did not initially work for PH2 or PH3
    - ?Dosing
    - ?pathway nuances
    - ? Genotype: phenotype
- **Other approaches under consideration**
  - Gene therapy
  - Small molecule
  - Multiple targets at once
- **Use of siRNA may allow kidney alone transplant in kidney failure** (without liver transplant)
- **Registries still essential to answer these questions; develop long term outcomes**

Conclusions

- **KHI project has worked as envisioned**
  - Stakeholder identified and engaged
  - ASN staff were instrumental for organizing the group, identifying next steps
  - Robust FDA involvement along the way
- **Project was “ripe” for this process**
  - Strong industry pipeline
  - Pressing need for consensus regarding trial designs for this rare disease population since standard double blind trials with hard endpoints may not be feasible or timely
- **Pooling data in retrospective registries was crucial to understand this monogenic disease**
  - define natural history and disease surrogates
  - Attract industry and technology
  - Support regulatory approval
- **In 2024 there are 2 approved therapies for the devastating disease PH1!**

Hard work towards newer treatments

Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE

RARE KIDNEY STONE CONSORTIUM

rarekidneystones@mayo.edu
www.rarekidneystones.org
1-800-270-4637

Questions?
Lieske.John@mayo.edu

Case Example Reactor Panel

Reactor Panel

Catherine Lerro, PhD, MPH, Oncology Center of Excellence, FDA
Kirtida Mistry, MBBCh, DCH, MRCPCH, Center for Drug Evaluation and Research, FDA
Jill Morris, PhD, National Institute of Neurological Disorders and Stroke, NIH
Catherine Pilgrim-Grayson, MD,MPH, Center for Drug Evaluation and Research, FDA

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Thank You!

Meeting materials will be posted on:
www.reaganudall.org

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