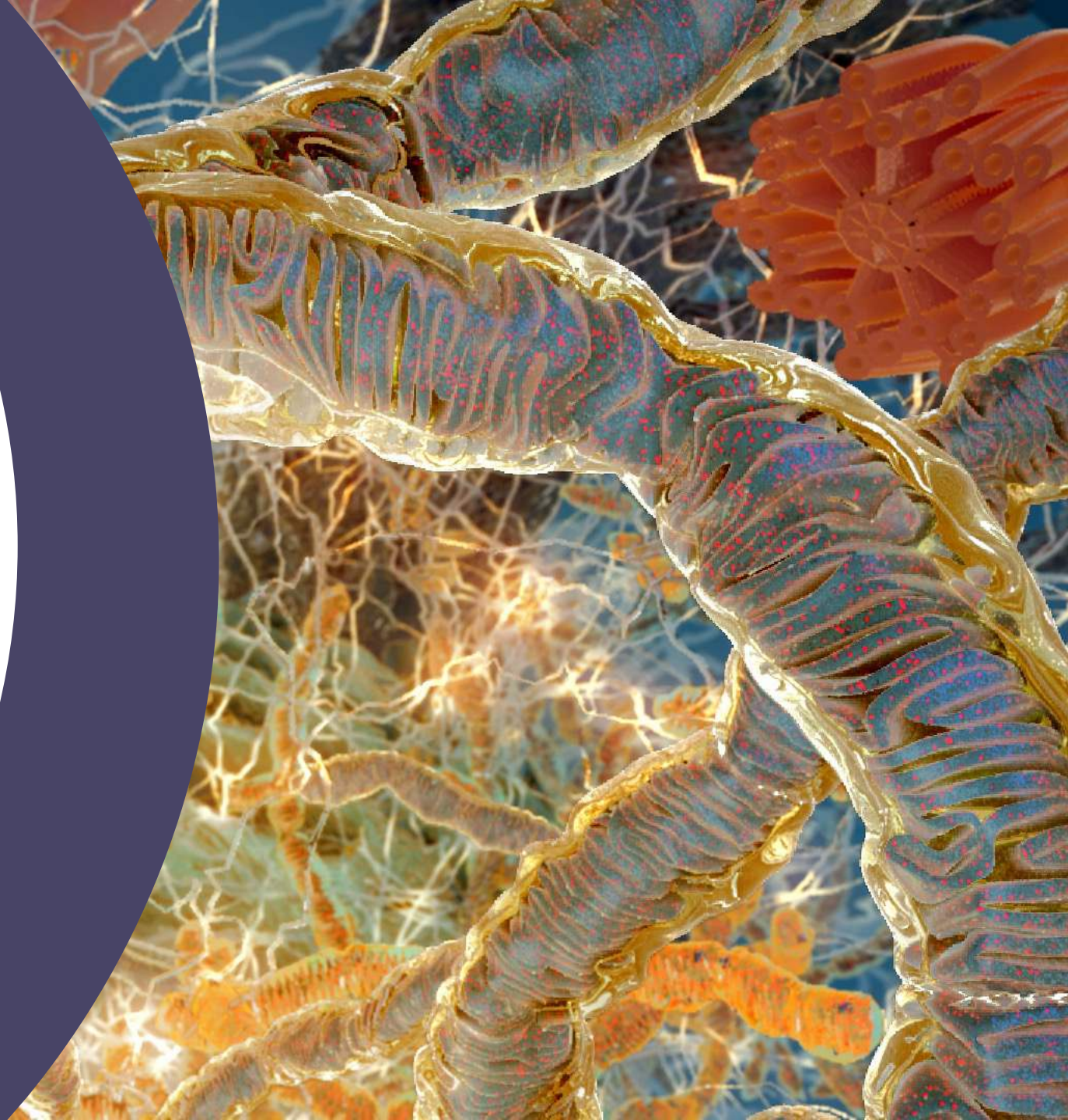
Stealth BIOTHERAPEUTICS

Why Your Voice REALLY Matters in Ultra-Rare Drug Development



MitoAction
October 7, 2023

Drug Development Challenges are Exacerbated in Ultra-Rare Diseases

Barriers to innovation and strategies to overcome these barriers

Today we discuss some of these barriers and strategies to overcome

- Early partnering with patient advocacy; early patient identification
- Challenges in finding enough patients to enroll for a clinical development program
- Disease education, data and development of patient reported outcome assessments
- Natural history limitations
- Natural history to inform endpoints and external controls
- Limited or no regulatory precedent + unvalidated/non-predictive animal models = lessons may be learned in the clinic
- Open-ended interviews to inform clinical relevance
- Expanded access to inform relevance beyond trial population
- Inconsistent application of regulatory flexibility
- Investor disinterest

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“Too Rare” Is Not An Answer

“It’s becoming more and more of a problem. The FDA or anybody who’s industry can’t just look people in the face and say, well, you have an ultra-rare disease, abandon all hope and we’ll never get any treatments for you. Even if it’s a fatal disease, it’s too hard. Well, that isn’t right.” Janet Woodcock quoted in Pink Sheet, July 2021

“Too Rare” Is Not An Answer

“Ultra-rare” disease is not defined in the US.

- Europe defines as diseases affecting less than 6,000 Americans (extrapolated to US population)
- Some rare disease advocates define as diseases affecting less than 2,000 Americans
- This could include many rare mitochondrial diseases:
  - Barth syndrome
  - TK2d
  - Senger’s syndrome
  - MNGIE
  - DCMA
  - Pearson syndrome
  - MEPAN
  - and others…

Historically, Breakthrough Approvals Have Driven More Innovation

1990 2000 2010 TODAY

Multiple sclerosis

1993
First approval
Betaseron

TODAY
>20 drugs approved

Amyotrophic lateral sclerosis

1995
First approval
Rilutek (riluzole)

TODAY
7 drugs approved

Duchenne muscular dystrophy

2016
First approval
Exondys 51
(eteplirsen)

TODAY
5 drugs approved

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Why is Ultra-rare so Hard? Few Patients = Poor Statistics

Challenges in Finding Patients to Enroll in Clinical Trials can Result in Underpowered Studies

Sometimes it's about the mechanism of action and the treatment effect of the therapy. So, if you have a very modest effect of a therapy that's harder to test in a very, very small population. If you have a very large effect of a therapy, then you may not need that many people." Kerry Jo Lee, CDER Office of New Drugs quoted in Pink Sheet 2023

~250 individuals affected with Barth syndrome worldwide

- Only 2 multi-disciplinary centers worldwide[1]
- Not all patients can participate in clinical trials:
  - Variability of disease presentation at different ages
  - Many patients have had heart transplants or have implantable cardioverter-defibrillators
  - Anxiety and depression may render some patients unsuitable for trial participation
  - Travel imposes significant burden, particularly since chronic neutropenia ratchets risk of infection

Statistics Pointers

- *It is much harder to show statistically probable findings in small data sets – which is part of the reason why Congress gave FDA more flexibility to make decisions on rare disease drugs*
- *The lower the p-value, the more convincing. FDA usually wants to see a p-value of <0.05*

~10% of the worldwide Barth syndrome population has died since the end-of-Phase 2 meeting with FDA in 2019

[1] Kennedy Krieger at Johns Hopkins in Baltimore, MD, USA and Barth Syndrome Clinic at Bristol Royal Hospital for Children in Bristol, UK

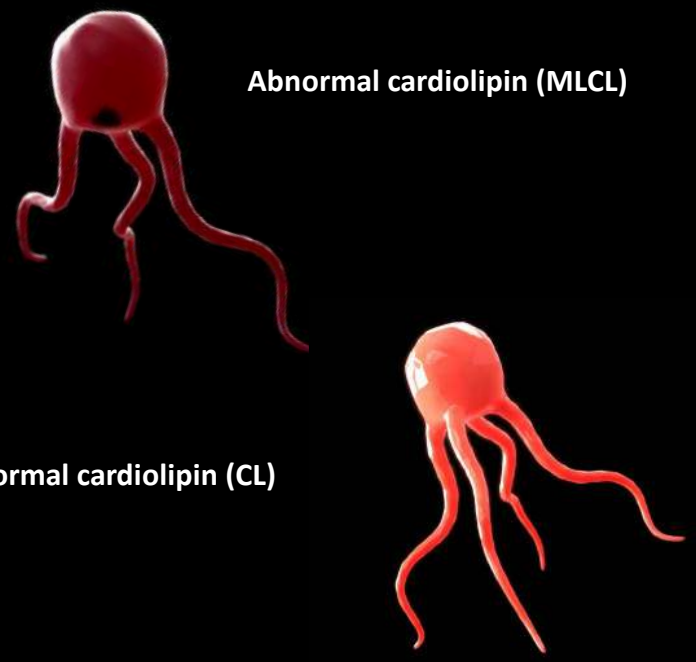
Barriers to Innovation: Regulatory Precedent

Poor Disease Understanding + Mixed Receptivity to Mechanistic Data

Ultra-rare diseases are "a place where mechanistic reasoning may really play a major role." Janet Woodcock quoted in Pink Sheet July 2021

- Some diseases are better understood than others, e.g., FDA has issued guidance supporting accelerated approval in the context of diseases of enzyme deficiency[1]
- In some diseases emerging scientific understanding about biomarkers may support accelerated approval despite a lack of association with clinical benefit in the data, e.g., neurofilament light chain for ALS[2]
- Educating regulators about rare diseases for which there are no approved therapies – including most mitochondrial diseases – takes time and repeated engagement
    - For example, in Barth syndrome, the cellular defect (abnormal cardiolipin) has been associated with severity of clinical presentation[3]

Barth syndrome is diagnosed by the ratio of abnormal MLCL to normal CL (MLCL:CL ratio).



85% of universally early deaths by age-5

[1] Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Result From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies FDA Guidance for Industry March 2020

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887s000lbl.pdf

[3] Bowron et al., J Inherit Metab Dis, 2015; Thompson et al., Genetics in Medicine, 2016

Barriers to Innovation: Financing

*Is There a Value Proposition? (development costs for rare diseases typically >$100M)**

Strengths

- ✓ Mechanistic plausibility
- ✓ Motivated patient advocacy
- ✓ Unmet medical need

Weaknesses

- ? Poor understanding of mechanism and progression of disease
- ? Unvalidated animal models
- ? Limited natural history data
- ? Lack of regulatory precedent

Opportunities

- ✓ Rare pediatric designation
- ✓ Orphan drug designation
- ✓ Potential to improve diagnostic journey with disease education and therapeutic options

Threats

- ? Powering considerations and inability to conduct multiple clinical trials
- ? Regulatory uncertainty
- ? Small commercial opportunity; diagnostic barriers due to poor disease awareness

* Berdud et al, Cost Eff Resour Alloc., 2020; Schlander et al., PharmacoEconomics, 2021

Our Experience: Lack of Regulatory Flexibility

"Randomized controlled trials "made for tremendous, tremendous improvement over clinical anecdotes in the 60s and 70s…but the argument that "this is the gold standard and this is the only way to do things – I don't think that point of view has a tremendous amount of merit." Janet Woodcock, quoted in Pink Sheet, July 2021

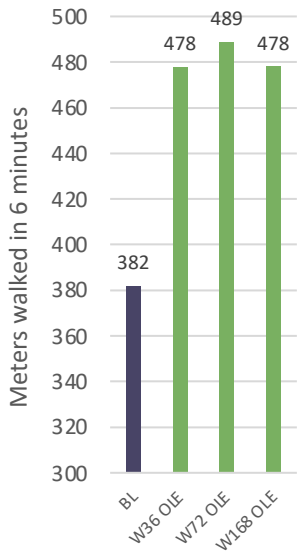
2014

Barth Syndrome Foundation (BSF) + Johns Hopkins proposed development citing "lock and key" mechanism

2019

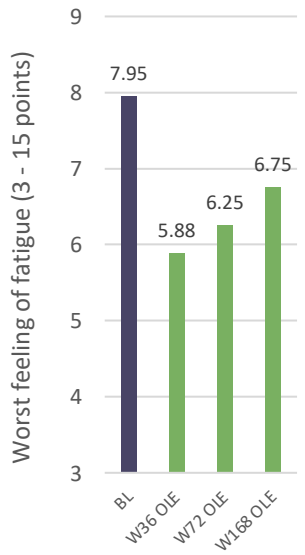
P2 primary analysis not met; open-label data promising; well-tolerated by most subjects

6MWT (n=8) ↑



W72 OLE p=0.0124
W168 OLE p=0.0032

BTHS-SA fatigue (n=8) ↓

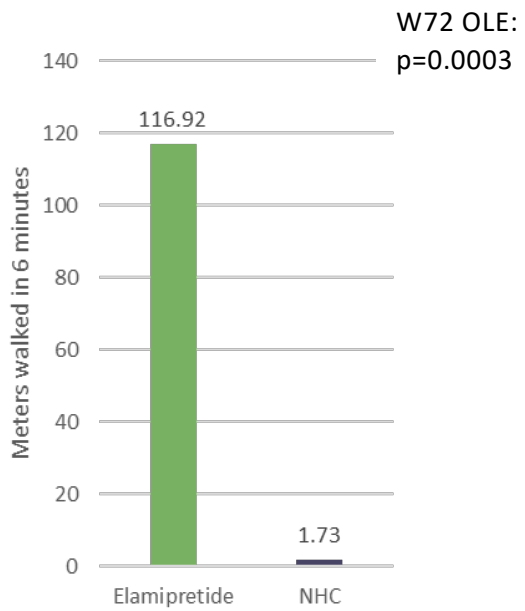


W72 OLE p=0.0656
W168 OLE p=0.2056

2020

Positive P3 natural history control trial

6MWT Δ



2021

FDA refused to review new drug application

2022

Positive changes in biomarkers of heart function and cardiolipin ratio

2023

No regulatory path forward

Possible next steps:

- NDA resubmission
- Likely FDA refusal to review
- Program termination

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Strategies: Education + Data

"The 50-year investment in basic science has to merge with clinical methodology and we have to stop just thinking that empirical evaluation is the only way of determining truth." Janet Woodcock, quoted in Pink Sheet, July 2021

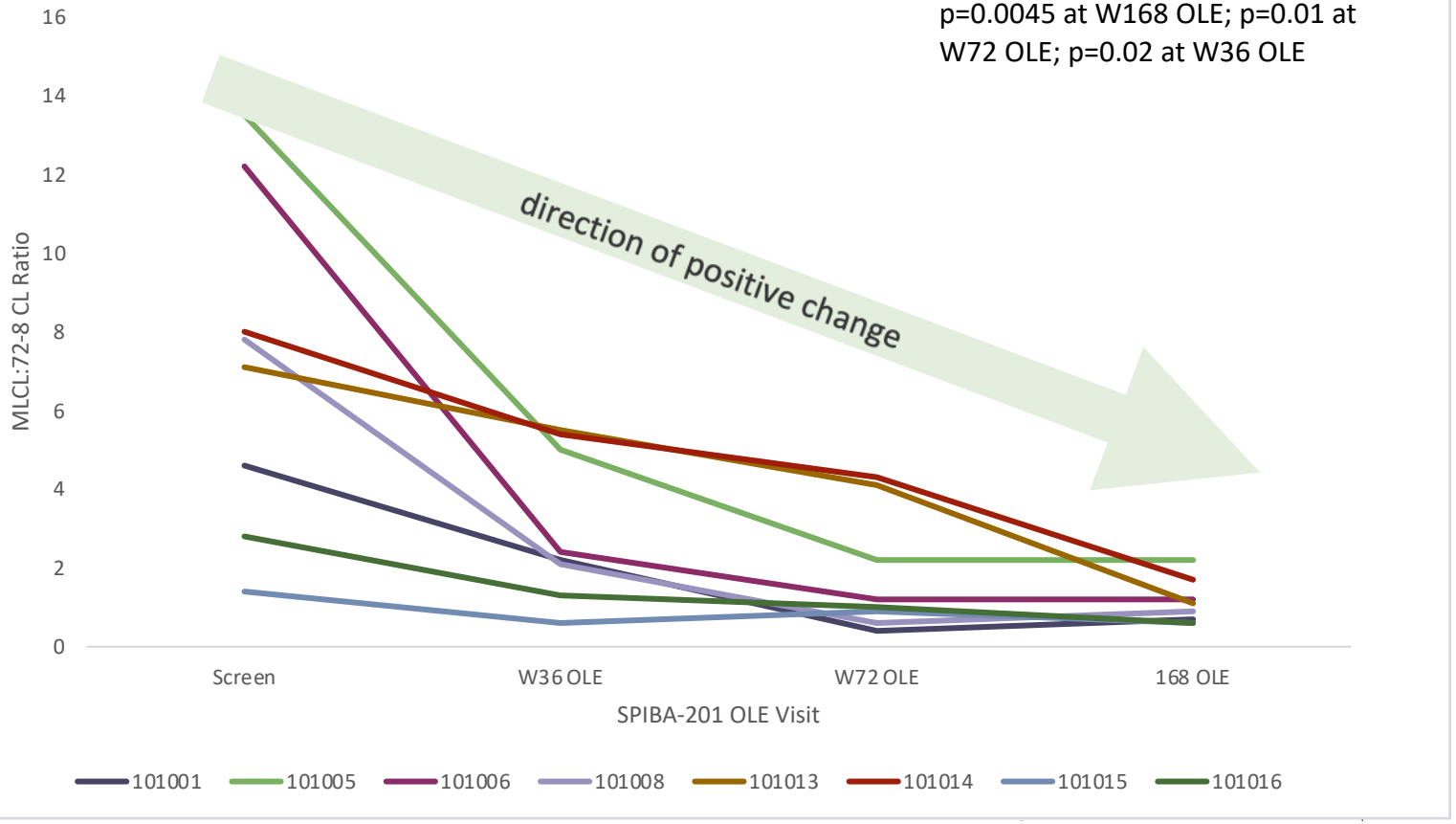
Barth syndrome was first diagnosed in 1983, so disease awareness is poor.

- >35 publications in peer-reviewed journals since 2020
- >50 presentations since 2020
- 4 patient advocacy meetings with FDA to educate on disease burden (2018, 2019), patient tolerance of risk of uncertainty of benefit (2020) and ultra-rare prevalence (2021)

Elamipretide Targets and Stabilizes Cardiolipin

Elamipretide Improved the Ratio of Abnormal to Normal Cardiolipin for All OLE Patients*

p=0.0045 at W168 OLE; p=0.01 at W72 OLE; p=0.02 at W36 OLE



* N=8 long-term OLE participants shown; 2 OLE early termination patients also demonstrated improvement from screening at final visit.

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Strategies: External Controls

"Most rare diseases continue to lack an FDA-approved treatment, and there remain numerous obstacles for investment in research and development. One way we're working to overcome these hurdles is by providing important funding for clinical trials and natural history studies to advance rare disease medical product development." Janet Woodcock quoted in Rare Disease Advisor, Oct 2021

GUIDANCE DOCUMENT

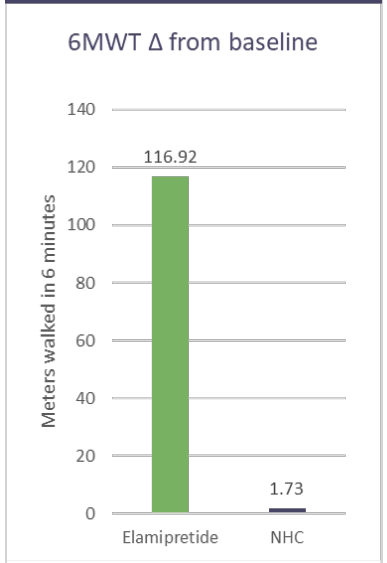
Rare Diseases: Natural History Studies for Drug Development

Draft Guidance for Industry

MARCH 2019

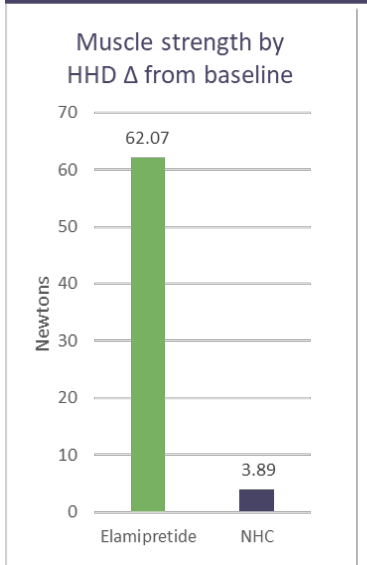
FDA receptivity to natural history control studies may vary by Division (Neurology has recognized, Cardiology & Nephrology has not) and choice of endpoints (subjective versus objective)

PRIMARY ENDPOINT

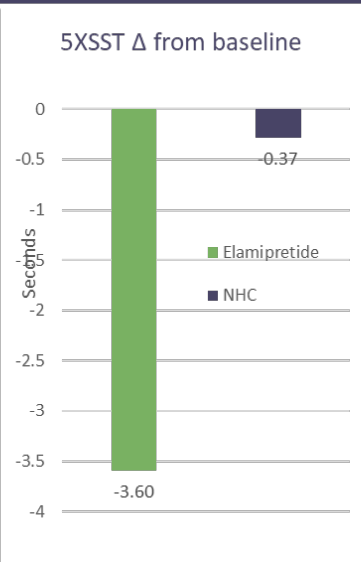


Week 72 OLE: p=0.0003
Week 36 OLE: Elam 80.30, NHC 0.60, p=0.0004
Week 48 OLE: Elam 91.86, NHC 0.89, p=0.0005

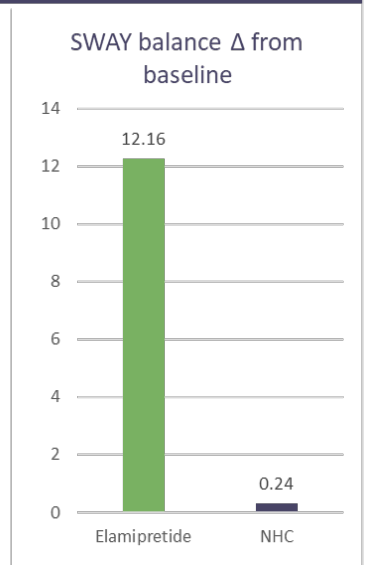
SECONDARY ENDPOINTS



Week 72 OLE: p=0.0002
Week 36 OLE: Elam 41.79, NHC 1.04, p=0.0002
Week 48 OLE: Elam Δ 48.67, NHC Δ 1.97, p=0.0005



Week 72 OLE: p=0.008
Week 36 OLE: Elam -2.36, NHC -0.002, p=0.042
Week 48 OLE: Elam Δ -2.83, NHC Δ -0.003, p=0.034



Week 72 OLE: p=0.03
Week 36 OLE: Elam 7.40, NHC 0.86, p=0.13
Week 48 OLE: Elam 8.81, NHC 1.08, p=0.12

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Why?: Inconsistent Use of Regulatory Flexibility

"The FDA has no mechanism to find or tradition to cite similar cases when weighing evidence for approvals, resulting in standalone, bespoke decisions. These decisions show highly variable criteria for "substantial evidence" when flexible evidential criteria are used…" Janiaud et al., Annals of Internal Medicine, 2021

Drug/Indication	Approval	US prevalence	Randomized controlled trial?	Pre-defined hypothesis?	Absence of bias?	Positive data?
Cholbalm/bile acid disorders	2015	6,660-3m				
Xuriden/hereditary orotic aciduria	2015	~20				
Brineura/Batten disease	2017	400-500	NH control			
Mepsevii/MPS VII	2017	<200				
Revcovi/ADA-SCID	2018	<250				
Sohonos/fibrodysplasia ossificans progressiva	2023	400	NH control			
Elamipretide		<150	NH control		Supported by objective findings	

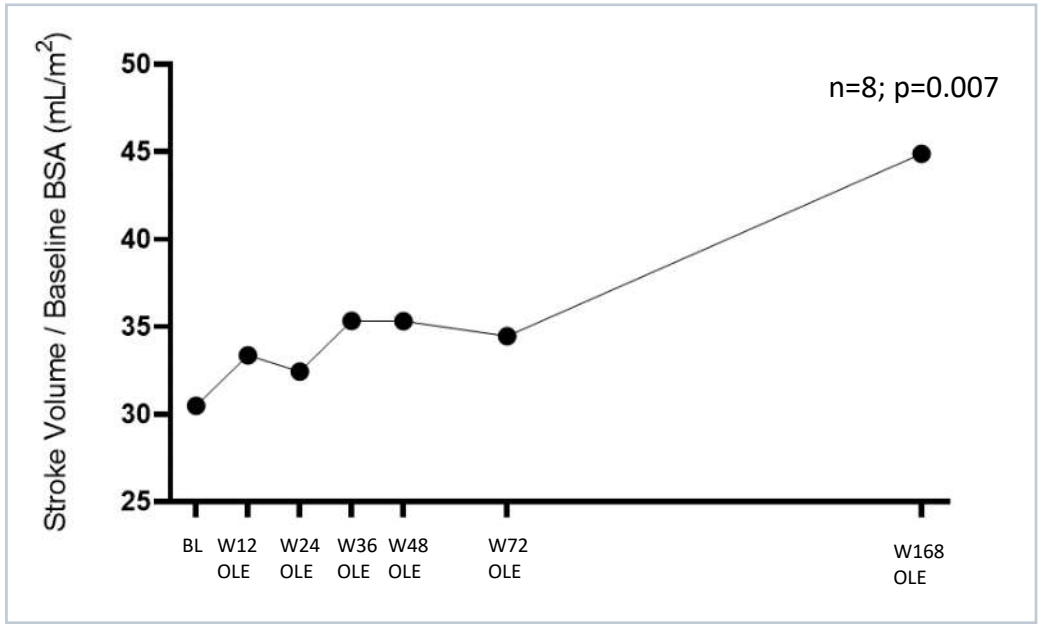
No Yes Regulatory guidance recognizes natural history controls in certain circumstances, but not as rigorous as placebo control

Strategies: Natural History

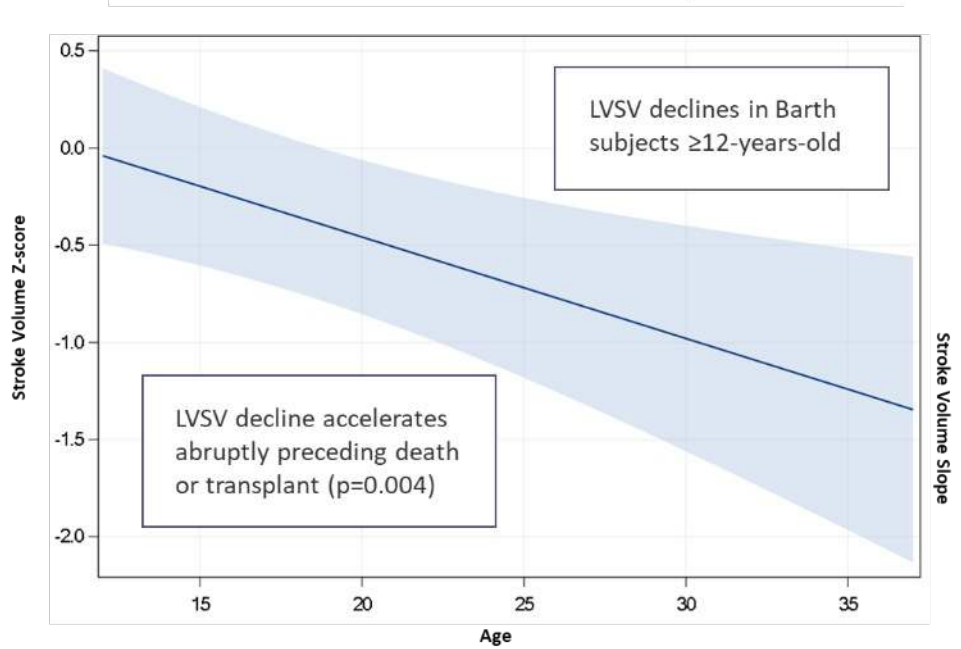
Can inform trial design and improve interpretability of trial results

An Unexpected Finding: In Barth syndrome, dilated heart failure is common in infants and young children but was thought to "resolve" for many patients in older childhood. We discovered that all trial subjects (>12-years-old) had extremely impaired left ventricular volumes and low cardiac output – a different but no less challenging cardiac phenotype. We then interrogated the natural history of older individuals and learned that this is common in the disease.

Heart function measured by LV SV increased with elamipretide



Heart function measured by LV SV declines in Barth natural history



LV SV: left ventricular (LV) stroke volume (SV)

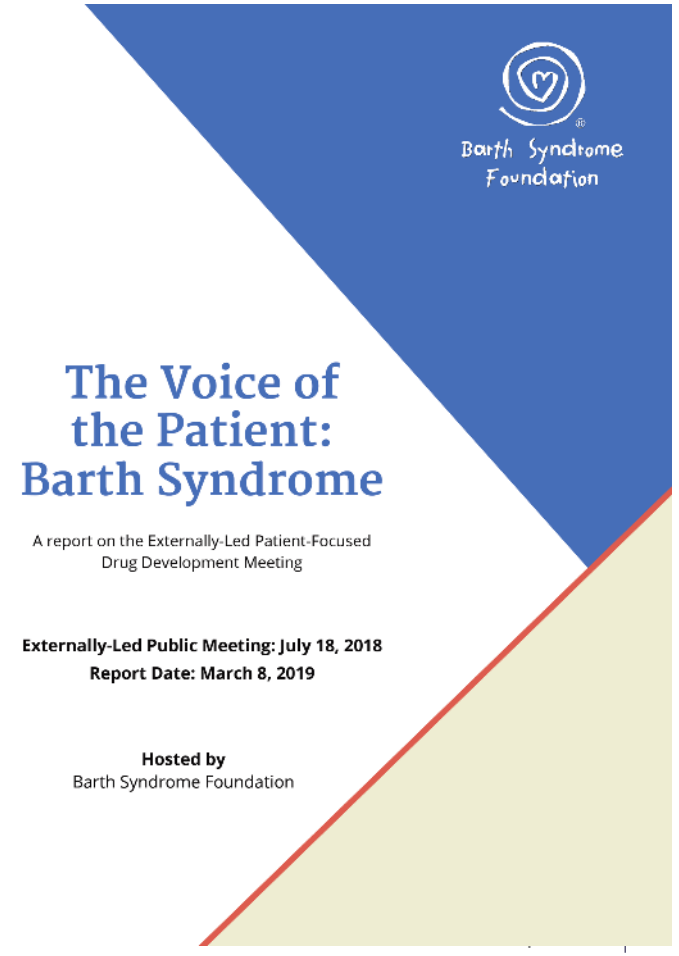
Strategies: Patients as Partners

Early Partnering with Patient Advocacy

"The FDA has not figured out how to deal with ultra-rare diseases…We just really need the FDA to exercise the authority that they have been given in terms of being flexible on how they can interpret the reams of data that they have. The problem, of course, is that it's only on eight patients. It's very hard…but I think the preponderance of evidence is overwhelming." Kate McCurdy, Chair, Barth Syndrome Foundation, quoted in Boston Business Journal, August 2023

Barth Syndrome Foundation:

- Lobbied for Stealth development efforts in 2014
- Scientific and Medical Advisory Board approved protocol in 2016
- Voice of the Patient meeting with FDA in 2018; PACE meeting with FDA in 2019
- Attended 8 FDA meetings on IND in 2019, 2020, 2021, 2022, 2023
- Submitted a petition signed by 4,256 individuals in 2020
- Submitted 2 doctors' letters in 2020 and 2021
- Met with FDA in 2021 to discuss tolerance of risk of uncertainty of benefit
- Met with FDA in 2022 to explain ultra-rare disease prevalence and progression



Breaking the Dome of Development Silence – Research Collaboration

Data Sharing

✓ Multiple sources of natural history data contribute to disease understanding and inform clinical development and regulatory strategy

❑ Complications arise if different assessment modalities are utilized – e.g., 2-D versus 3-D echocardiograms – or if important information is not collected – e.g., concomitant medications

Collaboration can inform development

- Team at Bristol, UK shared data from failed trial of bezafibrate to confirm relationship between LV volumes and clinical benefit for P4 modeling required by FDA
- Teams at UW, Duke, MUSC and Hopkins pooled cardiac natural history data to contextualize LV volume improvements
- Taken together, we have studied patient-level longitudinal natural history and interventional trial data for **>30%** of the worldwide Barth syndrome patient population

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Breaking the Dome of Development Silence – Industry/Advocacy Collaboration

"It is important that we view rare diseases as a spectrum with N of 1, ultra-rare and then rare being along the spectrum and it's important that we recognize the common challenges as well as the unique challenges. From our standpoint we really prefer to view rare diseases along the spectrum as opposed to various categories that would then have different regulatory sort of tools or even frameworks." Patrizia Cavazzoni quoted in Pink Sheet, August 2023

"Can you talk to the Hill about creating a new standard that would enable us to evaluate risk versus benefit for ultra-rare diseases?" Office and Division Director verbal remarks to Sponsor (paraphrased), 2020-2021

- Some individuals at FDA say new standards are needed to allow risk versus benefit decision making in rare diseases
- FDA senior officials say that FDA has the flexibility it needs, most recently citing guidance including acceptability of external controls[1] for rare diseases
- Companies are disinclined to share information about development challenges or regulatory setbacks
- Congress is (appropriately) unwilling to consider product specific development challenges, but does want to hear from industry (i.e., in addition to advocacy)
- Shared information about common development and regulatory challenges can be important to inform these discussions

Barth Syndrome Foundation®

mito ACTION

[1] https://everylifefoundation.org/wp-content/uploads/2023/08/FDA-response-to-Congressional-letter-2023.pdf?eType=EmailBlastContent&eId=8e3cefff-58dd-47f7-baf7-259c7ed0045b

Strategies to Amplify the Patient Voice

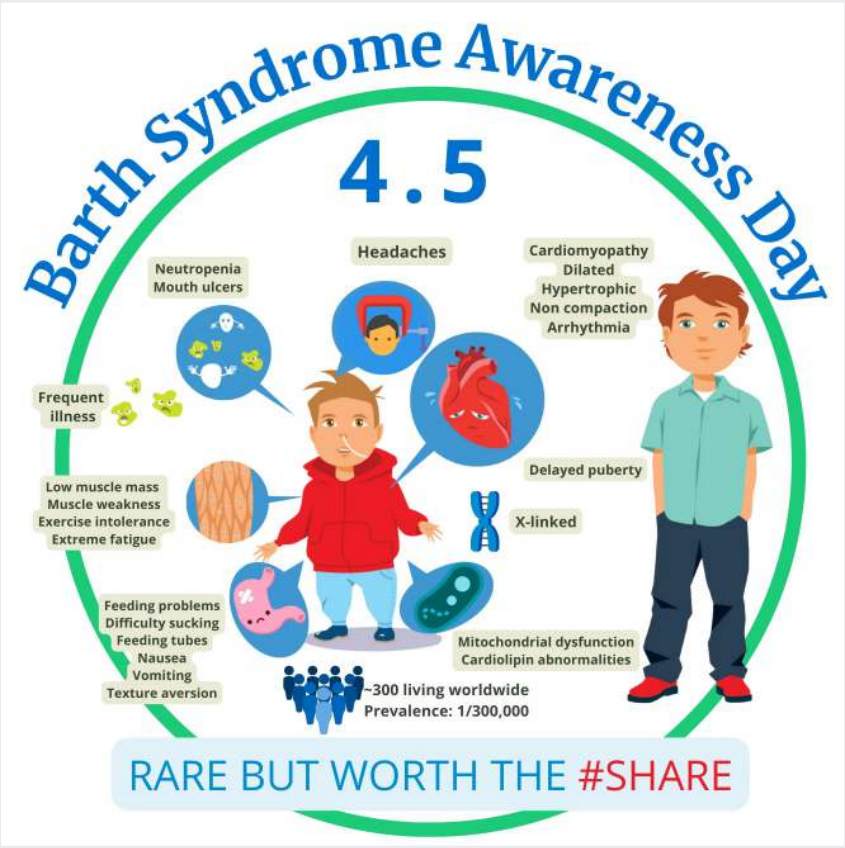
Congress oversees the FDA, so writing to your Congressional representatives and attending targeted Hill meetings can inform and motivate Congressional oversight.

Congress is interested in needed POLICY changes, so how are FDA policies on ultra-rare, with examples such as we've seen in Barth syndrome, affecting broader ultra-rare communities?

Media can help educate and influence Congress about needed policy changes. Media can also inform FDA of degree of public interest in policy change.

Why the Patient Voice is Critical

"One of the few areas where both sides of the aisle agree is improving health equity for children living with ultra-rare lethal diseases." Paraphrased from discussion with office of House Mitochondrial Disease Caucus chair



On April 3, 2023, Congressman Paul Tonko (D-NY) introduced H Res 276 with Congressmen Gus Bilirakis (R-FL), Ralph Norman (R-SC), Rep. Dunn, Neal P. (R-FL), Rep. Nancy Mace (R-SC) and Rep. Doris Matsui (D-CA) as co-sponsors to recognize April 5 (4/5) as Barth Syndrome Awareness Day and highlight the need for increased awareness, improved diagnosis, new therapies for this disease and regulatory pathways for ultra-rare drug development.

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Why the Patient Voice is Critical

"When the [first Duchenne muscular dystrophy drug was approved] in 2016, …In addition to difficult science and trial evaluations, the FDA cited enormous political pressure in the case of DMD in its summary report, citing the example that then FDA Commissioner Dr. Robert Califf received 2,792 emails from patient advocates alone urging…approval. The approval…raised speculation regarding the future of drug approval to focus more on patients' needs for new pharmaceuticals." Mattingly et al., J Manag Care Spec Pharm. 2017

Like media, signatures on a petition to FDA can inform FDA of the degree of public interest in policy change. Direct letters to FDA can also be informative.

Key Take Aways

- >90% of rare diseases do not have a single FDA-approved treatment.[1]
- Strong + unrelenting patient advocacy support is critical to ultra-rare development efforts
- Breaking the dome of development science among developers, doctors/researchers and advocates in the ultra-rare disease space is critical to inform advocacy for change
- ADVOCATING FOR CHANGE can create opportunities and potential for positive change

[1] NORD Avalere Report: ORPHAN DRUGS IN THE UNITED STATES: An Examination of Patents and Orphan Drug Exclusivity, 2021; [2] FDA does not define “ultra-orphan”; in Europe, it is considered to apply to diseases with a prevalence of <1 in 50,000, National Institute for Clinical Excellence. NICE Citizens Council Report Ultra Orphan Drugs. London, NICE, 2004.