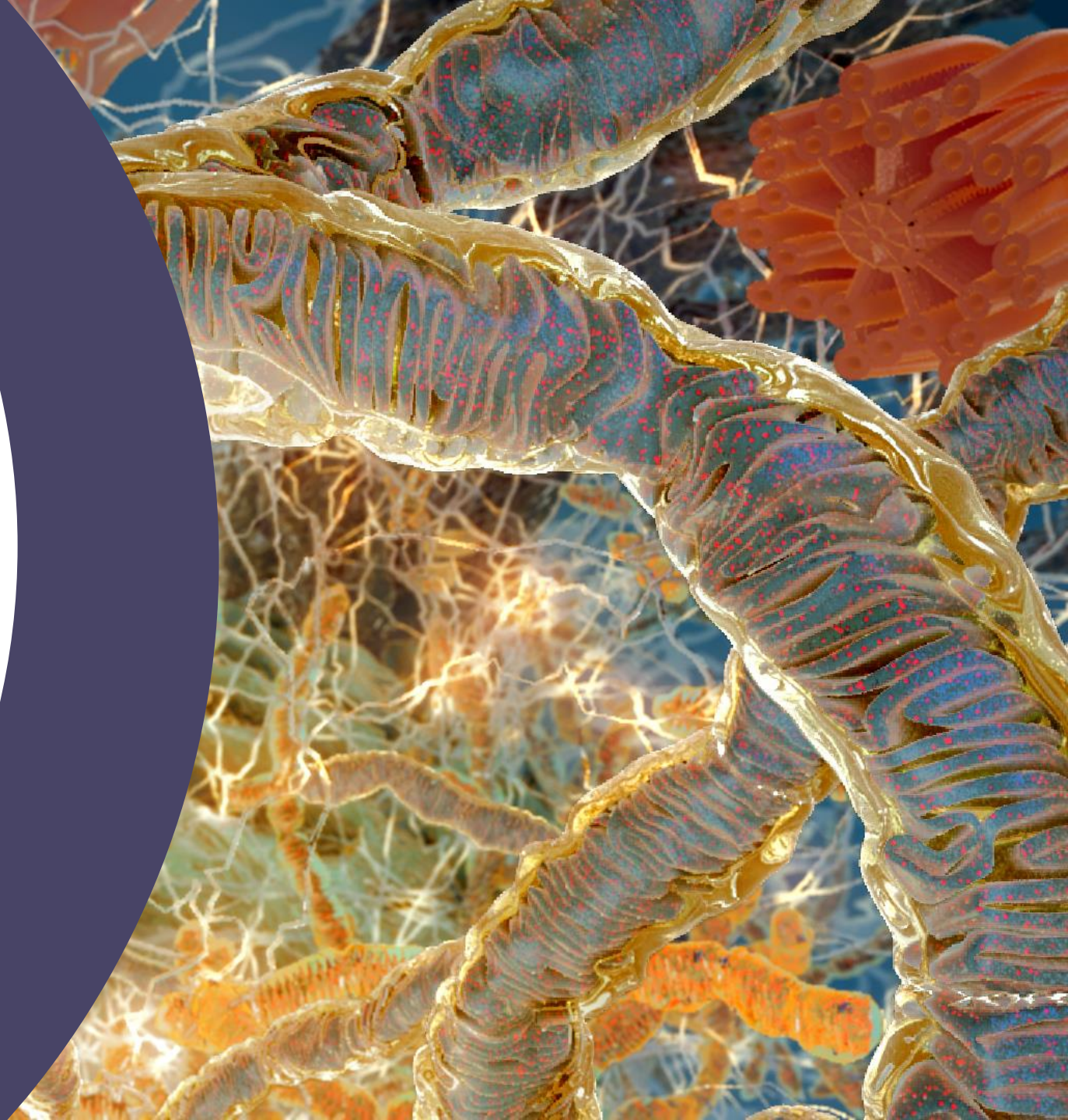
Stealth BIOTHERAPEUTICS

Opportunities and Challenges in Ultra-Rare Drug Development



World Orphan Drug Congress
May 25, 2023

Key Take Aways

- Strong + unrelenting patient advocacy support is critical to ultra-rare development efforts
- >90% of rare diseases do not have a single FDA-approved treatment.[1] New incentives for ultra-rare diseases[2] may be needed: Wall Street views rare diseases that affect <10,000 individuals (for small molecules) or <1,000 individuals (for gene therapies) as un-investible
- Small biotechs remain more active in ultra-rare drug development than big pharma – increasing funding uncertainty (and need for incentives) particularly in poorly performing financial markets[4]
- FDA regulations do not distinguish between rare and ultra-rare diseases in applying regulatory flexibility despite the significantly increased risk of Type 2 error (the risk of not approving an effective drug) in ultra-rare diseases – and decisions on when and how to apply flexibility are often *ad hoc*[3]
- Accelerated approval for ultra-rare diseases presents opportunities, challenges, 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.; [3] Isakov et al., MIT,.edu 2016; Janiaud et al., Annals of Internal Medicine, 2021; [4] Yates, Hinkel, Clin Transl Sci. 2022

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Barth Syndrome is an Ultra-rare Cardioskeletal Myopathic Disease

Affects ~150 Americans and ~250 Individuals Worldwide

85%
mortality
by age 5

90% report
cardiomyopathic
symptoms

>85% report
muscle weakness and
fatigue

"He worries too much about things a 9-year-old should not worry about. He asks me every night to listen to his heart. Sometimes he says he doesn't want to die. We went for a trip to Italy this year and had to toss a coin in a fountain and make a wish. His brother wished for getting all the Transformer toys. He wished for a cure to Barth."

-BTHS caregiver

"On April 23rd in 2000, I suffered my first cardiac arrest at age 11, and I had my first defibrillator implanted. On April 17th, 2018, I suffered my eighth cardiac arrest and was saved by the shock of my fourth defibrillator."

-BTHS affected individual

"My son is not strong enough to open up a bag of chips. He cannot pop off the top of a ketchup bottle and the list goes on and on."

-BTHS caregiver

Barth Syndrome Voice of the Patient Report, August 20, 2019, https://fda.report/media/130562/EL-PFDD+Meeting+on+Barth+Syndrome+Voice+of+the+Patient+Report.pdf

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Is there a Value Proposition?

Development Costs for Orphan Diseases Estimated at $500M (versus $1B Across All Cardiovascular Diseases)[*]

Strengths

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

Weaknesses

- ? Poor understanding of mechanism and progression of disease
- ? Unvalidated animal models
- ? Lack of regulatory precedent

Opportunities

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

Threats

- ? Powering considerations and inability to conduct multiple clinical trials
- ? Small commercial opportunity
- ? Diagnostic barriers due to low disease awareness

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

Our Barth Syndrome Development Journey

9 Years of Clinical, Regulatory and Market Challenges Inspired by Unwavering Advocacy Commitment

Walker Burger, 33, gained access to an experimental drug to treat Barth syndrome through a clinical trial. Now, he's concerned he may lose access after regulators declined to review the medicine. *STAT July 2022*

- 4 Patient Focused Drug Development or Listening Sessions
- 2 Clinical Trials
- 13 Expanded Access cases
- >30 Publications or Presentations
- 12 FDA Meetings Across 4 FDA Review Divisions
- Refusal to File
- NASDAQ Delisting/Going Private Transaction
- Accelerated Approval Pathway

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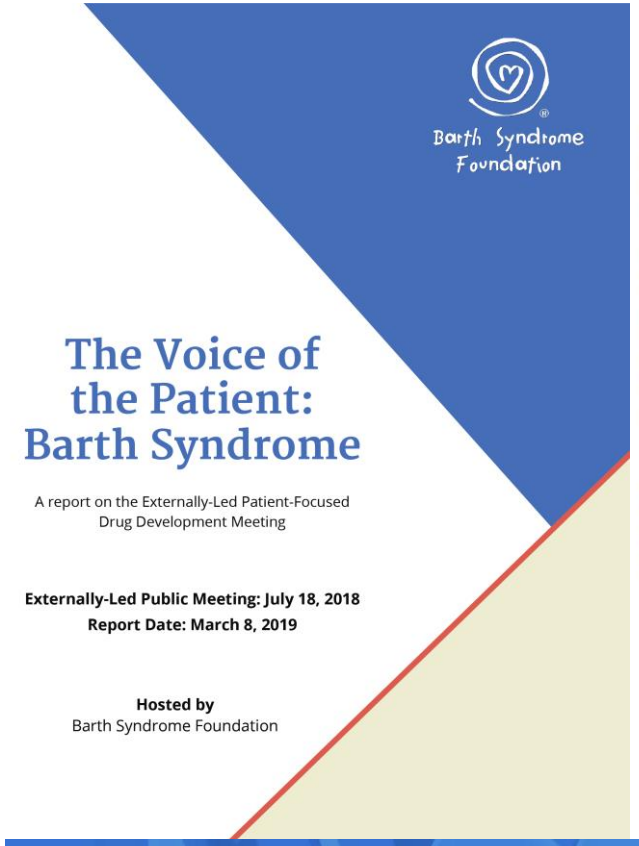
Our Barth Syndrome Development Journey

Unwavering Advocacy Support

Barth Syndrome Foundation:

- Submitted a petition signed by 4,256 individuals
- Submitted 2 doctors' letters
- Met independently with FDA >6 times
- Attended 7 Sponsor-FDA meetings



FDA & STEALTH BIOTHERAPEUTICS: ALLOW INDIVIDUALS WITH BARTH SYNDROME ACCESS TO ELAMIPRETIDE

Elamipretide, produced by Stealth BioTherapeutics, is an experimental drug that has been shown to reduce debilitating fatigue and potentially improve important baseline health measures in people with the ultra-rare disease Barth syndrome. Given the risk of life-threatening cardiac complications in this population, individuals with Barth syndrome cannot wait for additional studies of elamipretide before receiving access.

FDA has repeatedly signaled the importance of incorporating the "patient voice" in drug development. This is especially critical in rare diseases. The 21st Century Cures Act requires sponsors to include and FDA to consider the patient perspective. The voice of affected individuals and organizational advocacy is critical in communicating to FDA the extreme unmet need in Barth syndrome. In 2018, the externally-led Patient-Focused Drug Development meeting on Barth syndrome revealed that 100% of patients experience fatigue, 90% (based on cardiomyopathy occurrence) have heart failure or other life-threatening cardiac complications related to their disease, and 100% of patients surveyed would like access to therapies that improve quality of life even if they do not reverse disease.

As of today, there are only 126 known affected living individuals in the United States. In a very small clinical trial like TAZPOWER, it is very challenging to see compelling clinical data that reach statistical significance. The majority of trial participants experienced improvements in fatigue, strength, and quality of life. The patient voice becomes particularly critical in this setting. **We are asking FDA and Stealth to work together to provide access to elamipretide to people with Barth syndrome as soon as possible.**

KEY MESSAGE

FDA seeks to hear the patient voice and understand patient tolerance of risk of uncertainty of benefit, but application of learnings and regulatory flexibility may vary

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Our Barth Syndrome Development Journey

Clinical Challenges

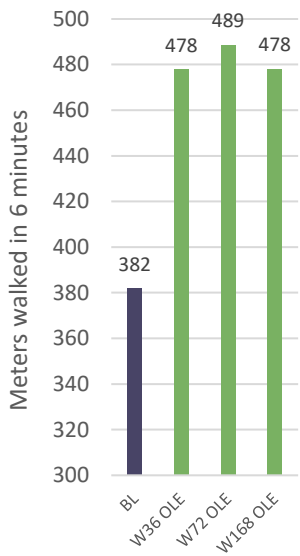
2014

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

2019

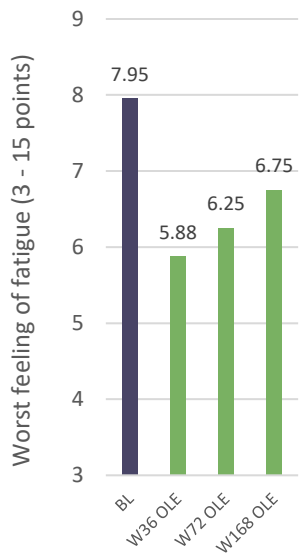
P2 primary analysis not met; open-label data promising

6MWT (n=8) ↑



W72 OLE p=0.0124
W168 OLE p=0.0032

BTHS-SA fatigue (n=8) ↓

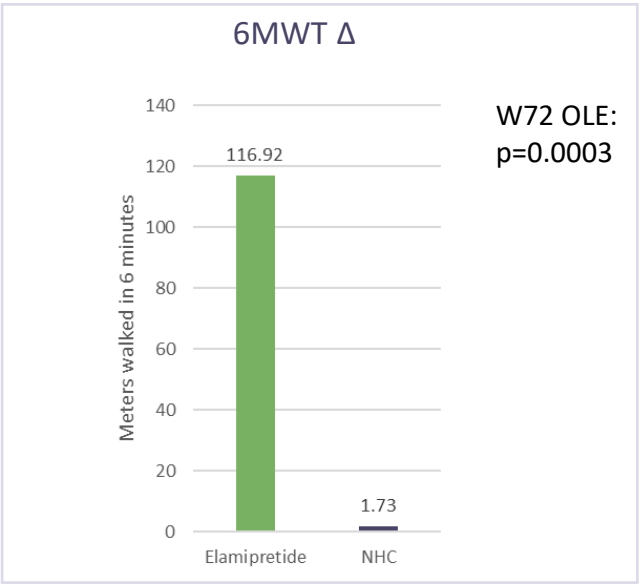


W72 OLE p=0.0656
W168 OLE p=0.2056

↑ ↓ *denotes direction of positive change*

2020

Positive P3 natural history control trial



KEY MESSAGE

In ultra-rare diseases, developers may only have one shot on goal, which may be poorly informed by unvalidated animal models. Innovative approaches to acquiring and interpreting data may be needed.

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Why is Ultra-rare So Challenging?

Statistical Considerations with Small Sample Sizes in Heart Failure (HF) Trials

"Janet Woodcock said in a recent speech about ultra-rare disease drug development that this is "a place where mechanistic reasoning may play a major role" and "we have to stop just thinking that empirical evaluation is the only way of determining truth." STAT First Opinion, 9/14/2021

- Between our P2 trial, enrolling **12** Barth syndrome patients, and our P3 trial, in which an additional **19** natural history control patients were studied, we assessed **>20%** of the US Barth syndrome patient population
- In hypoplastic left heart syndrome, a rare disease affecting ~54,600 Americans, clinical trials of ~30 patients (5% of the US population) are typical. Enrolling 20% of the US hypoplastic left heart syndrome population would require **~11,000 patients**
- In heart failure with preserved ejection fraction (HFpEF), a common diseases affecting >2.5m Americans, clinical trials of ~6,000 patients are typical. Enrolling 20% of the US HFpEF population would require **500,000 patients**

+

- FDA requires association between cardiac improvement and clinical benefit.
- For HF diseases in which patients lose ambulation (Friedreich's ataxia, Duchenne) or which are ultra-rare (Barth syndrome) this means extremely long, extremely large, outcome trials.
- These cannot be completed within "a few years" of accelerated approval.

KEY MESSAGE

FDA regulations do not distinguish between rare and ultra-rare diseases for evidentiary purposes, yet it is MUCH more difficult to power clinical trials in ultra-rare diseases.

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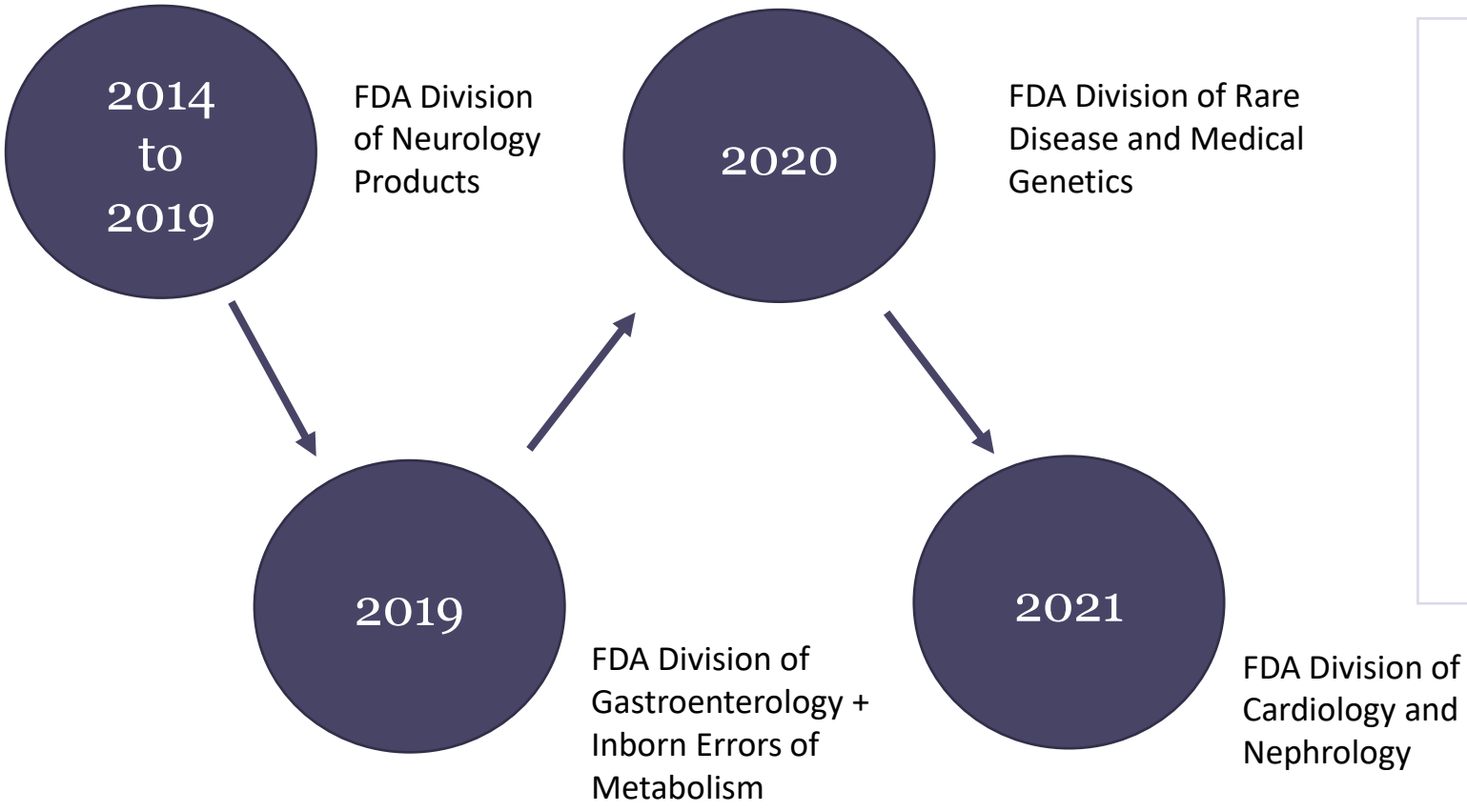
Our Barth Syndrome Development Journey

Regulatory Challenges



MedCity News

PHARMA, BIOPHARMA

FDA refusal of Stealth Bio drug shows challenges of ultra-rare disease studies

The FDA refused to review Stealth BioTherapeutics' Barth syndrome drug, telling the company results in a study of just eight patients are insufficient to support its submission. The impasse highlights the challenges of testing drugs for ultra-rare diseases. Barth is so rare that Stealth is unsure it can recruit patients to run a new study.

By FRANK VINLUAN

Post a comment / Oct 21, 2021 at 11:08 AM

KEY MESSAGE

FDA regulations do not distinguish between rare and ultra-rare diseases in applying regulatory flexibility, increasing the risk of Type 2 error. Perspectives on flexibility and review pathways can vary between centers, divisions, and even clinical reviewers.

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Why is Ultra-rare So Challenging?

Ad Hoc Exercise 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

"I don't think there's good visibility about what FDA is going to do. In many ways, it's a black box and the variability of the different arms of the organization makes it more complex." Gil Blum, Needham, quoted in STAT, 7/26/2022

GUIDANCE DOCUMENT
Rare Diseases: Natural History Studies for Drug Development
Draft Guidance for Industry
MARCH 2019

GUIDANCE DOCUMENT
Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
FEBRUARY 2023

Brineura® (cerliponase alfa)

Effectiveness data from prognostically matched natural history controls.

SKYCLARYS™ (omaveloxolone) 50 mg capsules

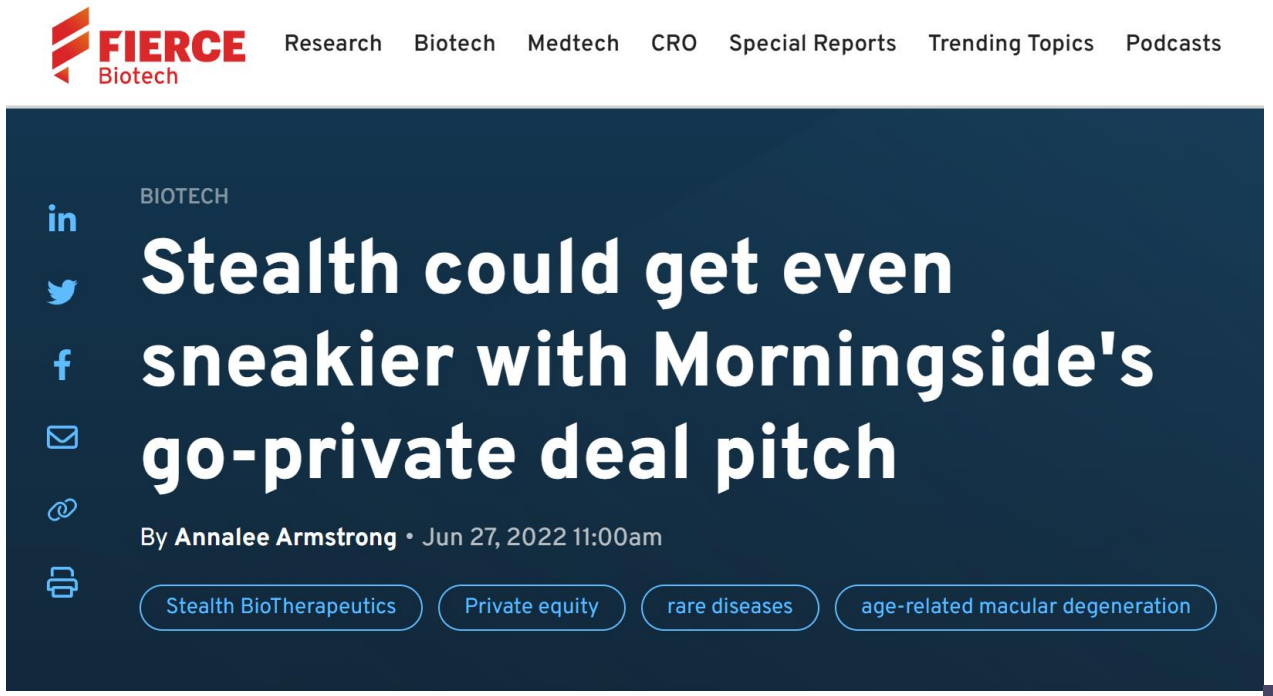
Effectiveness supported by post-hoc analysis of prognostically matched natural history controls.

KEY MESSAGE

FDA's application of regulatory flexibility *even for ultra-rare diseases* can be inconsistent across centers, offices, divisions, and even clinical reviewers, increasing regulatory and investment risk.

Our Barth Syndrome Development Journey

Market Challenges



The biotech, which has struggled to get its Barth syndrome drug elamipretide before the FDA for consideration, could become private again if it agrees to the transaction from Morningside.

KEY MESSAGE

Most ultra-rare drug development is conducted by biotech companies (not big pharma), increasing funding uncertainty particularly in challenging market conditions.

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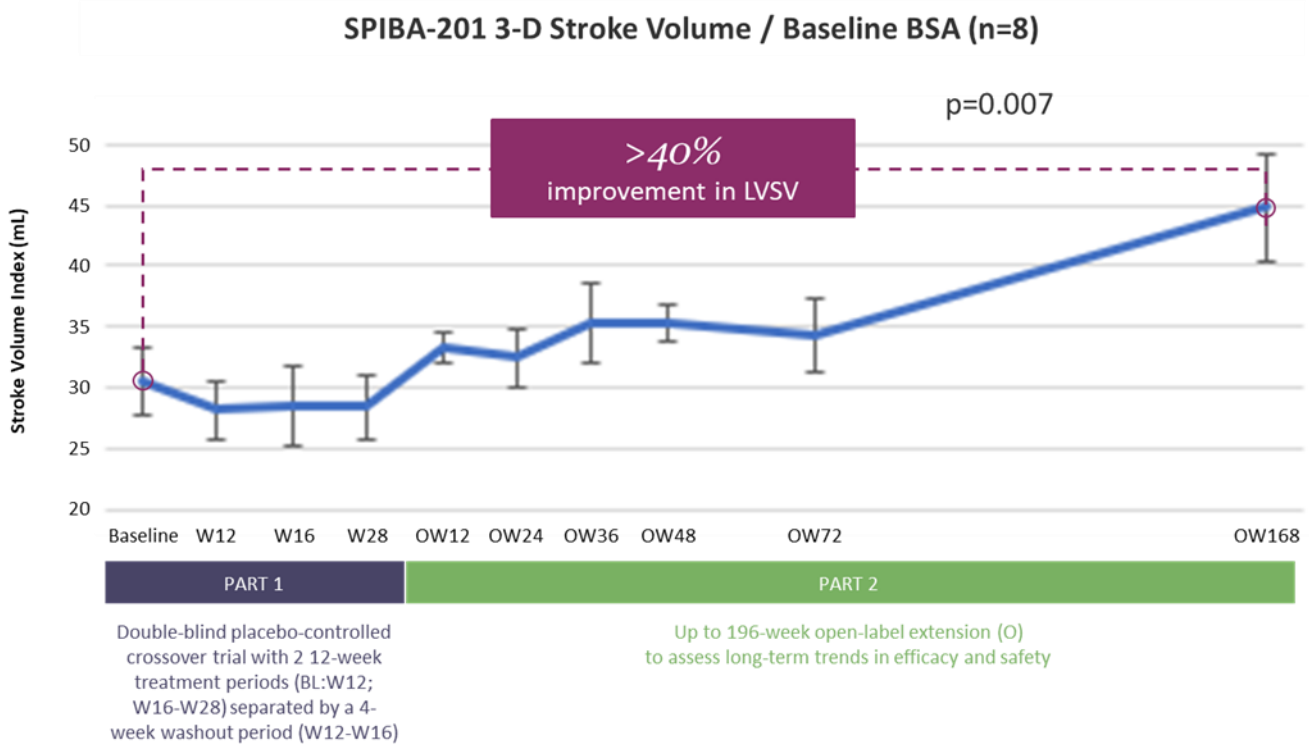
Our Barth Syndrome Development Journey

Accelerated Approval Pathway: Opportunities, Challenges, and Potential for Positive Change

Long-term Cardiac Data at P2 Study Close-Out May Support Accelerated Approval – with a Catch



However…

- FDA may require a demonstration of the association between the surrogate endpoint (cardiac improvement) and clinical benefit (exercise tolerance) to inform post-marketing trial design.
- This requires extensive NH history data which may not exist (or may be challenging to acquire) in ultra-rare disease setting.
- This exercise can delay regulatory progress by months (in our case, approximately a year).

KEY MESSAGE

FDA flexibility in the design of post-marketing trials for ultra-rare diseases could expedite access to therapy for patients with high unmet needs.

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Post-marketing Commitments – Other Potential Challenges

Requiring Enrollment of Post-Marketing Trials by Time of Approval Jeopardizes Viability of Pathway

- Under Food and Omnibus Reform Act (FDORA) (2023), FDA has the authority to require that drugs approved under Subpart H (accelerated approval, or AA) have a post-marketing study underway prior to approval or within a specified time after approval. This can be waived by FDA.
- FDA appears to be interpreting this as requiring full enrollment of post-marketing trials at the time of approval.

New requirement may introduce >2.5-year delay for ultra-rare approvals, increasing risk of program discontinuations

- 3.2 years median time to full-approval for all AA drugs[1]
  - 1-year for clinical trial start-up (site contracting, IRB approvals)[2]
  - 18-months for enrollment[2]
  - Additional timeline challenges for ultra-rare diseases in which trials take longer to complete than in common diseases and enrollment challenges are exacerbated post-COVID[3]

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Evaluate Vantage December 09, 2022

Not so fast for some accelerated approvals

Jacob Plieth

The US conditional approval pathway has enjoyed years of expansion, but now the FDA is trying to put the toothpaste back into the tube.

By Annalee Armstrong • Nov 8, 2022 10:25am

KEY MESSAGE

Requiring full enrollment of post-marketing studies for ultra-rare diseases further stresses the already challenging value proposition for ultra-rare disease drug development, requiring significant at-risk investment in a post-marketing trial predicated on uncertain regulatory approval.

[1] Kaltenboeck et al., Institute for Clinical and Economic Review, 2021; Beaver et al., JAMA Oncol., 2018; [2] Lamberti, et al., Therapeutic Innovation & Regulatory Science, 2018; post-COVID, these timelines are even longer Hillman, Castañeda, Clinical Trials Arena, Mar 2022); [3] Bell, Smith, Orphanet J Rare Dis. 2014; Clinical Trials Arena, Clinical-Trials-in-2022-Highlights-for-the-year-ahead

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Our Barth Syndrome Development Journey

Accelerated Approval Pathway: Opportunities, Challenges, and Potential for Positive Change

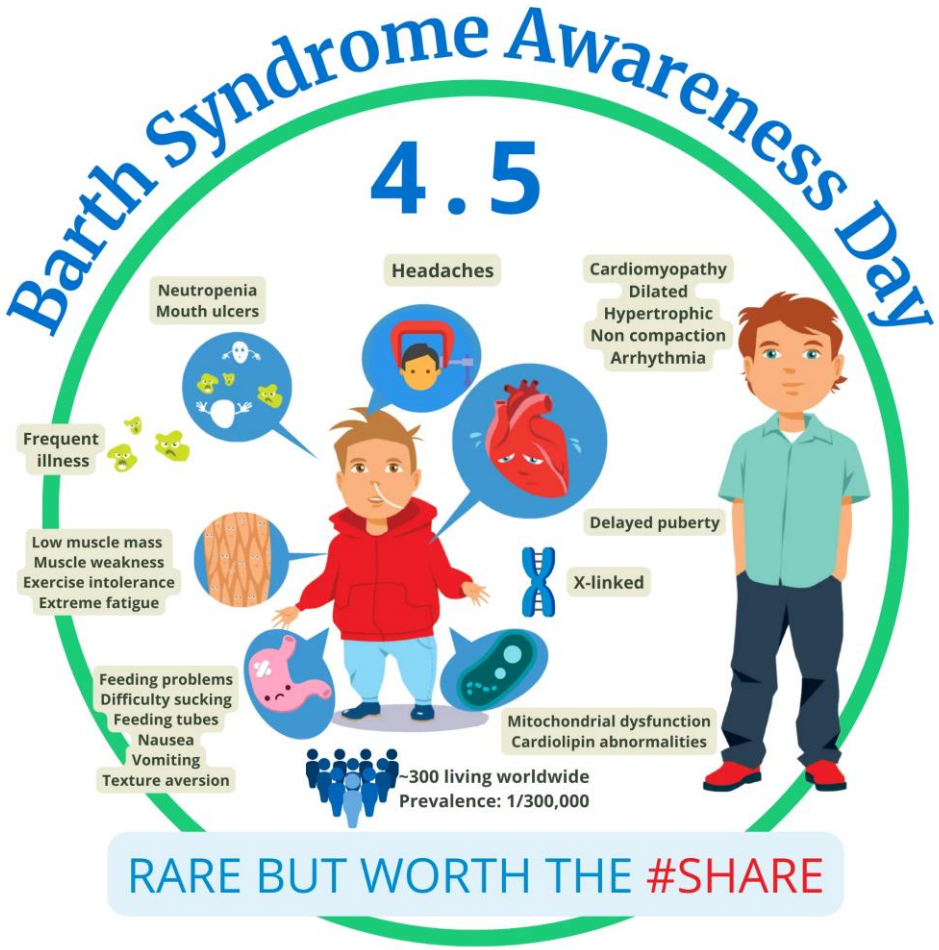
- Define a threshold for ultra-rare diseases entitled to maximum regulatory flexibility
  - Consider utilizing the intermediate clinical endpoint arm of Subpart H to require further data collection to support efficacy post-marketing
  - Embrace acceptability of real-world evidence (including registries) and natural history controls to support ultra-rare approvals and post-marketing commitments
- Expand upon CDER's Acclerating Research and Cures initiative to improve cross-Agency oversight and consistency of ultra-rare decision-making
- Expand priority review voucher incentive to ultra-rare diseases as a joint patient-taxpayer-pharma solution to rationalize more investment in our most vulnerable patients

KEY MESSAGE

- Defining ultra-rare diseases opens door to improved regulatory flexibility and sensitivity to Type 2 error – without setting precedent for larger diseases
- Broader cross-Agency awareness of ultra-rare disease "stopping decisions" – RTFs, CRLs, etc. – may improve consistency of regulatory approach
- Explore innovative pathways to incentivize pharma investment

Our Barth Syndrome Development Journey

Congrats to the Barth Syndrome Community on Congressional Recognition of Barth Syndrome Awareness Day



- Barth syndrome is caused by a mutation in the tafazzin gene (TAFAZZIN, also called G 4.5)
- 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.

ReCap

- There are tremendous healthcare inequities for ultra-rare disease patients – with Wall Street, regulatory, and clinical odds all stacked against them
- New incentives and differentiated ultra-rare regulatory pathways may be needed to motivate investment in our most vulnerable patients
- FDA should recalibrate the risk of Type 2 error for ultra-rare diseases and take steps to improve the public trust in the consistency of its decision-making
- Policy changes should explore innovative incentives to motivate industry support of ultra-rare therapeutic development – such as expansion of priority review voucher awards to developers of therapies for ultra-rare diseases

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[1] NORD Avalere Report: ORPHAN DRUGS IN THE UNITED STATES: An Examination of Patents and Orphan Drug Exclusivity, 2021; [2] Isakov et al., MIT,.edu 2016; Janiaud et al., Annals of Internal Medicine, 2021; [3] Yates, Hinkel, Clin Transl Sci. 2022