Barth Syndrome Foundation®

Dr. Norman Stockbridge, MD, PhD, Director
Division of Cardiology and Nephrology
Center for Drug Evaluation and Research
U.S Food and Drug Administration
Silver Spring, MD 20993

February 22, 2022

Dear Dr. Stockbridge,

I hope that you and others in DCN are doing well and have been able to stay healthy in 2022.

I am writing you now to follow up on your suggestion that the Barth Syndrome Foundation (BSF) request a meeting with you to discuss "broad issues in developing a therapy for this terrible disease," and I have copied Bridget Kane on this letter, as you said she would be involved in organizing this.

We have been struggling to identify how we at BSF might best move forward to develop therapies for our disease, given just how ultra-rare it is. The practical considerations associated with the challenges of drug development in Barth syndrome are based on the facts shown in the figure below. These numbers include all U.S. Barth patients down to the youngest deemed at all feasible by Stealth BioTherapeutics in the latest protocol they have proposed for further elamipretide studies:

#BTHS Individuals in the U.S. ≥ 10 Years Old as of 12/31/21*	96
MINUS those with heart transplant (estimated at 16%)	-15
MINUS those with ICDs (estimated at 28% of those ≥ 15 years old)	-20
MINUS current elamipretide EAP participants	-7
TOTAL Available in U.S. ≥ 10 Years Old for Clinical Trial	**54**

*from the BSF Barth syndrome patient database

Several crucial implications of this very limited cohort include:

- It is SIMPLY IMPOSSIBLE to muster the number of participants required to power a clinical trial that meets generally required p-values typical of larger indications that have much larger participant pools from which to draw.

- Practical considerations aside, *if* 24 participants might be required for a "well-powered" randomized, double-blind, placebo-controlled study in Barth syndrome, that would represent 44% of that entire population!!! And that assumes that everyone in the eligible age range would qualify based on other inclusion/exclusion criteria, which we know is not the case even with very inclusive parameters. If this same 44% percentage of population were required of larger indications, a similarly proportioned trial for a potential treatment for type 2 diabetes (which affects 37.3 million Americans, according to diabetes.org), would include 16.4 million individuals! By raising this very practical reality of powering limitations, we are not seeking lowered standards for ultra-rare diseases but rather fairness on a par with larger indications that still indicates efficacy. Ten percent is the rule of thumb for the maximum number of participants that can be recruited from a patient population, not 44%.
    - The data that were generated by the twelve individuals in the elamipretide study represented 22% of the relevant age group in the U.S. at the time. (NOTE: This calculation is understated because it does not account at all for the reduced size of the eligible cohort based on other inclusion/exclusion criteria such as weight, medication stability, ambulatory ability/impairment or ICD discharges.) Results from such a large proportion (more than double the 10% rule of thumb) of our patient population, even if difficult to interpret due to limited statistical power or other sources of residual uncertainty (e.g., open-label nature), MUST count for something, as they absolutely give an indication of broad efficacy. Ultra-rare diseases, by virtue of our small numbers, simply cannot conform to the same statistical standards. The Barth syndrome patient community has clearly expressed its tolerance for the acceptance of residual uncertainty that results in less confidence in treatment benefits inherent in this ultra-rare disease dataset.
- The fact that, even if a study were ever able to enlist the number of participants required to meet standard p-value requirements (which would presumably take many years to fully enroll, if it were ever possible at all), the execution of those trials would necessarily mean that recruitment for any future trials of other potential treatments would be <u>completely</u> crippled. To require that traditional statistical power standards be met (thus requiring, in our case, that nearly half of eligible individuals participate), the Agency is indirectly stunting any additional contemporaneous R&D efforts for our community. We, and other groups like us, have to be permitted to support more than a single trial in order to develop treatments for our patients. We know that not all trials are successful, and our goal is to save lives that are much too frequently lost at a young age, as you know.

The practical possibilities available to all of us who work in rare diseases currently are a mere subset of those afforded larger populations and leave us with very few options, *if any at all*. There is a reason that more than 95% of all rare diseases lack even a single FDA-approved therapy. This is a clear bias that results in a very real disservice that impacts not only those with Barth syndrome but also the estimated 25-30 million U.S. patients living with rare diseases. There MUST be other approaches available for ultra-rare disease trials and regulatory review, especially when the particular rare disease communities themselves are well-informed

of and have expressed tolerance for the tradeoffs of Type 1 and 2 error that this necessarily entails.

We would really welcome the chance to brainstorm with you about new avenues and out-of-the box ways of thinking to solve this critical problem, including both (1) your creative notion of possibly utilizing the statutory foundation on which the animal rule is based to allow alternative sources of efficacy data where traditional clinical studies are infeasible and (2) consideration of our community's accepting greater uncertainty of treatment benefit by prespecifying p-values that are commensurate with feasible study designs.

Please let me know what I should do to help plan such a meeting.

Best regards,

Kate McCurdy
BSF Board Chair and Mother of Son with Barth Syndrome (Deceased)

cc: Bridget Kane, FDA Senior Regulatory Health Project Manager