FARA Friedreich's Ataxia Research Alliance

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December 12, 2022

Via Electronic Submission

Food and Drug Administration
Docket No: FDA-2022-N-2394
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA CBER OTAT Public Patient-Focused Drug Development Listening Meeting – Patient Perspectives on Gene Therapy Products; Request for Comments (Docket No: FDA-2022-N-2394)

The Friedreich's Ataxia Research Alliance (FARA) would like to thank OTAT for hosting a virtual patient-focused drug development listening meeting to hear patient perspectives on gene therapy. FARA is a non-profit research advocacy organization based in the United States, representing multiple stakeholders in the Friedreich ataxia community including individuals with the disorder, their families, researchers, and clinicians.

Several members of the Friedreich's Ataxia (FA) community, including a patient, parents of children with FA, as well as the CEO of FARA, were able to speak at the listening session. We would like to restate our perspective here on the important issues we raised at the meeting.

While the FA community looks forward to participating in gene therapy trials, they are carefully weighing associated risks along with the possibility that a gene therapy treatment would interfere with participation in future trials with the potential benefits. The community believes that FA will be treated by a cocktail of medicines, and that gene therapy will be an important part of this cocktail. Our patient representative stated that the community is grateful for the FDA's guidance to industry for gene therapy for neurodegenerative disease that puts patient safety first. However, there are serious concerns with the recommendation of a unilateral intraparenchymal injection as the first administration in the first-in-human (FIH) trials. Not all areas of the brain function perfectly bilaterally. One such area is the dentate nucleus of the cerebellum, an important treatment target in FA. The circuitry of the cerebellum is complex in that some pathways cross to and synapse on the other side of the brain and some do not. This configuration means that each cerebellar hemisphere affects both sides of the body to some degree, especially for speech and balance. It follows then that unilateral administration to one dentate nucleus will not restrict the effect of treatment to one side of the body. If damage results from the administration, both sides of the body are likely to be impacted. If the treatment works, there is also potential for a unilateral administration to exacerbate dysfunction rather than to improve it. We know that the guidance is intended to decrease risk by sparing of the other side of a bilateral brain area if unilateral treatment caused damage. Unfortunately, in the case of FA and the dentate nucleus, unilateral treatment will not result in a unilateral effect and has the potential to worsen a patient's neurological function. We find the risks posed by unilateral treatment to be unethical and unacceptable, even for a handful of patients in an early-

phase trial. We ask that the FDA reconsider this guidance in the context of intraparenchymal CNS treatment of FA.

The parents of children with FA who spoke at the meeting reiterated the concern with unilateral administration, stating that, while well intended, the anatomy of the target nuclei in FA does not function as a bi-lateral structure and unilateral administration does not de-risk the procedure and may cause harm.

In addition, these speakers raised the concern that sham surgeries requiring anesthesia present an unacceptable risk to people with FA, who are particularly vulnerable to any surgical procedure. While a placebo group in a well-controlled study is acceptable, subjecting someone with an elevated risk for harm to a procedure unlikely to maintain the blind in a trial is not acceptable to the community.

Finally, as parent of children with a progressive disease, the FDA requirement of a five year follow up for children treated with gene therapy presents a heart-breaking dilemma. If participation in a gene therapy trial for one symptom of FA excludes a child from other trials, a child may develop another symptom of FA but be unable to participate in a trial specifically aimed at treating that symptom. The FA community, especially those caring or children with FA, ask the FDA to reconsider the five year follow up period for progressive neurological diseases in pediatric patients.

As CEO of FARA, I addressed the need for OTAT to identify mechanisms for reducing to practice the use of natural history and non-interventional data, as suggested in various FDA guidance documents, in the development of innovative and adaptive trial designs including those where such data can supplement control or comparator arms.

FARA has worked with the clinical research community to carefully study and understand the natural history of FA. There is an ongoing prospective, longitudinal, non-interventional, observational trial that is entering its 20th year with nearly 1500 individuals enrolled. The participants in the trial represent the overall FA population and, given the size and duration of the trial, there is the ability to also evaluate subgroups. All endpoints are pre-specified with standardized collection procedures. The data has been collected and curated in a 21 CFR part 11 compliant electronic data capture system. The investigators and sites involved in this study are also experienced in interventional trials in FA using many of the same assessments.

This non-interventional study has contributed to the understanding of the natural history of disease, development of clinical outcome assessments and patient reported outcome measures and informed clinical trial designs published in more than 25 peer-reviewed manuscripts. In addition, data from this study and other FA clinical trials are available in the Rare Disease Cures Accelerator Data and Analytics Platform (RDCA-DAP), an FDA supported initiative that provides a centralized and standardized infrastructure for sharing and analysis of such datasets. Many more details can be provided to OTAT about this trial and the practices and procedures employed to ensure integrity and interpretability of the data.

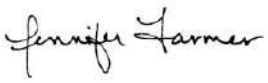
FDA guidance documents including the Rare Diseases: Natural History Studies for Drug Development and Human Gene Therapy for Neurodegenerative Diseases and many others acknowledge opportunities for using such natural history data in clinical development. However, there seems to be gaps in reducing this to practice, especially when considering leveraging such data sets in control or comparator arms for trials.

We agree with FDA guidance and recommendations that optimal study design is randomized and controlled so that results can be quickly and accurately interpreted, and that innovative and adaptive designs may also be employed to facilitate product development. We see an opportunity now to work with the FDA to identify mechanisms where such trials and datasets can be used to inform and support adaptive design approaches such as Bayesian methods of borrowing historical data. These novel methods for borrowing data to supplement control or comparator arms can address some of the challenges in conducting trials in rare diseases – specifically reducing size of placebo arms and overall number of participants, time, and resources to conduct trials.

We are encouraged by the recent announcement that has elevated and increased resources for OTAT. It is critical that you have the human and technology resources needed to meet the growing demands of translating, evaluating, and approving these novel therapies, which have the potential to meaningfully improve the lives of people living with Friedreich's Ataxia and many other rare diseases.

We look forward to opportunities to work with OTAT on the feedback from this listening session to further incorporate patient preference and experience in to the drug development and regulatory review process.

Sincerely yours,



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