August 13, 2021

Kathleen Donohue, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Rare Diseases and Medical Genetics
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: August 3, 2021 FDA-NPC Community Listening Session

Dear Dr. Donohue:

On behalf of the Ara Parseghian Medical Research Fund, the National Niemann-Pick Disease Foundation, and the International Niemann-Pick Disease Alliance, we would like to convey our appreciation for the engagement and transparency of you and your Agency colleagues in the August 3, 2021 Listening Session (Session). You will recall we began the Session stating our appreciation was paired with a fair amount of skepticism. Unfortunately, many in our community had even more reservations after the meeting as several core concerns were not addressed. Specifically, they did not hear enough about how benefit and risk, regulatory flexibility, and the totality of years of data are used to evaluate current therapies.

We all agree strongly that continuing interactions between our community and the Agency to collaboratively address issues raised and alluded to in the Session can drive significant near-term progress in expediting potential therapies for Niemann-Pick Type C (NPC). Further, we want to note that given limited time and the robust exchanges in the Session, several of our community's key experts were unable to share views on regulatory flexibility and the NPC Clinical Severity Scale (CSS). Therefore, we do plan to share a summary of what we heard during the meeting supplemented by what we also planned to convey but were unable to present.

The central purpose of this post-Session correspondence is to:

1. Seek near-term clarification about several statements made by the FDA during the meeting so we can either confirm or curtail some key concerns those statements raised within our community;

2. Recommend several short-term actions based on what we heard so we can work together to address multiple urgent concerns about both access and ongoing studies; and

3. Propose focused areas for follow-up discussions that are critical for the shared interest in bringing effective treatments to people with NPC.

What We Heard

During the Session, we captured several key points, summarized below, arising from comments by you and your Agency colleagues, the expert NPC clinicians, and patients and caregivers.

A. We appreciate that FDA is not insensitive to the frustration the community is experiencing with no prior approvals and an unclear path forward for several clinical programs, – as well as new restrictions on an Expanded Access program. However, we are concerned with the comment "if real" in reference to recent clinical trial results, with implied concerns about validity and variability of trial data, such as from CSS results. The statements/conclusions by recognized experts in NPC and families with direct experience portrayed these same results, obtained using standard research process, as very convincing. We require further rationale to understand the seeming discord in conclusions which FDA and experts/investigators have based on the same data. You recently received a letter signed by many clinicians, some of whom you said were among the best in the world, stating that these therapies are helping -and 'real.' Plus, you indicated that parents are the experts. Our understanding how you take this information to determine if it is "real" is critical.

B. The Agency could not comment on active studies, especially submissions under review. Some listeners postulated that this lack of response was due to standard sponsor-Agency confidentiality requirements, but others felt, along with repeated statements from FDA about the "next generation of trials," conveyed the Agency was moving beyond current studies due to interpretive gaps/issues with the CSS and that clinical work to date was a lost cause. Therefore, we respectfully request clarification of the Division's rationale in not addressing several specific points made by the community in this regard. As noted, this is the core issue of most families and access to these life-improving therapies is our number one priority.

C. We heard the Agency has concerns regarding the CSS. We had several experts comment on the use, development and validation, as well as note the presence of fidelity training and instructions for rating of the CSS in the Session. However, due to time limitations, not all were able to share their knowledge and expertise as planned. The CSS has been accepted globally by the Niemann-Pick community as a viable and meaningful clinical endpoint that is being used in all current clinical trials. The CSS is a consistent component within the natural history data for NPC. The data from the natural history studies and clinical trials are invaluable and irreplaceable. We encourage the Agency to work with the CSS experts so that the concerns of the FDA can be understood.

D. Dr. Berry-Kravis commented that reassessing CSS validation and standardization could in principle be possible using external objective measures for each domain from Rush/NIH. This could provide a near-term intervention--based on re-analysis of current data and pending trials which have utilized the CSS in their studies-- to supplement but not supplant current use. Our organizations are fully committed to directly engage with and support sponsor efforts of this nature if FDA can confirm there would be receptivity to such analyses. Without this confirmation, these pursuits would be futile and add considerable delay and further add to disappointments for patients

E. The community has been encouraged by previous discussions and FDA comments about regulatory flexibility and alternative trials, as well as understanding that heterogeneity concerns might be addressed with some modifications via more innovative analyses. Despite this, we have

yet to see change and innovation supported in practice. We wish to continue these discussions and to expand upon this viewpoint with respect to both current and future studies.

F. While not addressed directly, the FDA's acknowledgment of the community's broad risk and uncertainty tolerance would suggest that the major impediments to approvals appear to be in terms of sufficient efficacy assurances. If this is accurate, the relative benefit-risk calculus for rare versus prevalent diseases should be revisited; not so much in terms of lowering what we view as unrealistically high bars, but rather, with reasonable safety assurances in trials for rare diseases such as NPC, the minimal efficacy hurdle should be proportionate to the expectations for more prevalent disorders on a population-based factor. For example, using Alzheimer's disease as a contemporary comparator, the acceptance of sponsor data on aducanumab from thousands of patients without a clear/statistically significant efficacy signal, a putative positive biomarker finding, and small but significant risk for severe brain bleeds could translate into an ultra-rare disorder such as NPC for which no approved therapies are available. Applying this model to recent NPC trials, the absence of comparable life-threatening risks and the proportionate/equivalent benefit-risk expectation seem to satisfy the requirement set by the FDA for approval for several of the recent or pending NPC-related applications. Therefore, our community would value your explanation of how such interpolation would be viable for resubmissions or similar considerations.

G. For rare diseases such as NPC, the FDA should reconsider the use of Real-World Evidence (with separate standards from traditional substantial evidence) as the basis for expedited approvals compared to historical controls and/or within person comparisons of rates of decline, paired with totality of evidence in any new trials. While we understand FDA is not able to advocate for statutory changes, our community is committed to pursue such needed structural changes and wishes to understand FDA views on the approach. .

H. While the community is fully supportive of more data-sharing across trials, especially for placebo arms which might be aggregated to produce simulated natural history cohorts, this matter is largely in the hands of sponsors, and therefore requires further collaboration among companies, regulators, and our community to move ahead on such important initiatives. As with the recent gathering to explore platform trials, our organizations will be supportive of, but are not in a position to drive, this endeavor. Moreover, pre-competitive efforts such as these must be supported by a clear and reliable regulatory pathway which appears elusive at this point.

What We Propose

We suggest the following course of action to assure mutual progress.

A. A convening of sponsors, FDA, NPC clinical experts and community representatives to directly address the following issues:
   - Near-term regulatory flexibility which may be provided for recent/current trials;
   - Agreement on timelines and working groups to address FDA concerns regarding the CSS in the mid-term without dismissing the impact of current and past data; and
   - A shared recognition that a single approval of an NPC therapy which demonstrates even modest efficacy signals and no life-threatening risks, would engender broadened research and development in NPC similar to that which has occurred previously in fields such as Hepatitis C and Duchenne Muscular Dystrophy.

B. A conceptual agreement to reconsider applications based on agreed re-analyses as developed by recognized experts.

C. A willingness for FDA to broaden considerations for near-term flexibility in recognition of the pressing, unmet needs of the NPC community and in recognition of the community's willingness to work with the FDA on the shared goal of finding paths forward to regulatory approvals of therapeutic agents for NPC including identification of biomarkers and intermediate clinical outcomes to assist future expedited considerations.

Our organizations are committed to find near term solutions for patients' urgent and unmet needs which will be a springboard to ongoing advances in treating this disease. The August 3 Session can be a step forward provided it is incorporated into an ongoing effort between the community and the Agency rather than a single transaction to position commentary on the CSS. We invite you to join us in a transparent collaboration to identify a direct, successful path forward for each therapy in the NPC pipeline with a longer-term strategy of incorporating broader enhancements in the endpoints, conduct, and related advances in NPC therapy development and approval processes.

Your reply is requested by August 31, 2021 to ensure we build momentum behind this work. Please contact Sean Kassen (Sean.C.Kassen.1@nd.edu) for additional information.

Families are counting on all of us.

Sincerely,

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