VIA ELECTRONIC DELIVERY

December 13, 2021

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
1201 Pennsylvania Avenue, Suite 500
Washington, DC 20004

Dear Dr. McClellan,

On behalf of the Niemann-Pick Type C (NPC) community, we write to thank the Duke-Margolis Center for hosting a workshop with FDA for endpoint considerations to facilitate drug development for NPC disease. This is perfect timing for our rare disease community as the need has never been greater to build consensus on an endpoint(s) that can support the evaluation of therapeutics for the treatment of NPC. In fact, our community has granted significant resources in this area in the past and is in the process of launching a biomarker/endpoint initiative.

We are grateful for this opportunity and recognize that this is the beginning of a multi-year endeavor. At the same time, however, there is an immediate need in terms of how we evaluate disease progression today, especially as we have multiple therapies in clinical development that are helping NPC patients. We are at risk of losing access to those agents due to a regulatory framework and process that is not well-designed for rare disease patients. Additionally, industry partners investing substantial resources on NPC treatments operate under continually changing expectations and scientific second-guessing by FDA. This will continue without agreement on endpoints and pathways to meet regulator expectations.

Over the past 25 years, NPC pediatric neurologists and other clinicians, scientists, and rare disease experts developed and refined a tool, based on patient and caregiver input, to evaluate NPC disease progression, the Niemann-Pick Type C - Clinical Severity Scale (NPC-CSS). The NPC-CSS was used as the primary outcome measure in multiple trials and was used to provide breakthrough status designation on multiple therapies for the treatment of NPC disease. It has been clinically validated and published repeatedly, and there are multiple patient surveys that verify it captures what is important to the NPC patients. Additionally, studies show high rates of inter-rater reliability when using the 5-domain scale and it has been used for the collection of the NIH natural history study over many years. Discarding it now would be devastating and would threaten those important data.

Recently, the relevant review division at the FDA had a change in leadership and the new director has stated the NPC-CSS tool is not satisfactory for registration purposes. This change was quite a shock to our community as the data has been collected over many years, multiple clinical trials have been executed (and the tool was an agreed upon measure with the FDA), and recently a letter was sent to the FDA and signed by over 40 expert NPC clinicians stating that it is a valid and reliable way to evaluate disease progression given that NPC is an ultra-rare, heterogenous and fatal disease with no approved therapies.

Therefore, while we are eager to work with the FDA on the identification and validation of a new and improved endpoint(s) measurable in a shorter timeframe for future drug development, it is imperative we come to an understanding and agreement on the current regulatory utility of NPC-

CSS. Its importance to our community for both registration studies as well as access to life-improving therapies hangs in the balance for all NPC patients. Additionally, our community wants to ensure the data we have collected over the past 25 years are preserved and used as a foundation upon which other measures can be built.

Recently, some of us had the opportunity to speak to staff members at the Duke-Margolis Center and we emphasized these points as critical for inclusion in the upcoming program. In addition to the issues around the NPC-CSS, we also requested this meeting include: (1) exploring alternatives to demonstrate benefit; (2) preserving existing data; (3) use of the natural history data as a control, rather than a placebo; and (4) understanding the real-world effect of not treating, including certain death for NPC patients. We also sent along some information that includes an overview of our recent listening sessions with the FDA and the recent letters that were sent to the FDA addressing these NPC endpoint and related concerns. We also are able to send the published benefit/risk surveys and the overview of the Patient-Focused Drug Development meeting we hosted in 2018, which provided important information regarding patients and families benefit expectations and risk tolerance. We also will send additional publications, including those from the recent Hill briefing.

When the Duke-Margolis meeting agenda was published online, we noticed that the NPC-CSS will be a point of discussion and are grateful for that. The need for a collaborative scientific workshop for NPC is urgent and it is critical we have the right agenda items for the upcoming workshop. Therefore, as you prepare the agenda, we want your team to know we are interested in collaborating and providing more insight into the NPC community and these issues. While NPC is an ultra-rare disease, the community has a substantial wealth of talent supporting this disease. We have suggested speakers from the NPC community, especially those clinicians with extensive experience in development studies and NPC patient care.

For the workshop itself, it is our hope this background information our community provided will be read by all attendees prior to the session. Furthermore, while our community, which includes expert pediatric neurologists, scientists, families, patient organizations and rare disease experts, disagrees strongly with the FDA's assessment that the NPC-CSS is not a satisfactory tool, we also believe this workshop can provide a venue where we can discuss this in an open format and find points of agreement and an immediate path forward. This consensus will undoubtedly allow patients to continue access for current experimental therapies, which is a top priority, and be a building block for future therapies and identifying endpoints. To help facilitate these discussions, we also feel having a group of well-respected pediatric neurologists and rare disease experts in attendance to listen and offer an impartial view will be a great way to ensure we are moving in the right direction. I know our clinicians can suggest some individuals alongside any who might be identified by FDA or your group.

Please know we are committed to working with FDA and third parties to find a clear path forward for NPC therapy development and we absolutely must maintain access to existing treatments. We are happy to discuss these thoughts with you at your convenience and look forward to assisting with the development of the workshop and to actively participating as well.

Thank you again.

Sean Kassen, Director of the Ara Paraseghian Medical Research Fund at Notre Dame
Joslyn Crowe, Executive Director of the National Niemann-Pick Disease Foundation

Phil Marella, Founder of the Dana's Angels Research Trust, Parent of two children with NPC
Jonathan Jacoby, Founder of the Hide and Seek Foundation, parent of a child with NPC
Chris and Pam Andrews, Co-Founders of the FireFly Fund, Parents of two children with NPC
Sara McGlocklin, President Hope For Marian, parent of a child with NPC
Cristin Davidson, Project Manager, Support Of Accelerated Research for Niemann-Pick C
Cindy Parseghian, Founder and President of the Ara Parseghian Medical Research Foundation, Parent of 3 children with NPC
Justin Hopkin, Board Chair, National Niemann-Pick Disease Foundation