FDA Meeting 8/3/21
Closing Statement
Joslyn Crowe, Executive Director, NNPDF

We have come before you today united as a Niemann-Pick type C community, represented together by the National Niemann-Pick Disease Foundation, the Ara Parseghian Medical Research Fund, and the International Niemann-Pick Disease Alliance. We join together for the patients around the world today, and those who will live with NPC tomorrow, and also for all of the patients whose lives we have lost and who cannot speak for themselves today.

Our families talked about multiple investigational therapies in the NPC continuum - adrabetdex, arimoclomol, N-acetyl-L-leucine, and Trappsol cyclo, active in clinical trial, and also miglustat. You have heard from our families and our expert clinicians and researchers about several important issues:

1. The opinion and experience of so many expert clinicians and families confirming that the NPC CSS measures areas of change that are truly **reliable and meaningful** in both clinical trials and practice settings over time.
2. Our patients and families' sense of urgency about the unmet clinical need
3. Our NPC community's willingness to accept risk of uncertain efficacy of a potential therapy knowing that to do nothing will lead to neurologic decline and death
4. Our patients and families' informed tolerance of side effects and treatment risks, again knowing that the downward spiral of this neurodegenerative disease is certain without intervention

You also heard global experts highlight the decades of research leading to the development of the NPC-CSS as we use it today. The data that has been gathered over the last decades, at great sacrifice to the NPC community, is high quality data that has stood up to scientific rigor and has been endorsed by the patient community after careful consideration. We need to use the tools that we have today to bring approved and effective treatments to our families and change the course of Niemann-Pick diseases.

If there is still uncertainty within the FDA around the use of the NPC-CSS tool as the most effective tool to measure change in NPC to date, please hear us when we say that this is an uncertainty that our community is willing to accept. And, that *maintaining and improving quality of life is an endpoint for NPC families!*

We also ask you to consider and use all of the data that has been gathered at the sacrifice of the NPC community. Further, we believe that any initial positive decision by FDA will serve as a catalyst for incremental advances in future treatments—and regulatory flexibility will enable that first step toward cures.

So, what are we asking?

We are ready to join you in ongoing discussions on the NPC-CSS to better refine it for the future, but we ask you now for confirmation that clinical programs currently using the tools will not be negatively impacted while we have discussions about this tool. We need to know that the NPC-CSS will be considered valid in all circumstances where it has been used to date. The historical data that has been collected at such great sacrifice to the patients is invaluable to this community. This tool and the data represent the natural history of NPC as we all know it. While we explore improvements to the scale, we must be mindful that we do not

marginalize the data we have previously gathered using this tool. We must take into consideration that any potential changes we consider to this score will impact patients and decision makers globally as our INPDA colleagues noted. If the concerns you, the FDA, have regarding the scale relate to how it is implemented and monitored in trials, we want to collaborate here as well for improvement.

It is essential that decisions we reach related to the discussion today or future discussions support the future of research and clinical development in NPC ***and also*** support the clinical programs that are actively working towards approval today.

We cannot lose sight of the reality - this is a terminal disease and we need the shortest path possible. To make a perfect scale we could lose a generation of patients.

You've also heard the from our patients about the impact of this disease and what meaningful treatment would deliver. Our community came here to impress **two things** upon you:

- **What is the Level of risk that is tolerable with a therapy and,**
- **What degree of benefit is meaningful?**

We are specifically asking you to consider all evidence generated by the NPC-CSS to date as **reliable and meaningful.**

Why is this important? **Because no experimental treatment has a greater risk than the terminal effects of NPC.**

What's the Plan of action and next steps?

We'd like to hear from you following this meeting with correspondence we can share back with the community on the Agency's thoughts and recommended next steps for how we partner together for any refinements to the NPC-CSS for the future or data needed to inform your understanding of NPC patient preferences.

If there is no longer any doubt, please let us know that this is the agreed upon tool for the foreseeable future.

We stand committed to supporting your application of regulatory flexibility, enlightened benefit-risk considerations for Niemann Pick therapies, and to ongoing collaboration in the best interest of our patients and families.

As a community we ask that you remember the stories of these patients and the feedback from our experts when evaluating any potential therapy for NPC. Remember our unmet need, our tolerance of both uncertain benefit in therapy, as well as a tolerance for risk, and that you work with us to create an actionable and achievable path forward in situations where the therapies appear safe and the data suggests the therapy could be beneficial for some in our community.

This is a complex, unrelenting disease that will require multiples therapies to render it a chronic condition. We do not have the luxury of letting any potential therapies pass through our grasp.

Thank you for partnering with us today in this discussion.