



## Niemann-Pick Type C Community Listening Session

with the

U.S. Food and Drug Administration

August 3, 2021

Meeting convened and report prepared by:

Ara Parseghian Medical Research Fund  
International Niemann-Pick Disease Alliance  
National Niemann-Pick Disease Foundation

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## Summary Report

On August 3, 2021, the Ara Parseghian Medical Research Fund (APMRF), International Niemann-Pick Disease Alliance (INPDA), and National Niemann-Pick Disease Foundation (NNPDF) convened a listening session with representatives from the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of New Drugs (OND). This session, which was held at the request of the FDA, gave members of the Niemann-Pick Type C (NPC) community an opportunity to share thoughts on two key topics: the relative benefits and risks of NPC treatment options and the value of the NPC Clinical Severity Scale (CSS) in measuring disease progression. The session featured remarks from expert NPC clinicians, patients and family members, and NPC advocacy organization representatives (see agenda in Appendix A). Although titled a “listening session,” FDA staff were active participants in the session, responding to remarks from NPC community members and sharing their thoughts on NPC therapy development.

Over forty FDA representatives attended the meeting including leadership from several key agency offices. Most of the FDA participants work for the Center for New Drugs (CDER), which regulates over-the-counter and prescription drugs including biologics and generics. There also were several participants from the Division of Rare Diseases and Medical Genetics (DRDMG), the division responsible for reviewing and approving NPC therapies, including the Division Director Dr. Katie Donohue. In addition, Dr. Peter Stein, Director of the Office of New Drugs, of which DRDMG is a part, participated and spoke at the meeting. Dr. Naomi Knoble from the CDER Division of Clinical Outcome Assessment also participated in the discussion. Members of the CDER Professional Affairs and Stakeholder Engagement Team, which is a part of the CDER Director’s office, supported the planning process. Other FDA offices represented at the meeting included the CDER Office of Clinical Pharmacology and the FDA Office of Policy, Legislation, & International Affairs.

Following the session, there are still clear disagreements between the FDA and NPC clinicians, sponsors, and patients. In particular, the community remains concerned about the recent lack of approval of new therapies and limits placed on Expanded Access Programs (EAP)—despite trial evidence which they view as showing benefits exceeding risks—and the FDA’s seeming concerns about the NPC CSS. It is essential that this session spur additional interactions to resolve these disagreements with the ultimate goal of advancing NPC therapy development.

### *Introductions*

Tim Franson, MD, a Principal at Faegre Drinker Consulting served as the moderator and opened the session by outlining three overarching themes for the session:

- **Communication:** Participants will share perspectives on what is essential for better and expedited NPC therapy development outcomes.
- **Consensus:** Participants will define and agree on a path forward to achieve these results with current and future NPC treatment candidates.
- **Commitment:** Participants will share a responsibility to act consistently and with urgency to help meet the needs of NPC patients.

KayLa Miller, mother of Kamryn, a 10-year old living with NPC, began the session by describing her daughter’s journey with NPC. KayLa emphasized the importance of finding new therapies for NPC, noting that members of the NPC community are aware of the risks and uncertainties associated with potential new treatments. Her daughter has experience with two experimental NPC therapies through both clinical trials and an expanded

access program. KayLa noted that she and so many others in the NPC community are willing to take risk and accept uncertainty in new treatments because to not do so would mean resigning herself to the inexorable damage and ultimate death that NPC now brings.

### ***Regulatory Framing***

To introduce the first topic of the session on regulatory framing for NPC therapies, Sean Kassen, PhD, Director of APMRF, provided a background on the community's experiences with therapy development over the past two decades. He expressed the frustration felt by many NPC patients, families, clinicians, and advocates who believe there are multiple therapies (Miglustat, adrbetadex, and arimoclomol) that have gone unapproved by the FDA despite having demonstrated evidence of benefits for NPC patients. Dr. Kassen noted the domains and incremental measurements of the CSS reflect the community's views on the NPC symptoms that are most important to reduce or prevent. In addition, Dr. Kassen noted the NPC community's clear and longstanding commitment to advancing therapies by participating in clinical trials, raising money for research, and providing opportunities for the FDA to learn from the community through meetings and written reports. He implored the FDA to recognize that a progressive, fatal condition like NPC with a very small patient population warrants regulatory flexibility to address the critical unmet medical need of patients. Dr. Kassen expressed a willingness of the NPC community to continue to work with the FDA provided that the Agency demonstrates—and acts on—an understanding of the needs and priorities of the patient community.

Following Dr. Kassen's remarks, one NPC patient and two caregivers of NPC patients shared their experiences with the disease and candidate treatments. The following individuals spoke during this session:

- Alec Koujaian, a young man with NPC
- Krystal Samuelson, mother of Willow, a young girl with NPC
- Phil Marella, father of Dana, a young woman who passed away from NPC, and Andrew, a young man with NPC

These community members spoke about their positive experiences with experimental therapies for NPC and their willingness to tolerate side effects like hearing loss. They cited the notable benefits these therapies offered: a toddler who had lost the ability to crawl or feed herself regained both abilities; a young man has had no pneumonias and lived to an older age than his sister who had access to fewer treatments; another young man who graduated with an Associate's Degree, works, and drives. Although the three speakers have experience with different NPC therapies, this reflects the need for this patient community to have treatment options and be able to choose the therapy—or combination of therapies—that aligns with their needs and preferences. The speakers urged the FDA to take action to make sure that people with NPC have access to therapies now and in the future to address currently unmet needs.

Following the remarks from the patient and caregiver speakers, Dr. Franson opened the first discussion portion of the meeting. Dr. Katie Donohue, Director of DRDMG, responded to the community members. She acknowledged their frustration and thanked them for their willingness to speak to the FDA. She also acknowledged that the community views almost any treatment benefit—"if it is real"—as meaningful and is willing to tolerate a good degree of uncertainty. Dr. Donohue noted that although patients and families see a benefit from existing experimental therapies, it is difficult for the FDA to assess benefit from a scientific perspective.

Dr. Donohue also shared her strong view that NPC therapies should continue to be evaluated in placebo-controlled trials. In an effort to differentiate NPC from cancer, the latter of which has many approved therapies,

Dr. Donohue said most cancers are rapidly and uniformly progressive, whereas NPC has more heterogeneity and typically progresses over decades (it should be noted, however, that the average lifespan for most early and late infantile as well as juvenile patients is not decades: the median life span is 13 years and is well-documented). She also noted that oncology trials have a clear endpoint such as reduction in tumor size and have been tested for decades in larger, placebo-controlled trials. She cited the absence of persuasive scientific evidence from placebo-controlled trials as the reason why therapies have not been approved for NPC.

In response to Dr. Donohue, Dr. Liz Berry-Kravis expressed skepticism that a randomized, controlled trial (RCT) for an NPC therapy could provide the necessary results. She noted the challenge of actually running RCTs in a very small patient population and expressed concern that the data would need to be collected over many years, which many in the community would view as unethical. By contrast, family speaker Phil Marella noted that when he participated in a 2016 meeting with the FDA related to the development of adrabetadex, the agency said a trial greater than one year would be unethical for NPC patients. Dr. Berry-Kravis urged the FDA to consider other approaches to trials that would allow early approval followed by a long-term verification of benefit. Although NPC does not have endpoints as clear as those used in cancer, Dr. Berry-Kravis said this is not a reason to not have a disease-targeted path if there is an early indication of benefit. She pointed out the analogy of the FDA's recent accelerated approval of Aduhelm, a monoclonal antibody to slow the progression of Alzheimer's disease, based on reduction in an unvalidated surrogate (amyloid). In NPC, the reduction of cholesterol in the brain has a reasonable likelihood of showing clinical benefit and could be used as a surrogate endpoint. Dr. Berry-Kravis concluded her remarks by emphasizing the need to find a way to approve treatments for this ultra-rare disease using smaller amounts of evidence and to "not subject people to death by clinical trial."

Dr. Denny Porter spoke next, urging the FDA to develop a clinical trial model grounded in the realities of NPC including small patient population and disease heterogeneity. He spoke in support of approving therapies with a reasonable probability of being effective and then conducting five- to ten-year studies to collect more data on how the therapy impacts the disease.

Dr. Donohue responded to these remarks by agreeing that they need to address these realities and should start thinking about biomarkers and cholesterol reduction to measure the effect of therapies. She disagreed that RCTs are unethical, noting that there have been two- and three-year RCTs in other neurodegenerative diseases. She disputed the NPC community speakers' claims that the FDA has set too high a bar for NPC therapies and said she wants to help the community get over the bar by "bringing the very best minds to this" rather than "lowering the bar."

### ***NPC CSS***

To start the session on the NPC CSS, Dr. Marc Patterson delivered pre-recorded remarks discussing the development and utility of the NPC CSS. He explained that the NPC CSS is a clinically meaningful, reliable, and reproducible outcome measure developed through an iterative process and has been widely tested and proven to be an effective tool since it was introduced. The NPC CSS includes 17 domains designed to capture the full range of NPC manifestations based on prospectively gathered data from the NIH natural history study on NPC as well as retrospective patient records. Dr. Patterson noted that having so many domains is both a strength and a challenge of the NPC CSS and, following feedback from U.S. and European regulators, the more commonly used five-domain model was developed based on a survey of caregivers and clinicians to identify the domains of greatest importance. These two groups of survey participants chose the same five domains and agreed that a one-point change on any domain was clinically meaningful. Dr. Patterson also provided an overview of the many peer-reviewed studies that have confirmed the inter- and intra-rater reliability of the NPC CSS.

Dr. Patterson acknowledged that the heterogeneity and relatively slow progression (beyond early childhood) of NPC pose a challenge for using any instrument. He pointed out, however, that a significant risk of measuring the effect of any NPC therapy is that an effect may be missed and will only be seen in a longer period of study. As he explained, this may be especially true because the frequent delay in diagnosis of NPC means that patients who are available for trials often have a significant disease burden.

Dr. Patterson cited the example of the European Medicines Agency (EMA) conditional approval of Miglustat as a viable approach for other potential therapies. Miglustat did not show a particularly strong signal in RCTs, but the potential benefit it could offer led European regulators to approve the drug with the requirement that a registry be established to monitor its safety and efficacy on an ongoing basis. Dr. Patterson cited a 2020 article that concluded, based on extensive analysis of the registry data and other historical data, that Miglustat showed a clear survival benefit compared to no treatment.

Echoing what earlier NPC community speakers said about their commitment to NPC drug development, Dr. Patterson said the data collected in current and earlier NPC clinical trials, all of which have been based on NPC CSS measures, cannot be replicated or replaced. He emphasized that in ultra-rare diseases, all data must be captured and used to contribute to an improved understanding of the natural history of the disease and of therapeutic interventions whose effect may be difficult to demonstrate in one- to two-year trials. He cited the strength of the data from the NIH natural history study, noting that patients and families volunteered to undergo repeated, thorough evaluations to have the progression of their disease mapped with the NPC CSS. Dr. Patterson emphasized that a similar natural history cohort would be difficult to assemble in the foreseeable future given the limited number of treatment naïve patients in the U.S. and around the world.

Lastly, Dr. Patterson spoke of what he sees as a lack of alignment between the NPC community and the FDA's respective views of the benefit-risk ratio for NPC therapies. Describing the devastating nature of NPC, Dr. Patterson said it "inevitably and inexorably strips its sufferers of mobility, speech, cognitive ability, and ultimately, their life." Such a prospect leads patients, caregivers, and clinicians to be willing and able to accept risks that might be regarded as significant in other settings when those risks are balanced with the prospect of even a small amount of success.

Following Dr. Patterson's remarks, one patient and three caregivers shared their thoughts on the NPC CSS. The following community representatives spoke during this session:

- Pam Andrews, mother of Belle and Abby, two young girls with NPC
- Barbara Lazarus, mother of Daniel and David, two men with NPC
- Nicole Burgos, a young woman with NPC, and her father Frank Burgos

These speakers all emphasized the value of the NPC CSS in measuring the progression of NPC with some noting that they use the scale at home to track their child's progress between visits. They explained that the changes they have seen in the disease have correlated with changes in the NPC CSS scores even when those changes were quite nuanced. All of the speakers spoke of the benefits they have experienced from current experimental therapies for NPC and echoed a point often said by members of the NPC community: that even a small benefit as defined by the NPC CSS is hugely meaningful to patients and caregivers.

Following these remarks, Dr. Peter Stein, Director of OND, shared his thoughts with the NPC community. He pointed to the large number of FDA attendees at the meeting as evidence of how important NPC is to them. He acknowledged the desperation that patients and families feel and their willingness to tolerate risks in

treatments including intrathecal injections and hearing loss that offer even small, incremental benefits. Noting that it is important for the FDA to get the information they need to review and approve drugs, Dr. Stein said FDA is open to using regulatory flexibility to work with researchers, sponsors, and patients to figure out how to get that information. He also noted that FDA is open to looking at different endpoints and working with the community to make the NPC CSS better and more sensitive to show benefits that are important to the community. Dr. Stein said the FDA is open to meeting with the NPC community and sponsors whenever the community wishes to communicate with them. He expressed a desire to have more of these types of discussions so FDA can continue to hear the concerns of the NPC community.

In follow-up remarks, Dr. Katie Donohue agreed the NPC CSS tries to measure things that are important to patients and that even a small improvement—again saying, “if it is real”—is important. She attempted to assuage the community’s concern that changing or replacing the NPC CSS would result in years of trial data being thrown out by saying this would not occur. She explained that this “first generation of trials” has allowed the FDA to see areas where “commonsense changes” can be made to improve the endpoints. Dr. Donohue also raised concerns about the inter-rater reliability of the NPC CSS. She echoed her earlier point about the need for RCTs, saying that, in light of the need to still take that approach, making small changes to the NPC CSS should not be seen as a big setback.

Dr. Donohue then introduced Dr. Naomi Knoble from the Division of Clinical Outcome Assessments to offer her thoughts on the NPC CSS. Dr. Knoble commented on the strengths of the instrument, saying that the five domains are clearly representative of patients’, families’, and clinicians’ treatment priorities and that the interviews to validate the NPC CSS (Patterson et al, 2021) are some of the best the FDA has ever seen. She felt, however, that the validation work for the remainder of the tool “did not match that caliber”.

Dr. Knoble explained that when the FDA considers tools like the NPC CSS, they want to see discrete, non-overlapping scores and scores that can be determined clearly and easily. She noted the need for very rigorous standardization in how tools are implemented in trials. Dr. Knoble expressed a desire for three things to happen in the NPC clinical trial community:

- The formation of a consensus panel of experts, families, and regulators to provide recommendations on NPC clinical trial endpoints supported with systematic literature reviews.
- The establishment of a precompetitive collaboration across all NPC therapy sponsors to work to improve and refine the CSS.
- Cognitive interviews with clinical experts on the domains of this tool.

Dr. Knoble stated the FDA’s desire to see a clinical consensus on the way the NPC CSS is scoped and scored, noting that you can arrive at the same severity score in multiple ways. She cited the swallow domain as being especially difficult to score. She also noted that while a one-point change is meaningful to families, it is difficult to disentangle that from a measurement error.

Dr. Donohue reinforced her colleague’s remarks, saying that working on improvements to endpoints is something “we want to do with you, not to you”. She acknowledged that this would not be a quick fix that would result in the immediate approval of all therapies but is a practical step to move the pipeline forward. She reemphasized her earlier concerns about inter-rater reliability, saying that some investigators will observe a patient swallowing food or water first and then do the scoring, whereas others will talk to the patient’s parents first. These two different approaches add “noise” and, in a heterogeneous disease with small samples, Dr. Donohue said, “noise is the enemy.”

In response to the FDA's discussion of potential changes to the NPC CSS, family speaker Pam Andrews asked how such changes to the NPC CSS would affect the adrabetadex EAP and the arimoclomol clinical program. Dr. Donohue stated that she does not think the changes would have any effect on either.

### ***Conclusion***

Joslyn Crowe, Executive Director of NNPDF, gave concluding remarks at the listening session. She reemphasized the points made throughout the meeting including: NPC patients' and families' sense of urgency about the unmet clinical need, the community's tolerance of risk and willingness to accept modest incremental benefits as well as uncertainty in treatments; and their strong opinion that the NPC CSS is a reliable and meaningful way to measure change in NPC for regulatory as well as clinical purposes. In the face of the terminal effects of NPC, she noted, no experimental treatment has a greater risk than disease progression.

Ms. Crowe urged the FDA to remember what they heard from patients, parents, and clinicians during this and previous sessions and to consider that information when evaluating new treatments. She asked the Agency to consider all evidence generated by the NPC CSS as reliable and meaningful while recognizing that there is an opportunity to work together to refine the NPC CSS provided it does not negatively impact current trials. Ms. Crowe asked the FDA to respond in follow-up correspondence with recommendations for next steps to refine the NPC CSS. She emphasized the need for actionable next steps grounded in the needs of patients and families.



## Listening Session Agenda

### NPC Community Listening Session with the U.S. Food and Drug Administration August 3, 2021 | 1-3PM ET

#### I. Welcome (*Shawn Brooks, U.S. Food and Drug Administration*)

#### II. Introduction (*Tim Franson, MD, Moderator*)

Convene meeting and state ground rules

#### III. Opening (*KayLa Miller, Mother of Kamryn*)

Welcome participants and state goals for the session. Introduce family and briefly tell the patient's story.

#### IV. Regulatory Framing (*Sean Kassen, Ara Parseghian Medical Research Fund*)

Provide recap of NPC therapy development, summary of patient/caregiver survey data, highlights of patient preferences.

##### **a. Patient and Family Voices**

- Alec Koujaian
- Krystal Samuelson, Mother of Willow
- Phil Marella, Father of Dana and Andrew

##### **b. Discussion Questions (with input from NPC clinical experts: Elizabeth Berry-Kravis, MD, PhD and Denny Porter, MD, PhD)**

- Does the DRDMG have a comprehensive understanding of the patient preferences in NPC, both in terms of treatment effects and tolerance for risk even with uncertainty around effects?
- How can this knowledge be used to support both ongoing and future reviews of NPC candidates, as well as Expanded Access programs?
- What gaps in current patient and treatment data exist that can reasonably be addressed?

#### V. NPC Clinical Severity Scale (*Marc Patterson, MD*)

Present overview of NPC Clinical Severity Scale and the role of this tool in NPC drug development.

##### **a. Patient and Family Voices**

- Pam Andrews, Mother of Belle and Abby
- Barbara Lazarus, Mother of Daniel and David
- Nicole and Frank Burgos

##### **b. Discussion Questions (with input from NPC clinical experts: Fran Platt, PhD, FRS, FMedSci and Will Evans, MBBS)**

- What are the reliable methods to continue improvement of both the NPCCSS measures and the sponsor utilization of the tool, without creating unnecessary jeopardy to ongoing and future NPC trials?
- How can the NPCCSS results generated in trials be supported by patient experience data and real-world evidence?

#### VI. Call to Action (*Joslyn Crowe, National Niemann-Pick Disease Foundation*)

Provide a summary of the key points raised in the meeting.

## Speaker Remarks: KayLa Miller, Mother of Kamryn

### *Opening*

- Welcome and thank you for being here and listening to our collective, ultra-rare needs and perspectives at the patient listening session today.
- Our goals are to discuss critical course corrections, the Severity Scale, tolerance of trading uncertainties for access, and need for urgent, favorable intervention.

### *Journey*

- My name is KayLa, and I am the mother of Kamryn, a ten year old living with NPC who was diagnosed at 4 months.
- 10 years ago, we were blessed with a baby - who had NPC - and the odds weren't truly in our favor. I sometimes feel we have failed her: the universe, drug regulation, research, our decisions. As a parent, that is a terrible feeling.
- Initially, I was heartbroken, yet I was also optimistic. I felt confident that new treatments were on the horizon. I even hoped that Kamryn might actually be the child to beat NPC.
- Unfortunately, over the last decade, Kam has seen much progression while the community still faces the same access issues it faced in 2011.

### *Treatment Perspective*

- Despite the uncertainties, Kamryn began Miglustat, prior to showing neurological decline. While I know this is not the case for all children, she was not able to tolerate this therapy. Some treatments work for a child, while other therapies work for another.
- At 4, she started the Phase 2 Adrabetadex trial. We'd been following cyclodextrin since the day of her diagnosis and felt relieved to know she would finally have access.
- She received biweekly infusions until late 2019 when we changed to monthly infusions - so she would have a longer break between treatments. We did what we felt was best at that time. Then, due to sickness and COVID, from December 2019 to December 2020, Kamryn only received 6 treatments.
- Going from 24 to 6 annual treatments had a major impact. While we were already being forced to choose between two separate EAPs and weighing the uncertainties of therapies working, especially in light of many missed treatments, we were ultimately forced to stop the EAP, due to dysphagia progression.
- To be transparent, the progression and access loss were just as devastating as the original diagnosis.
- Yet, there was a glimmer of hope. This March, she started Arimoclomol, and hope was on the horizon again. Since then, Kamryn's dysphagia has improved. She's gone from not being able to drink liquids or eat without choking to drinking liquid and not choking at meals. She's happier and her quality of speech has improved. Her posture has improved, and she is more aware of her surroundings.
- Then, in June, the hope diminished as the drug that had merely no side effects was not approved, meaning there was no chance of getting out of the EAP and obtaining access to more than one therapy.

### *Risks, Uncertainties, Tolerance, Therapies*

- We've been willing to accept risks and uncertainties of efficacy to ensure access to prolonging progression and improving quality of life.

- We've flown across the nation, for years at a time. We've tolerated IT infusions in a sham trial. We've started medications that we knew may not have any positive impact and could have unknown side effects. We've had to choose between one treatment and another.
- Ultimately, due to the certainty of NPC fatality, we've traded uncertainty for access through three therapies separately.
- Our family is surviving on what I consider "bought" time. When considering a potential treatment, the most important factor lies in what WILL happen if we do not TRY. Due to progression and the overall nature of this disease, we cannot afford to sit back. We are desperate for a therapy that slows progression, and we would give anything to have the same opportunities as many other diseases.
- When considering a potential treatment, the most important factor lies in what WILL happen if we do not TRY. Due to progression and disease nature, we cannot afford to sit back and are desperate for a therapy that slows progression. We'd give anything to have the same opportunities as many other diseases. Yet, ten years later, we're still waiting for those opportunities.
- NPC has an impact on everyday life. Every aspect is a struggle or more difficult than it should be. From advocacy to access to insurance to specialists phone calls to the ongoing struggle of accommodating life as we know it. So much is against us, and the last thing we need is struggles for therapeutic options.
- While we may not find a cure in the next ten years, my dream would be to access multiple therapies that treat multiple pathways to ensure the best chance of slowing progression and improving quality of life. Other communities, such as oncology, are given multiple options. We deserve this and are still waiting on our chance too.

#### *Scale / Perspective on Components*

- The NPC Clinical Severity Scale outlines the 5 domains most impacted and meaningful to families. I have personally tracked my individual assessment of the scale since early 2017. Based on ten years of caregiver experience, I firmly believe that every progressive change from one level to the next, whether negative or positive, within a single domain is substantially meaningful and has a significant impact on the patient's life, family, and overall quality of life. Honestly, I wonder why this scale, which has been globally justified and used, outweighs the urgency and needs.

#### *Closing*

- I'm presenting to you one child's journey and one personal heartbreak, but I stand here today for a community of children and families who deserve help in this fight.
- I would like to propose a few thoughts for you to reflect upon, all of which I question as I lie in bed heartbroken each night:

Our community has watched with tremendous respect and hope as the FDA and other agencies came together to approve vaccinations during a pandemic and ensure families did not lose loved ones. Yet, I can't help but feel my daughter paid a price. As the world was worried about COVID, we were worried about much more - the inability to receive treatments because it was not FDA approved and COVID risks somehow outweighed that of NPC for our family.

What is holding us back? Is it a money issue? Is it the ultra-rare population? Is it truly the trial designs? Or the severity scale?

I am grasping for understanding. Please tell me. Who decides the value on life? Why is the life of our children less valuable? What makes my daughter's life less significant than an adult with Alzheimer's or another child with cancer?

- Today, you will hear from clinicians, organizations, and six other patient voices. I urge the FDA to truly listen to the families and experts as we discuss our perspective and work as a community.
- Our urgency. Our willingness to take risks. Our tolerance of side effects and uncertainty of therapies working. I ask you to reflect on the urgency, willingness, and acceptance of risks in making decisions about therapies under review today - and in the future. These elements must be interwoven into regulatory decisions deeply.
- While experiences may differ in severity, age, score, and treatment, one thing remains the same. We need options and opportunities - for treatments, access, and FDA's favor.

## Speaker Remarks: Sean Kassen

**Speaker:**        **Sean Kassen, PhD**  
                           **Director**  
                           **Ara Parseghian Medical Research Fund**

I want to say thank you to the FDA for taking the time to both listen to and engage with our community today. But, similar to what you heard from Kayla, you must realize I say thank you with a hope that is unfortunately, paired with a fair amount of skepticism. Because right now, the NPC community—families and patients, adults and children, including Kayla’s daughter, Kamryn—people who are suffering and dying from Niemann-Pick Type C disease, feel the FDA is not hearing our core message when it comes to what is a clinical benefit to them and the risks they are willing to take.

I do want you to know that we want to have an open and respectful dialogue with you. We do want to work together with the FDA on our common goals which is therapy approvals for patients with NPC disease and ultimately a cure.

In order to get there you need to understand why our community is skeptical and to do this you need to understand the history of this community. For that I would like to tell this story and I am actually going to start with the ending. The date was June 16, 2021 and I was in Cincinnati, Ohio. I just finished meeting with Jim McGraw, a recent widower and great supporter of the Parseghian Fund. I just finished telling him we are on the verge of our first approved therapy for NPC in the USA. And I also told him we are raising money for a new biomarker/surrogate endpoint initiative for the NPC community.

After that meeting I came back to my hotel and opened my email. There I saw a series of emails from the FDA in which, they were looking to host another listening session with the NPC community. This was the evening before the Complete Response Letter was received by Orphazyme. I quickly put two and two together and asked, does this mean they are not going to approve Arimoclomol? Then 36 hours the official news came out from Orphazyme. It was declined.

Like so many, I was angry, sad and frustrated for the patients and families who had been anxiously waiting for their first therapy approval. I was sad for Kamryn.

How did this happen? I thought back on the data Dr. Marc Patterson and the Orphazyme team has been presenting at conferences over the years that clearly showed a clinical benefit with Arimoclomol. I listened to parents speak time after time about how this therapy has improved their child’s life. We also assisted the FDA

with the publishing of multiple patient preference and community benefit/risk surveys and even hosted a Patient-Focused Drug Development meeting in hopes that it would help guide their decisions.

So what could have happened? Where is the disconnect on benefit-risk considerations?

The letter from Orphazyme said the FDA had an issue with the 5-point NPC clinical severity scale and specifically the swallowing domain. Still frustrated, I thought, 'you mean out of the totality of data presented, children are dying, and this is an essentially risk-free therapy that shows clinical benefit,'

This is why there is skepticism in our community. Our community feels the review division is asking for perfection without being flexible within the framework of current drug review standards which encourage taking these perspectives into account for serious, unmet medical needs such as ours.

Perfect is the enemy of good and our community feels that in this case the search for perfection is costing lives, and that regulatory flexibility for this rare disease is needed.

So let me take you back to the beginning of this story and let you know what this small ultra-rare disease community has already done.

Since the mid-90s, This community has raised over \$50 million dollars to support NPC research, we identified the NPC genes, better understand its pathway, have multiple life -improving therapies in the clinic

We have one therapy, Miglustat, that is approved in the EU, Canada and Japan, but not in the US. Even an independent committee voted to approve, but the FDA said no. Now, it has been over 10 years since the FDA declined to approve it and now multiple manuscripts have been published outlining its benefit for NPC.

We have another therapy, Adrabetadex. This was developed by the community, multiple scientists, families and clinicians working together, and has over 7 years of patient data showing benefit..and is now being denied to many children even via EAP.

And now, we have Arimcolomol, which, as I mentioned, showed reduction in disease progression in the recent trial but was recently denied.

...But back to your concerns with the data, based on your recent comments, we know the FDA is now concerned with the NPC severity scale that has been widely established, validated, and used to generate years of irreplaceable data.

Later in this session, you will hear from families that will tell you 'what they see in their child as clinical benefit is reflected in the severity scale when clinicians present data to them.' You will hear from clinicians who have used the scale to evaluate and treat patients, published in many manuscripts, and validated the scale and demonstrated its effectiveness. They will tell you for an extremely challenging rare disease with a small heterogenous population, the scale is not just good, but great; especially when compared to the alternative of a child's decline, leading to death.

Additionally, we will remind you that we have hosted meetings and published surveys that show you how this scale is reflective of what matters to the patients and what those benefits look like in the real world and even a small improvement as measured by the scale is very meaningful.

You will also hear about what families and patients will risk. As Rebecca Spencer, mother of Jonathon who has NPC said at our PFDD meeting, when asked what she would risk for a potential 3% benefit, said, 'I would take that 3%, because I have 0% without it.'

Although this is termed a "listening session", we also want to hear from you. It is not just a bunch of angry families that want to vent today. And specifically, they want to know how you use the information from patients and families in your decision making.

We also know in this dialogue today you want to bring up your challenges and concerns. We want to hear them, understand them and work towards solutions. But we need you to demonstrate you hear this community first, and the best way to do that is with reasonable immediate actions to provide access to therapies and use the totality of data available and the patient voice in your decisions.

I ask as we start this meeting today to reflect on the recent Listening Session the NPC community had with the FDA. In that you heard about a lot of needs from the community included benefit and risk and you also heard from patients specifically talking about the benefit of Adrabetadex.

Similar to after the PFDD meeting, I know families felt it was a positive experience and were excited about a dialogue with the FDA.

But with recent decisions from declining some children access to Adrabetadex, to the rejection of Arimoclomol, to the generic responses back from the FDA when letters were sent to your leadership from parents,...They are now deflated. They don't feel a dialogue with you today will lead to -clear and timely actions and you will often hear that in their tone.

As I stated, we feel the bar you are setting for trials for NPC disease to succeed are too high. And then on top of that you -seem to have shifting perspectives that send a confusing message to the community.

I ask you again to reflect today and realize we are a very small patient community with limited resource and are now so deflated that bar you are setting looks like it is hovering over the clouds. Maybe even higher than Jeff Bezos recent space flight!

But we are engaging today. Why? because we do have therapies that are helping these NPC children. We have years and years of published clinical and real-world data and patience experience demonstrating this. We want you to use this information. We also want you to know we want to work with you to better help you with trial designs incorporating patient perspectives.

My hope is though that today is the start of real change. We are not here for you to tell us that actually, 'the bar that is already too high that Jeff Bezos almost collided with has now been raised to Mars and can only be reached when Elon Musk colonizes it.'

Rare disease drug development is not rocket science – it is actually much more complex than that and deserves our best collective thinking...and flexibility. The regulators must embrace the dire, time sensitive dilemma which NPC patients face, where any delay in treatment may be the last opportunity.

We will keep an open mind in hearing FDA's views – but also expect the same from the Agency in accepting the broad risk tolerance in benefits these families accept in trials.... It sure beats watching their child decline and then die.

A dialogue on working with us today on the information we have, that is good, no...great, to get these therapies approved and we will work with you going forward to help you in evaluating therapies for NPC disease. It will be mentioned multiple times today and you should recall that today's breakthroughs in cancer therapy began with very small benefit profiles and significant toxicities less than three decades ago, and we look to our similar ascent to cures beginning today.

In conclusion, I go back to that donor I met with in Cincinnati, who recently lost his wife to pancreatic cancer. He is willing to support this new biomarker/endpoint initiative. We spoke to him because we know this is a tool for you, the FDA, the clinicians, and families and will help future for trials.

But you must know that these current therapies I mentioned are our priority today and patient access to these therapies is our number one priority. So we hope that you work with us on that in the near future, while we build improvements to better help you understand disease progression for the long term. So that is what we are setting up for you today. We want to work with you. But it only works if you align with us on the patient needs first.

## **Speaker Remarks: Alec Koujaian**

Hello. My name is Alec Koujaian and I have Niemann Pick Type C. I was diagnosed in January 2012 when I was 14 years old. I have been getting treatment since December 2013 via Dr. Kravis's expanded access program.

Couple of years ago I felt really good after my presentation to the FDA at the PFDD meeting. I thought the FDA understood our struggles and concerns Boy was I wrong. The FDA did not hear us, and we are in a worse spot now than we were a couple of years ago.

I keep reading about the concerns the FDA has when comparing risks to the benefits of potential treatments. Since I am somebody living with NPC and getting treatments for the past 7 and a half years, I thought I would tell you, again.

Let's talk about hearing loss. Did you know that NPC also causes hearing loss? For those of us who experience it, all we do is wear hearing aids. And as we all say, "I rather be deaf than dead?" Let me say it again one more time so that it really sinks in. "I rather be deaf than dead".

Let's talk about Lumbar puncture. I have been getting treatments via lumbar puncture for over 7 and a half years without any issues. It takes about 12 minutes. We all talk, sing, and crack jokes during the procedure. It's that simple. In fact, I would welcome any one of you to come and watch the procedure so that you can understand it better. I can send you my videos as a follow up.

Let's talk about the benefits. There are too many to mention. It all comes down to that I live a normal life. I graduated from college with an Associate Degree in Fire Science. I work over 30 hours a week and drive a car. I do chores around the house and take my dog Rocky out for walks. I enjoy going out with my friends to eat, go to movies, concerts and playing sports. I play pickleball with my dad every week. Life is good.

Now just imagine what would happen if this drug is no longer available? Where would I be? What would become of me?

I need this treatment to continue to enjoy my life. We cannot live in this constant state of worrying if these treatments, that many have been on for many many years, are no longer available.

Why do we have to suffer because of inconsistencies in approving drugs? Why don't treatments for our community have the same sense of urgency as other divisions within the FDA for other conditions? Did you know that the Cancer division has approved 15 drugs in the past 3 months and we can't even get one over the past 10 years? When will this bias end? How many more of us will be denied treatment and unnecessarily suffer and die?

Please do what is right. You have the power to change course and approve these treatments based on the data that is available today and the benefits many of us are seeing.

Here are my takeaways:

- My wish is to be able to take care of my parents when they are older, not the other way around. Give me a chance to do so.
- These treatments are safe, and the benefits are real. Let me repeat. These treatments are safe, and the benefits are real.
- If we are willing to accept the risk knowing the benefits, then so should you.
- If these treatments are no longer available, you know what will happen to me and everyone else. Is that acceptable?
- Step in our shoes and walk the life we are living. If you get as far as we have, then maybe, just maybe, you will see how strong and resilient we are and our willingness to fight for access. Please fight with us. Not against us. Please join me on the right side of history.

Thank you.

### **Speaker Remarks: Krystal Samuelson, Mother of Willow**

My name is Krystal Samuelson and I am the mom to Willow. Willow, who is 4 years old, was diagnosed with NPC in April of 2020.

Willow was declining quickly. She had lost her ability to cruise furniture, crawl, feed herself, and was sleeping all day. Our pediatrician told us she only had a few months left to live.

After receiving Willow's diagnosis, I looked into available clinical trial medications and opted to go with Arimoclomol as our main goal was not to sacrifice her quality of life. By quality of life, I mean that Arimoclomol allowed us to stay home and give the medication orally. Arimoclomol was the riskier decision as it had not been around as long, however, we would have gone with whatever clinical trial was available despite any risks. The thing to understand about NPC is that it is fatal, there is no question about that. I know my child will pass away from this disease. Why would I not try any clinical drug despite the possible risks if it means a chance at having my daughter around even a little while longer?

When we started Arimoclomol, I was just hoping for more time with my daughter, but I have gotten so much more than that. Willow is back to crawling, feeding herself, and engaging in conversations. All things I would have never got to experience with her again if I hadn't gone with a trial drug. And as an added bonus, we have seen no adverse side effects for this drug.



In conclusion, the point I want to get across and I know I am speaking for the other parents who have a child with NPC is that this condition is fatal and we would give anything for just 1 more day with our kids. Please try to put yourselves in our shoes and imagine it was your child, wouldn't you risk anything for the possibility of more time?

## **Speaker Remarks: Phil Marella, Father of Dana and Andrew**

I'm Phil Marella. My wife Andrea and I have four children. Two were born with NPC; our daughter Dana who was diagnosed at age 8, passing away 8 years ago at age 19, and our son Andrew who is now 22.

Andrew was diagnosed at age 4 and has been on Miglustat for 17 years, and Adrabetadex for 7 ½ years; and he is doing well, with no ongoing side-effects.

While I am thankful to the FDA for this meeting, I am equally frustrated to be speaking to you for the fourth time about the same urgent need for thoughtful and caring consideration of treatments for our children.

The first time I spoke before the FDA was at the January 2010 Advisory Panel for Miglustat. With my entire family at the podium, we demonstrated the obvious benefit from early treatment with Miglustat. While the panel recommended approval, the FDA made what we all now know was a tragic mistake by declining approval. Numerous studies now have shown the critical, long-term benefits from Miglustat. The drug is approved for NPC in much of the world, but not in the US. And this week our family is back fighting with insurance about Andrew's prescription.

My second meeting with the FDA was in July 2016, with this division and Vtesse about the Adrabetadex trial. Vtesse asked two important questions of the FDA:

First, should a two-year trial be considered instead of one year? The FDA answered that keeping patients on control for two years would be unethical.

Second, and critical to today, was the FDA satisfied that the composite endpoint, our severity scale, is clearly meaningful? The FDA's response was that it had been demonstrated to be meaningful.

To both questions, the FDA gave the correct answer, then and now.

My third opportunity was at the NPC Patient-Focused Drug Development meeting in March 2019. As parents and patients we described living with NPC, how therapies were providing clinical benefit in swallowing, ambulation and cognition; all critical to health and quality of life, and important elements of the clinical severity scale.

And now I must speak to you again to ensure the FDA hears the clear voice of the patients to inform better decisions.

Our daughter Dana, who only had access to Miglustat, died at age 19, and for many years required 24/7 care; Dana could not walk, talk, had a feeding tube for all of her nutrition, had a trach, a respirator and suffered many pneumonias.

Andrew, at 22, has had no pneumonias, can converse, spell and do mental math. Andrew still feeds himself; there is no feeding tube, and he can walk with some assistance or at times only supervision. Dana had lost all of that by the age of 14 or 15.

Andrew and Dana both started life as seemingly normal children until the age of 5. Andrew, however started Miglustat at age 5 before his symptoms took hold, where Dana started at age 11, already in a wheelchair and using a feeding tube. This is an amazing result from Andrew's treatment, with easily tolerated risks and side effects.

This is what the severity scale captures; how our clinicians have demonstrated the effectiveness of treatments for years. This is what we see and what matters to us.

I am devastated that the agency might ignore 15 years of clinical data and analysis.

I am astonished that the risk of a lumbar puncture and partial hearing loss is, in your eyes, too risky, even as Andrew's hearing is corrected with hearing aids, and has been stable for years. Andrew generally doesn't even feel the procedure.

You simply must use the data and regulatory flexibility that is available to help guide your decisions and listen to the patient voice on what matters and the risks we are willing to take.

This must change for our families. Thank you.

## Speaker Remarks: Elizabeth Berry-Kravis

**Speaker:** Elizabeth Berry-Kravis, MD, PhD  
Professor, Department of Pediatrics  
Rush Medical College

### **About Risk Tolerance and the Development Path, I have four points to make:**

**1) Risk Tolerance:** We heard from Alec about the risk he and others are willing to accept

- He watched NPC take his sister who accessed treatment late in disease, so he has painful awareness of what the disease does

- He started treatment through expanded access after early but CLEAR cognitive decline and has not only stabilized but improved across multiple areas of function over the past almost 8 years

- acceptance of risk and early access has given him the chance to still do all those things he told you he wants to do

- this illustrates why we need to accept risk when we have a drug with some early evidence of benefit - early access is critical for mildly affected patients who cannot even qualify for standard trials, as these ARE the patients we can help the most and maintain the best quality of life. Evidence of benefit for these patients cannot be generated in the timeframe of a one or even two year RCT so...

- an accelerated approval process with a mandated post-approval 10 year study would allow the patients for whom we can best maintain quality of life to get and maintain access, and for us to do the study that truly addresses a meaningful long-term outcome

**2) Achievable standards:** NPC is a highly variable ultra-rare disease in which it is dubious that a fully statistically convincing randomized controlled trial can ever be done, so when there is a significant or trend result showing a

small benefit in a year we need to recognize that signal of benefit, as families tell us its important and its the best we will do in an RCT.

- not only is the feasibility of RCTs in question at the current time as much of the patient population is treated with other disease impacting therapies, but also a placebo-controlled trial of the multiple years needed is not ethical

- when unrealistic and impossible standards result in a long time to move therapies through the regulatory process, patients become irreversibly impaired or die. We can't keep asking rare disease kids and families to suffer that. We need models for long-term studies that will give us real answers and will not leave people without access to a potential treatment only to lose their mind and being and then find out later that it works

- this argument also supports a strategy of early approval after demonstration of small levels of benefit, followed by long-term verification of benefit.

**3) Need for Combinations:** We all know that NPC, like many neurological diseases has a complex mechanism and will be like cancer and AIDS; we will need multi-drug therapy. Also like cancer and AIDS, different drugs will work better for different subpopulations of NPC, based on mutations, age, stage of disease, and many undefined factors, so we need choices for what will be best for the individual patient.

- we can't get started on exploring the relative benefits of combinations until we get therapies approved so the lack of ability to get drugs approved which dates back to miglustat, is hindering the field from moving forward

- when accelerated approval was initiated for AIDS – this resulted in many approvals and combination therapy that made the disease treatable – we need this approach for NPC

**4) Paths in Rare Neurodegenerative Disease to Minimize Loss of Function:** Neurodegenerative disease is hard as we don't understand all the mechanisms, but if we have early evidence something might help, a partial benefit or prolongation of life quality is very important and is what patients want

- FDA has accepted accelerated approval and early access to drugs for cancer and AIDS due to the high risk of the disease

- this is no less true for neurodegenerative disease like NPC, which is worse, because not only will you die, you will lose every bit of what makes you human and allows you to function along the way, you will have to watch yourself become completely dependent

- although the outcomes are harder to prove than tumor size for instance, this is NOT a reason to just NOT have a reasonable path for disease-targeted treatment development for this devastating disease, that allows early access even if the risk of lack of benefit is higher....

- the Alzheimer's community made this very clear to the FDA recently, resulting in an accelerated approval for which the FDA concluded that despite the fact that the relationship between the biomarker substance and dementia was recognized to be "more complicated than originally thought," there was a "reasonable likelihood" that the biomarker reduction would slow the disease. The agency approved the drug based on that "surrogate marker" and directed the company to conduct a long-term trial to verify the clinical benefit.

- in NPC we have shown cholesterol can be removed from the brain and this is a proximal marker of the disease mechanism, so one could conclude, in similar thinking to that of FDA for the Alzheimer's product, that although the relationship between cholesterol removal and CNS progression in NPC might be "complicated" there is a "reasonable likelihood" that cholesterol reduction would slow the disease, and the agency could approve the drug and direct a 10 year trial to establish benefit.

- A well-articulated rationale was given by FDA about the Alzheimer's approval, explaining the risk-benefit calculation. A rejection could mean patients "could suffer irreversible loss of brain neurons and cognitive function and memory" as the agency waited for definitive proof of effectiveness. It was also cautioned that the

expedited approval meant that “patients must be willing to accept some residual uncertainty regarding clinical benefit — and therefore be willing to take a drug that may ultimately prove ineffective along with the risks of the drug, in order to gain earlier access to a potentially valuable treatment.”

- As with the Alzheimer’s community the NPC patients have clearly told you they too are willing to accept the risk and residual uncertainty....but although this ultra-rare disease is supposed to have regulatory flexibility and get treatment approved with less certainty based on provisions for rare disease in the 21<sup>st</sup> century cures act, because of recurrent rejections and barriers at FDA, NPC patients ARE already suffering “irreversible loss of brain neurons and cognitive function and memory” as well as motor and swallow functions, as the agency waits for definitive proof of effectiveness.

- how many years of life have NPC patients in the USA lost already because they could not get insurance approval for miglustat, a drug which has now been shown to have a clear survival benefit based on 10 year data? While patients in other countries had access because of the provisional approval mechanism – even today the FDA - with this 10 year survival data in hand and clear data showing delay of swallowing problems, in a setting where we get insurance approval easily just by sending them the scientific literature – still has refused to approve miglustat for NPC even when it seems FDA has accepted this as the standard of care – this is a travesty in a rare disease where the occasional patient in the USA still does not get insurance approval and is blocked like Russian roulette from disease lengthening therapy

- For all the reasons stated, we need a new path for NPC approvals and we need drugs, currently in use, with good evidence of effectiveness as ultra-rare disease goes, on both clinical measures and biomarkers, to be approved more expeditiously. If this can be done for other diseases, it is an inconsistency and inequity that it cannot be done for NPC.

### **Points for Scale Discussion**

- 1) The 5 domain scale can detect only small amount of change in 1 year but no other one performance-based measure or clinician-rated measure can detect change better, this is the nature of the disease not the scale, and does not indicate any of the scales are bad. Further we cannot use any one other scale as the primary outcome in a trial as each one covers only one domain of dysfunction and different patients move in different areas during a trial so one has to assess all the important areas
- 2) the 5 domain scale is very relevant to what is important in the disease to patients and clinicians, a one point change in any of the domains, by design, represents a meaningful clinical change associated with loss of quality of life, and this has been shown through parent and clinician interviews
- 3) the scale is quite sensitive to change and reliable over multiple year studies, which are actually what is needed to show convincing long-term effects in NPC anyway
- 4) any variability in scale rating will at most make it harder to demonstrate a treatment effect – the variability in the trial is going to be present in both the placebo and treated group so a trial that shows a small effect in favor of drug over and above scale variability is still valid
- 5) We can do a better job of fidelity training in future studies, as the nature of things is to improve upon the technique and methodology with time, and we WILL do this, but we cannot throw out the data which exists and is good (if not perfect)
- 6) We can validate each domain of the 5 domain NPC-CSS against existing datasets at Rush and NIH of external measures that are performance-based and indeed have already done some of this with the swallow, cognitive, speech and are working on fine and gross motor and showing correlations with multiple measures. Again, it is important to emphasize these scales can be used for validation but they can’t be substituted in trials as no one of them captures the whole disease. We can also create a linear scale for swallow and show it correlates with the current scale and with external objective swallow measures. The question is whether these validation analyses will be accepted by and enough for the FDA?

## **Future Discussion About the Ethics of Long Placebo-Control Trials Where Kids Lose Function Permanently or Die**

Let's look at an example of a less rare disease, we celebrated the approval of Spinraza for SMA with the RCT data that clearly showed benefit for the survival outcome, and watched videos of kids walking who never should have walked and this was a great achievement as an example of a horrible untreatable progressive neurological disease treated with a genetic disease modifying strategy – but we never saw the videos of the funerals of those babies diagnosed in the first month of life and randomized to sham early in life when the drug would have clearly made a difference – randomized to death while the next baby randomized to improved life and walking, those babies and families gave the ultimate sacrifice so future SMA patients could survive. We have to ask ourselves – is this OK? This is not war. These babies did not die to protect democracy. They died because we could not accept good natural history (which existed through the NIH-funded NeuroNext network) as a control group. We need to rethink this. It is not OK for kids to lose their being and die so we can have a control group in a trial when good analysis methods for real world data with natural history and pre- and post-treatment trajectories exist. We can't keep asking rare disease kids and families for that when we are not even sure we can mount a statistically adequate RCT. We need models for long-term studies that will give us real answers and will not leave people without access to a potential treatment only to lose their mind and being and then find out later how well it works

### **Speaker Remarks: Marc Patterson**

**Speaker:**        **Marc C. Patterson, MD**  
                         **Professor of Neurology, Pediatrics and Medical genetics**  
                         **Chair, Division of Child and Adolescent Neurology**  
                         **Mayo Clinic**

Thank you for the opportunity to participate in this session. My name is Marc Patterson. I'm a child neurologist who has been involved in research studies, in advocacy, and most importantly, in the care of children and families with Niemann-Pick Disease Type C since beginning my fellowship at the National Institutes of Health with Roscoe Brady and Peter Pentchev in 1990.

All of us recognize that having a clinically meaningful, reliable, and reproducible outcome measure is essential to making progress in Niemann-Pick Disease Type C. Joe Higgins, myself and other colleagues at the National Institutes of Health made a first attempt of this in the early 1990s. That scale, which was based on a relatively small dataset, was not widely accepted.

However, in 2006, Matthew Pineda's group in Barcelona published a four-domain clinical scale based on a comprehensive clinical database of 51 items that was designed to describe the clinical evaluation of Niemann-Pick Disease Type C and to identify the factors involved in the diagnosis and severity of the disease. These four domains formed a basic building block for the clinical scales that followed.

Most importantly, Denny Porter and his colleagues at the National Institutes of Health developed a comprehensive 17-domain NPC clinical severity score, or NPC CCS, based on prospectively gathered data from their natural history study, supplemented by retrospective data available in their records. This databased instrument, which was designed to capture the full range of manifestations of this disease, was widely accepted in the NPC community.

The initial description of this study in 2010 reported interrater reliability above the usually accepted threshold for acceptable reliability of 0.7 with a global Cronbach's alpha of 0.846 and a weighted Cohen's kappa coefficient

(k) of 0.888. There was also evidence supporting construct validity of the NPC case with significant correlation between all major domains and the total score, with R-squared values greater than 0.8 except for the hearing domain.

In addition, a separate study which was reported by Shin and colleagues in 2010, correlated the NPC CCS evaluations performed by five college students who independently scored one NPC patient's medical record and found a correlation of 0.76.

A much larger mixed group of 64 undergraduate and postgraduate students from a variety of disciplines were trained in the use of the NPC CCS and were able to identify consistent disease progression curves from clinical histories, which mapped back with close correspondence to the same curves previously reported in the initial development of the scale.

One strength, but also one challenge, of this instrument is its breadth and depth, which makes it difficult to use in daily practice. In addition, some domains, particularly seizures, movement disorders, and psychiatric symptoms are potentially modifiable by symptomatic therapies and could thus potentially contribute confounding data in a clinical trial.

To address these concerns and concerns expressed by regulators in both the European Union and in the United States, a group of 23 clinicians and 49 patients and caregivers were surveyed to determine which of the 17 domains would be NPC clinical severity score they regarded as most clinically important.

Both the clinicians and the patients and caregivers chose the same five domains: Ambulation, fine motor skills, swallowing, cognition, and speech. Members of both groups agreed that a change of one point on any of the five domains would be clinically meaningful. Indeed, they regarded any deterioration as clinically significant.

The criterion and construct validity of this scale were assessed using clinical trial data from 43 subjects. There was a correlation of 0.97 between this five-domain scale and the 17-domain NPC scale supporting criterion validity of the five-domain NPC CSS while convergent validity was demonstrated with moderate to large correlations of greater than 0.5 between relevant domains of the five-domain NPC CCS, the 9-Hole Peg Test and the scale for assessment and rating of ataxia known as the SARA.

Several patients and parents volunteered to permit video recordings of their clinical examinations. Thirteen raters were asked subsequently to score the performance of the subject on these video recordings using the five domain NPC CSS. The intra-class correlation coefficient or ICC agreement statistics were high for both intra-rater reliability with a value 0.94 and inter-rater reliability with a value of 0.99. There were also correlations of 0.647 and 0.785, respectively, between the Clinical Global Impression Scale severity, or CGIS, and the five-domain individual and total NPC clinical severity scores calculated from the video recorded reliability study. The study also demonstrated increasing five-domain NPC clinical severity scores as the level of clinician-rated severity increased with a P value of 0.0001.

The findings I have described have been published in peer reviewed literature. We're happy to provide copies of these papers if anyone has not had the opportunity to review them and read them in detail.

The NPC Clinical Severity Scale in its different forms is designed to capture the most important manifestations of this disease in a reproducible and reliable fashion. Using any such instrument in a clinical trial is challenging in Niemann-Pick Disease Type C because of the heterogeneity of the disease and because of its relatively slow progression beyond early childhood. Indeed, a major risk of traditional clinical trials performed using such an

instrument is that they may miss an effect which may only become obvious over a longer period of study. The case of Miglustat serves to illustrate this point.

The clinical trial of Miglustat, which was a randomized trial of the agent versus standard clinical care, was published in 2007. This study utilized horizontal saccadic eye movement velocity as a surrogate outcome. Horizontal saccadic eye movement velocity was selected as a relevant surrogate given that the majority of patients had complete or near complete vertical saccadic paralysis at the time of their entry into the study and it was known that horizontal saccadic eye movement abnormalities invariably followed the vertical saccadic paralysis and would progress in a typical, almost linear fashion. These movements could be recorded and assessed by blinded evaluators. This measure was supplemented by a number of relatively simple clinical outcome measures.

The data from this study were used as the basis for approval in the European Union and, subsequently, in a number of other jurisdictions worldwide. A condition of the approval by the European Union was that a registry be established in order to monitor both the safety and the efficacy of this agent. An extensive analysis based on data from this registry, combined with several historical data sets, was published in 2020. This supported a clear survival benefit for patients treated with Miglustat versus untreated subjects in real life setting.

The magnitude of this survival benefit was a mean of 10 years from date of neurological onset or five years from date of diagnosis, which was typically delayed four or five years from clinical onset in this and other historical data sets.

This experience emphasizes a number of critical points. First, in an ultra-rare, heterogeneous disease such as Niemann-Pick Disease Type C, all data must be captured and used to contribute to our understanding of both the natural history of the disease and the effective therapeutic interventions in order not to overlook interventions whose value may be difficult to demonstrate in traditional clinical trials performed over one- to two-year period. I should also note that the historical delay in diagnosis means that patients available for clinical trial participation typically have a significant disease burden at the time of their entry into the study. The presence of neurologic symptoms and signs reflects a combination of irreversible and potentially reversible neuropathology, which raises a further challenge in demonstrating benefit beyond stabilization or slowing of progression.

Second, the strongest dataset we have is that obtained from the natural history study conducted at the National Institutes of Health. The patients and their families who participated in this study have volunteered their time to repeatedly undergo remarkably thorough, not to say exhaustive, evaluations and their clinical progression has been mapped using the NPC Clinical Severity Scale.

Given the broad approval in other countries of Miglustat and the use of this agent off label in the United States, in addition to the several clinical trials and expanded access programs currently active, the pool of treatment-naïve patients in the United States and indeed worldwide is small. And it seems most unlikely that we will be able to assemble a comparable natural history cohort in the foreseeable future.

For this reason, we would urge acceptance of the NPC Clinical Severity Scale as the current gold standard outcome measure, recognizing that there may be elements which could be refined and improved, provided that any such modifications can be mapped back to the original data set. We must not lose this unique and irreplaceable data.

Third, the approval process for Miglustat in the European Union serves as a useful model for this disease. The data from the initial study, although consistent with a positive therapeutic effect, did not show a strong signal, but given the potential benefit-risk ratio, approval was given with the proviso that continued monitoring be performed. The benefit of this approach was that a very large number of patients were able to access this therapy. Subsequent experience has demonstrated no further safety concerns and, as I have already mentioned, provided strong evidence of a clear survival benefit. I would respectfully commend consideration of such an approach to the agency for Niemann-Pick Disease Type C and for comparable ultra-rare diseases.

I would like to take this opportunity as well to comment on perception of the benefit risk ratio. All of us in the Niemann-Pick Type C community understand and respect the concern of the agency for the safety of patients, but we perceive a misalignment between the community perception of the benefit-risk ratio and that of the agency at the risk of being redundant.

I must emphasize that Niemann-Pick Disease Type C is a disease which inevitably and inexorably strips its sufferers of their ability to speak, cognitive abilities, and, ultimately, their life. In this respect, Niemann-Pick Disease Type C and comparable ultra-rare neurodegenerative diseases are perhaps the most devastating that any human being can face.

With such a prospect, patients, caregivers and clinicians are willing and able to accept risks that might be regarded as significant in other settings when these are balanced against any prospect of benefit, recognizing that stabilization or slowing of progression is a clear benefit in this disease. None of the agents currently under study have presented risk which is regarded as unacceptable by members of this community. For example, just as patients with leukemia routinely undergo frequent spinal taps without significant complication, those receiving intrathecal adriamycin have tolerated this route of drug delivery with minimal problems. Concerns have been expressed regarding hearing loss, which is itself a manifestation of Niemann-Pick Disease Type C. With only a few patients has this been of clinical significance. It is my understanding that this is a risk which the participants have been comfortable accepting.

With respect to the benefit-risk ratio, I would also respectfully point out that many therapies have been approved by the Agency for malignant diseases which carry predictable, significant morbidity far in excess of adverse effects reported with potential therapies in Niemann-Pick Disease Type C. This perceived inconsistency in the assessment of benefit-risk ratio across severe diseases is a cause for perplexity and concern in our community.

In summary, patients, parents, clinicians and researchers in the NPC community have worked together now for several decades to assemble data sets and construct means of measuring progression, specifically, the NPC Clinical Severity Scale. These tools may be imperfect, but they cannot be replicated or replaced and we look forward to working with the agency to find a path forward to approve desperately-needed treatments for children and adults afflicted by Niemann-Pick Disease Type C.

I thank you for the opportunity to participate today.

### **Speaker Remarks: Pam Andrews, Mother of Belle and Abby**

My name is Pam Andrews and both of my daughters, Belle & Abby, were diagnosed with NPC in March of 2016. They would agree with you Dr. Donohue, that this is hard. They would agree with you Dr. Porter that this is unfair. And, Dr. Kravis, I know they hope to be able to give you the additional 10 years you want to study them.



They love coming to Chicago. But what they need you guys to do, despite the fact that this is hard and unfair, is to approve these therapies for them.

My daughter Belle was diagnosed just before her sixth birthday and 10 days later our pain more than doubled when our baby, Abigail, was diagnosed before any visible signs or symptoms of the disease at 18 months old. The doctors were clear about the outcome for the girls if we were to leave them untreated – the diagnosis is a death sentence.

When Belle was diagnosed she was tripping and falling a lot and choking on thin liquids and saliva and her speech was slushy and difficult to understand. She also had a tremor and vertical gaze palsy. We made the decision to enroll Belle into a clinical trial and investigators logged Belle’s baseline NPC CSS at 7.

What we know now, is that Belle was in the placebo arm of the trial. We watched in terror as she lost her ability to walk and as other abilities slipped away. Eight months into the trial Belle was slipping through our fingers and her score revealed the same – it more than doubled to a 17. She worked hard during her time in the study, leaving it all on the field as they say. A 6 year old little girl, literally giving her blood, sweat, tears, loads of CSF and lest we forget, the ability to walk – all of these things that Belle gave to the NPC community. To researchers and regulators to study and learn from. She met the criteria to cross over into the treatment arm and was finally going to be treated. We were grateful.

Within months Belle’s swallowing improved and she was no longer despondent or on the verge of seizures. It felt like our little girl was coming back to life and her CSS score reflected the same as it had rebounded to a 13 and for those of you listening today from the FDA, I assure you that what we were seeing was “real” and each and every one of those points are meaningful to us. We saw stabilization in some areas, and we continue to see improvement every day in others.

Abigail was too young for the trial. With a baseline score of 1, she immediately began taking adraβetadex through expanded access. Today she is 7 years old and her NPC score is a 0. Abby’s life today is very different from her sister’s life. She flips on the bars at gymnastics and performs at Christmas in The Nutcracker Ballet. She swims independently, rides a bicycle, and jumps on the trampoline sometimes for hours a day. We are grateful that she has remained asymptomatic and we are painfully aware that she is now older than Belle was when Belle lost the ability to walk.

To really give patients a chance, NPC expert clinicians have stated over the years that it will take multiple drugs treating multiple pathways. Despite the fact that regulators didn’t approve Miglustat as a treatment for NPC, my husband and I decided to listen to the expert clinicians, and we added Miglustat to our daily treatment regime. We have seen benefits to adding Miglustat and are grateful that we listened to the experts.

My husband and I understand that this isn’t magic or a fluke. This is science. Belle & Abby are using two drugs that are attacking the disease in different ways and slowing the progression of NPC. Today, our daughters are no longer taking these drugs because of “hope.” We no longer have uncertainty regarding the effectiveness of the medication we choose to give our daughters. And we accept any risks associated with this medication as minimal compared to the risk of leaving NPC untreated.

I share my family’s NPC journey with you today in hopes of you better understanding two things.

1. Leaving the disease untreated is not an option
2. A one point change in the clinical SS is meaningful. For example, when my daughter Belle lost the ability to walk it was reflected in a one-point change on the scale.

In last week's congressional hearing, Dr. Cavazzoni stated that the "FDA stands ready to exercise its regulatory flexibility when reviewing potential treatments for neurodegenerative diseases." Today, we are all here to let you know, we need you to do just that – Please exercise your regulatory flexibility to immediately approve the treatments that NPC patients are currently taking through EAP's.

## **Speaker Remarks: Barbara Lazarus, Mother of Daniel and David**

Hello and thank you for giving me the time to share my thoughts today.

My name is Barbara Lazarus and I am the mother of two sons, Daniel, age 34 and David, age 32. Our lives followed a typical family path through their childhood and teen years and into college. Both sons have college experience. Daniel had three years in college before his symptoms interrupted his studies and he was unable to continue. He went on to complete a certificate program at a local community college. David graduated with an Associate's degree in Automotive Technology and a Bachelor's Degree in Business management, his dream one day to own an automotive repair business like his Dad. Unfortunately, neither worked for long in their chosen fields before the diagnosis of NPC robbed them of their dreams and ambitions; Daniel at age 30 and David at age 28. Our path to diagnosis took 10 years from Daniels' first symptoms. The difference from the beginning in symptom presentation between siblings was stark, ranging from mainly physical and cognitive issues in Daniel to various mental health diagnoses for David, and only further confused and delayed the process of identification. Daniel is currently enrolled in the expanded access program for Trappsol cyclo IV treatment and David's only option is the expanded access program for arimocloamol.

Once we received the diagnosis of NPC and began to process our shock and grief, we became familiar with the Clinical Severity Scale which helped us frame our son's level of disability and differences. It has given us a way to understand their profiles by providing baseline information, changes and current level of functioning. We, along with their medical providers, use the CSS as an effective guide by which to measure maintenance, stabilization and change - both positive and, unfortunately, negative at times. The five domains capture those symptoms and issues that are most important to us, but more importantly our adult sons, in maintaining an independent and productive lifestyle.

Over the course of these past few years, we've found that our observations of our son's symptoms correlate accurately to their scale scores, especially as some symptoms are more difficult to quantify than others. For instance, in terms of swallowing, we have two vastly different pictures of how this skill is impacted in daily life. While one son has difficulty with the oropharyngeal phase and needs reminders to chew before swallowing, our other son has difficulty with coughing on thin liquids. These are very different functions of the same symptom but the scale allows us to rate their level of interference with specific markers such as liquids, solids and so forth and ranges from normal to tube feeding, allowing for an accurate description of their level of functioning. I have also found this to be true of the other CSS domains.

I have found in my career as a speech pathologist that scales are a useful and reliable tool to assess current level, plan appropriate programs and interventions and gauge change, progress or regression. These scales rely on a combination of clinical and/or parental/caregiver observations and anecdotal information. Given the very different profiles of our sons, the CSS has been meaningful when meeting with medical professionals, as together we translate our collective observations into a score by which to accurately judge stabilization or improvement. In summary, the CSS provides a level of understanding and a measure of reassurance for patients, families and caregivers in a disease which at best is confusing and scary and at worst is terrifying and devastating.

## Speaker Remarks: Nicole Burgos and her father Frank Burgos

**Frank:** Good afternoon: I'm Frank Burgos, Nicole's father and we'll be co-presenting today.

**Nicole:** Hello, I'm Nicole and thanks for listening to us.

**Frank:**

Nicole was diagnosed with adult-onset NPC almost two years ago. Her initial manifestation was psychiatric, but after being diagnosed we realized she had multiple symptoms outlined in the Clinical Severity Scale:

- Top 10% in high school that started struggling with academics in college
- Once in college there was slow down in her speech
- She became very clumsy, dropping things and falling down quite often
- Frequent cough while eating and drinking.

Then, in August 2019, she developed a sudden and severe psychosis requiring hospitalization for four months until she was diagnosed with NPC in December 2019. During her time in the hospital, her fine motor skills significantly declined, we had to cut her food and feed her, and she could not walk from the bed to bathroom. Once Nicole was out of the hospital, she required 24x7 attention. She was almost non-verbal. My wife had to quit her job to become Nicole's primary caregiver.

Nicole started on Miglustat in January 2020. Six months later, she started Occupational Therapy. The first thing her therapist did was administer a battery of tests to get a baseline. Three months after that baseline, in October 2020, she started arimoclomol.

About six weeks after starting arimoclomol, the first thing we noticed was she became significantly more verbose, using full sentences, initiating conversation and tonality returned to her voice. Two weeks ago, her therapist retested Nicole to measure progress over the last year against the baseline.

**Nicole:**

Swallow: While I was in the hospital in 2019, I went code blue 2 times because I choked while eating. Today I no longer cough while eating and haven't choked since leaving the hospital.

Ambulation: When I started therapy, I could not stand only using my left foot, today I can stand for 34 seconds. For standing only on my right foot: last year it was five seconds, today I can do it for 58. Early last year, I was not walking much at all. Today, I go on two- to three-mile walks several times a week.

Fine motor skills: I no longer need help cutting my food. In the Beery Visual Motor Integration test, my score last year was 77 which is low, today its 103 which is average. In the Motor Coordination test, my score last year was 45 which is very low, and today its 102: also average.

My psychiatric manifestations have not returned.

**Frank:**

Our allotted time today is limited, thus can't cover all her tests results, but we can make those available to you.

The real question today is: Are we happy with the progress being made with Miglustat and arimocloamol? YES! Time is not on our side. We'd much rather have access to multiple medications today that have a REASONABLE CHANCE of improving a symptom or two rather than do nothing while waiting for the miracle drug that will cure everything to be developed, tested and then approved, all while this degenerative condition takes its toll.

**Nicole:**

I've improved a lot since starting on arimocloamol. My doctors are amazed at my progress and several have volunteered to provide you with supporting documentation for your review.

I URGE you to find a path forward so I can continue to have access to this medication.

## Speaker Remarks: Will Evans

**Speaker:** Will Evans MSc MB ChB  
General Practitioner  
Honorary Assistant Professor, Division of Primary Care  
University of Nottingham

*Note: As indicated in the agenda, Dr. Evans was one of the NPC clinical experts slated to speak during the discussion of the NPC CSS. Due to time constraints, he was unable to deliver his remarks, which are included below for reference.*

Regarding the NPC CSS, I would like to bring your attention to additional work recently conducted. The manuscript is currently under review but a preprint is available [here](#). An international panel of 19 NPC disease experts were asked to form a consensus, through a Delphi method, on the use of clinical severity scales in three scenarios: routine clinical care, assessment for trial enrolment, and as clinical trial outcome measure. Recommendations included the use of the five-domain NPC CSS in routine clinical practice, and the 17-domain scale in clinical trial settings, whilst prioritizing the domains in the five-domain scale as the primary endpoints.

Further, I was hoping to explore with you how can the NPC CSS results generated in trials be supported by patient experience data and real-world evidence. Our concern is this information is currently undervalued.

Indeed, I would have addressed the comment made by Dr. Donahue that the agency needs to consider patient preference, patient perspective, and scientific evidence when assessing a product. Patient perspective, when captured correctly, is scientific evidence and this information should be given the appropriate weight and value it deserves in an assessment that considers the totality of evidence.

I would also wish to strongly challenge that the solution to the difficulties of conducting trials in NPC are longer RCTs. A two- to three-year RCT in Niemann-Pick Type C is, I believe, neither ethical nor feasible.

Finally, as a parent of a child affected by NPC I feel it is important that the agency understands that although many will accept substantial risk and uncertainty, the community is not homogenous in their views. The decision of what is an acceptable risk weighed against the potential benefit is complicated and personal taking into consideration the impact of a therapy that far exceeds the side effect profile of the candidate drug. The making of such decisions is something all families have walked in partnership with their clinicians. It is therefore unreasonable to assume that the patient community will accept any degree of risk or uncertainty for the

suggestion of benefit and that when the community reports that a therapy's risk benefit profile is acceptable this has not been considered deeply.

## Speaker Remarks: Joslyn Crowe

**Speaker:**       **Joslyn Crowe**  
                          **Executive Director**  
                          **National Niemann-Pick Disease Foundation**

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 - adrabetadex, 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.

## Follow-up Email to FDA

*As of the date of publication of this report, the FDA had not provided a full response to this letter.*

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.

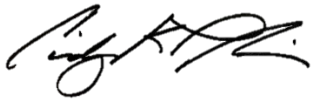
- B. A conceptual agreement to reconsider applications based on agreed re-analyses as developed by recognized experts.
- C. A willingness for FDA to broaden considerations for near-term flexibility in recognition of the pressing, unmet needs of the NPC community and in recognition of the community's 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](mailto:Sean.C.Kassen.1@nd.edu)) for additional information.

Families are counting on all of us.

Sincerely,



Cindy Parseghian  
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Ara Parseghian Medical Research Fund



Sean Kassen, PhD  
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Justin Hopkin, MD  
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