February 18, 2022

Mark McClellan, MD, PhD, Director
Duke-Margolis Center for Health Policy

Delivered via email

Dr. McClellan:

Thank you and Duke Margolis, in partnership with FDA, for convening the two-day workshop on Niemann-Pick Type C (NPC) that not only included broad participation and input from the medical and stakeholder communities, but also brought in new voices with important perspectives. Due to your team's efforts, we are encouraged that all participants, including the FDA, better understand the challenges and opportunities to transform the NPC landscape from a universally fatal condition to one with multiple therapies to improve the quality and length of life. We were particularly pleased that the NIH was represented by a leading scientist, Dr. Forbes "Denny" Porter, who has long worked on NPC and understands the disease incredibly well. He noted that making a difference for people with NPC is going to require thinking about, "how we get drugs approved in a different manner than I think what we're doing today." And Dr. Maynard saying "that's important because we need data, supporting the benefits of the drugs, and that those benefits outweigh the risks in order for it to be approved."

Our community faces urgent needs in terms of continued access to experimental and off-label therapies, and seeks pathways to expedite these therapies to market based existing data. As Dr. Cavazzoni said in her opening remarks, "time is of the essence"; without continued access to these therapies, lives are at stake. Although speeding therapies to market was not specifically addressed at the meeting, this remains at the forefront of our work, and we feel it is important for your team to keep this practical need in mind in evaluating and summarizing the workshop input which at times focused on future development programs.

As your team develops the follow-on report, we believe there are key takeaways from the speakers that merit inclusion and accompanying recommendations. Those include:

- FDA speakers affirming that the domains of the five domain NPC-CSS are content valid and Dr. Mariz from the EMA saying that the NPC-CSS is a good instrument that his Agency finds valuable in evaluating drugs for NPC when he said "that we shouldn't throw out the NPC-CSS". Dr. Noble stated, in the first panel, that "It's clear that the five areas of function identified: speech, ambulation, fine motor, swallowing, and cognition are relevant concepts."

- FDA speakers affirming their commitment to collaborate and innovate; to do so they must leverage their existing regulatory flexibilities and guidances. These include Dr. Cavazzoni saying in her opening remarks that the FDA has a “long-standing commitment to regulatory flexibility for serious and life-threatening rare conditions with unmet needs, such as NPC.” Dr. Stein said that we need to “look at other innovative strategies to support product development” and that “it’s important for us to discuss and understand these challenges and to consider innovative strategies to support the element of treatments for NPC.”

- Dr. Mariz affirming that single-arm trials are acceptable in rare diseases, saying that EMA had “a lot of experience in single-arm trials.”

- Dr. Porter from NIH saying, during the first panel, that it is difficult for a one-year trial to yield the magnitude of results FDA appears to be seeking, “I’m not convinced that there’s an easy, quick, answer - that you can apply across patients to show progression and lack of progression, because we’re not expecting improvement, so the delta we’re looking for is even smaller - that you can reliably see in a sensitive manner in one year. And that becomes a limitation when you start to think about trials…the only tool I really have to describe the clinical progression of the disease across all patients is the CSS.” He also said that “It takes years to achieve these endpoints, specifically, real life efficacy for this disease will take years to establish.”

- The need to do more at-home testing/observation and acceptance of caregiver-reported information about the patient’s abilities, which was discussed by Dr. Marsh in the third panel and all of the speakers on the fourth panel.

- Several panelists recognizing that performance measures developed for other diseases fail to account for the heterogeneity of NPC. Some speakers noted that these performance measures similarly share the consistency and implementation concerns expressed about the NPC-CSS. Dr. Patterson, specifically noted that these alternatives were considered and often integrated into the NPC-CSS; the total of the presentations suggests that there is no single tool that is better suited than the NPC-CSS; this supports the continued use of the NPC-CSS, complemented by other measures of individual domains. Dr. Freilich from the FDA also noted that there is “a challenge to find the right endpoint that will capture meaningful change in the broadest group of patients…there is such heterogeneity that one instrument might be good for one population but not another. Trying to find that one domain that could be suitable and capture change in the time of a study that will be clinically meaningful."

- Multiple experts, including Dr. Porter affirming that the goal of treatment is not to cure, but rather to slow the progression of the disease, saying “symptom reversal is unlikely. Our goal is to slow or halt progression. Ultimately combination therapy will be required.”

That said, we were concerned by other comments, where participants raised issues, without proposing solutions, and the comment more generally revealed a lack of understanding of NPC. They include:

- Certain panelists, in discussing the use of other measures for the clinical domains, discussed many measures that have already been considered and rejected or already being used concurrently with the NPC-CSS, and provided recommendations for new tools. Unfortunately, they did not address or seem to consider whether the new tools should be developed in addition to, or instead of, to be done in combination with the NPC-CSS. For example, Dr. Phillips talked about locomotion tests and the SARA scale. Dr. Patterson and Dr. Berry-Kravis both spoke about the other scales and considerations that went into the development of the NPC-CSS. Dr. Freilich suggested a gait assessment, which has already been considered and integrated into the NPC-CSS.

- An academic researcher, who said "Niemann-Pick Type C, of which I know a little about" suggested (1) that clinical rating scales are universally insensitive to change, and (2) that alternative measures provided by wearables and other remote monitoring tools, while more sensitive, are largely untested and would be difficult to interpret, and (3) that natural history studies should be re-done using the as yet untested remote monitoring methods.

The concerning comments listed above, if taken at face value, would sacrifice the lives of patients who are living with this disease today by discounting the value of existing datasets and tools in use today. Proverbially speaking, we cannot throw the baby out with the bathwater. Any approaches that do not try to build on the foundation that so many NPC and NIH experts shared would be truly deaf to the urgency the caregiver participants shared that patients are facing today, and would further delay access to safe and effective therapies – both those of today and in the future.

We were also interested in statements that we hope your team can help clarify:

- Dr. Maynard stated that "walking, thinking, swallowing and speaking" are some of the endpoints for NPC. NPC experts and caregivers all report that cognition is an important metric. Dr. Porter stated that the cognitive impairment of people with NPC is one of the important points of heterogeneity, saying "we've had kids running up and down the hall but absolutely in a cognitive fog. Contrast that with another child sitting right beside them that you can have a full conversation with but they are completely motor impaired. That is this disease." Yet, cognition was not included in the Duke Margolis meeting and was omitted as a primary endpoint for a newly enrolling NPC trial.

- The apparent inconsistency of the FDA's position on the NPC natural history study despite agency guidance on how to use natural history studies as controls in clinical trials

- The FDA's intransigence with respect to approving drugs for NPC when it has approved drugs in other diseases, such as pancreatic cancer, MS, and Duchenne, for small gains which later allowed more data to be gathered and encouraged further development. The example of miglustat is one that looms large in that the FDA disagreed with its advisory committee on the approval and now the drug is standard of care for many NPC patients. Ten years of data have shown that the medicine works and extends life span for the significant number of patients able to tolerate it. It is considered to be the standard of care by the experts.

- The feasibility and utility of remote patient monitoring for young children, including those under 2 years old.

- FDA's apparent concern that using a clinically reported outcome scale in the context of NPC is inappropriate because it is not "objective," even though FDA has on numerous occasions, in other contexts, accepted and suggested the use of clinically reported outcome scales - such as gait - as "objective" measures.

Finally, we think that the following steps are important to build on progress made at the meeting, and we would be pleased to partner with Duke-Margolis to help make them happen:

1. The issuance of a summary report to frame key findings and next steps to better inform and expedite drug development for NPC, in the immediate- and long-term, including calling out where existing tools and approaches should be maintained, even if there is an opportunity to build upon that foundation. Ideally, this report will include actionable suggestions for how regulators can leverage the findings at the meeting to help speed the review and approval of drugs to treat NPC;

2. A follow-up workshop with the Duke-Margolis Center to dive deeper into some of the issues not fully explored including natural history and the feasibility, utility and ethics of placebo-controlled trials for NPC, and opportunities to allow for multi-drug approaches that allow patients to maintain access to existing therapies while continuing to develop new ones.

We thank you, and the Duke-Margolis team, for your efforts to help patients with NPC and their families. The workshop allowed us to hear many of the best minds come together to address some of the problems in developing drugs for NPC. Some of the ideas, like continuous monitoring and comparing each patient to themselves, were insightful, and we want to work with the community to ensure these happen.

Thank you for your continued commitment to combating NPC and to the NPC community.

Sincerely,

Organizational Signers:

Hope for Marian	National Niemann Pick Disease Foundation
Niemann Pick Canada	Ara Parseghian Medical Research Fund
NPUK	International Niemann Pick Disease Alliance
Firefly Fund	Dana's Angels Research Trust
SOAR	Hide and Seek Foundation for Lysosomal Disorders
NPi Suisse	Associazione Italiana Niemann Pick
Hope for Hayley	International Niemann Pick Disease Registry

Individual/Family Signers of Children and Adults With NPC:

United States

Cindy K Parseghian, parent of and in loving memory of children Michael, passed at 10 years old, Marcia, passed at 16 years old, and Christa, passed at 10 years old
Sara and Paul McGlocklin, parents of Marian, 6 years old
Pam and Chris Andrews, parents of Belle and Abby, 11 and 7 years old
Andrea and Phil Marella, parents of Andrew Marella, 22 years old and in loving memory of Dana Marella, passed at age 19
Harry, Gail and Alec Koujaian, parents of Alec, 23 years old and in loving memory of Hayley
Alec Koujaian, adult with NPC
Jonathan Jacoby and Hope Grossman, parents of Joshua, 19 years old
Meredith and Evan Piotti, parents of Reagan, 8 years old
Mihaela and Nick Costache, parents of Vivi, 11 years old
Jessica, Scott, and Madison Lansdown, parents and sibling of Will, 12 years old
Rebecca Spencer White, parent of Johnathan, 15 years old
Jen and Duane Barton, parents of Elise, 16 years old
Nadezhda Kiseleva, parent of Denis, 14 years old
Gary and Julie Moore Family, parents of Brynne and Kendall, 13 and 10 years old
Garland, Melissa, and Claire Alvey, parents and sister of Abigail, 6 years old
Abigail Alvey, child with NPC, 6 years old
Dena and Scott Ruthven, parents of Cody and Kayla Ruthven, adults with NPC, in loving memory of Lana Jo Ruthven
Cody Ruthven, adult with NPC
Kayla Ruthven, adult with NPC
Pamela Gallimore-Wong and Philip Wong, parents of Charles, 24 years old
Guy, Havilah, Mason, Riley and Jayden Martinez, parents and siblings of Mason, 19 years old
Sara and Mitch Peterka, parents of Emma, 3.5 years old
Karen and Gene Quandt, in loving memory of son Ty Quandt, passed at 20 years old
Kaylee Beresford and Bentley Sepesy, parent and sibling of Brodie Beresford, 3 years old
Keri, David, and Owen Sellers, parents and sibling of Gwenyth, youth with NPC
Gwenyth Sellers, youth with NPC
Wade & Lori Wells, parents of Kristen, 24 years old
Cara Gilmore and Bradley J. Kowalski, adult with NPC and partner
Teleasha Smith, parent of Wyatt, 18 years old
Chris and Doug Berns, parents of Samantha, 25 years old
Samantha Berns, adult with NPC, 25 years old
Wendy B Peebles, adult with NPC, 54 years old
Tonya and Jason Kain, parents of Julia, 21 years old
Gwen S Hughes, parent of Daniel, adult with NPC

Chip and Dawn Stites, parents of Cole, 14 years old
Bradley Weets, Jenna Weets and Claire Weets, parents and sister of Jeg, 8 years old
Debbie and Steve Kaflowitz, in loving memory of daughter Rachael, passed at age 33
Larissa Andrews, parent of Noah, 2 years old
Rickey and Denise Miller, parents of Woodrow, 2 years old
Mary and Gary Womack, parent of Joel, 42 years old
Joel Womack, adult with NPC
Amy and Sean Recke, parents of Adam, 22 years old
Amy Whaley, parent of John Michael, adult with NPC
Jennifer and Jordan Mitchell, parents of Liam, 7 months old
Michael and Amanda Wallace, parents of Brody, 3 years old, and Owen, 2 years old
Elsa I Nazario and Frank Burgos, parents of Nicole, 29 years old
Deanna Odeh and Kamel Hamad, parents of Osama, 5 years old
Annapurna Kambhatla, parent of Sanjay Kambhatla, 25 years old
Sanjay Kambhatla, adult with NPC
KayLaura Miller Smith and family, parent of Kamryn Brumbeloe, 10 years old
Tiffany Ruben, parent of Mason, 6 years old, Logan, 4 years old, and Ethan, 1 year old, and in loving memory of Jacob, passed at 7 years old
Meghann Ferguson, parent of Liam, 7 years old
Barbara and Gary Lazarus, parents of Daniel, 35 years old, and David, 32 years old
Daniel Lazarus, adult with NPC
David Lazarus, adult with NPC
Jeffrey and Jeanne M Padden and Emily Marron, parents and sibling of Timothy, 37 years old
Hugh and Chris Hempel, in loving memory of daughters Addison and Cassidy
Kimberly and Brian Coppola, parents of Andrew and David, adults with NPC
Andrew Coppola, adult with NPC
David Coppola, adult with NPC
Bryan and Lindsay Woodard, parents of Caleb, 8 years old
Wallisa and Issac Marsh, parents of Justin, 22 years old
Linda Dundas, in loving memory of son John Porter, forever 36
Bryan Hadley, parent of Peyton, 24 years old, and Kayla, 21 years old
Krystal Samuelson, parent of Willow, 5 years old

<u>International</u>

Paul and Cheryl Marcogliese, Canada, parents of Daniel, 7 years old, and James, 5 years old
Mark Novakovic, Australia, adult with NPC, 42 years old
Marlo Schmidt, Canada, parent of Rocco, 2.5 years old
Lesley Petts, parent of Kelly Goodridge, 38 years old
Kelly Goodridge, Canada, adult with NPC
Renee Staska, Australia, parent of Hudson, Holly and Austin, 7, 5 and 3 years old
Vyskoreva Victoria Viktorovna, Russia, parent of Tymkiv Taisiya, 8 years old
Alicia Demarte, Australia, individual with NPC
Iryna Talko, Ukraine, parent of child with NPC
Крылов Даниил Дмитриевич, Russia, adult with NPC
Attie ten Napel, The Netherlands, parents of Sem, 20 months
Leonnie Blick, Australia, adult with NPC, 65 years old
Rachel Cooke, Aaron Burroughs, and Chelsey Burroughs, UK, parents and sibling of Taylor, 9 years old
Taylor Burroughs, UK, child with NPC, 9 years old
Jodie Ogrady, UK, parent of Joshua Cullip, 15 years old
Janaina Beserra, Brazil, parent of Arthur, 7 years old
Michelle Taylor, UK, parent of Yasmin, 21 years old
Siri S Blegen, Norway, in loving memory of daughter Karen Marie, passed away at 9 years old

Nataliia Stratiichuk, Ukraine, parent of Viktor, 30 years old
Zakieh Jalali, Iran, parent of Sara Oslobi, 12 years old
Fiona Dunne, UK, in loving memory of children Harry, passed at 7 years old, and Grace, passed at 13 year old
Dave Roberts, UK, in loving memory of Caroline Owen, 30 years
Silvina Luz Schmittlein, Argentina, Felipe Ramos, child with NPC
Christoph Poincilit, Switzerland, parent of Alix and Zita, and in loving memory of Mathias
Dorothea Seifert, Germany, parent of Marius, 25 years old, and Roald, 20 years old
Julie and Keith Algie, UK, parent of Blair, 9 years old
Marie Tauszig, Germany, parent of Audrey, child with NPC
Nadia Slatch, UK, in loving memory of son Zayn Slatch who passed away at age 5