Duke | MARGOLIS CENTER for Health Policy

Endpoint Considerations to Facilitate Drug Development for Niemann-Pick Type C (NPC)

Introduction

Niemann-Pick type C (NPC) is a rare genetic lysosomal storage disorder caused by mutations in either the *NPC1* or *NPC2* genes. These genes are responsible for intracellular lipid transport. Mutations result in impaired intracellular transport of cholesterol and other lipids leading to aberrant lipid accumulation within multiple organs, predominantly the liver, spleen, lungs, and brain.[1] NPC has an estimated incidence of one case per 100,000 live births.[2] Although disease presentation can vary widely, NPC typically results in progressive neurological symptoms and organ dysfunction. NPC has historically been considered a childhood-onset disease, but an increasing number of patients with adult-onset symptoms are being identified. In newborns, the disease presents primarily as a liver disorder and can lead to rapid liver failure. In juvenile patients, NPC commonly manifests as developmental delay with cognitive impairment and motor impairment. In adult-onset patients, cognitive symptoms often occur along with psychiatric symptoms. Life expectancy for patients diagnosed with NPC can range from a few days to several decades.[2]

The rarity of NPC, the wide range of onset and presentation, and the complexity of diagnostic testing has led to common misdiagnosis or delayed diagnosis and can make proper care more difficult for patients to access.[2] The clinical presentation of NPC is highly heterogeneous, traditionally requiring a complex diagnostic process that can require clinical assessment in addition to complex biochemical and molecular genetic laboratory studies. Early neurological symptoms may differ as they are dependent upon the age of onset and can range from delayed developmental motor milestones in infants and clumsiness and problems experienced with schooling in juveniles to psychiatric disturbances in adults.[3] Diagnosis therefore requires clinical recognition of several non-specific systemic and neurological signs and symptoms.[4] Confirmation of a diagnosis of NPC requires consideration of historically diagnostic biomarkers (filipin staining and plasma based biomarkers currently under evaluation) in addition to the identification of one or more disease-causing mutations in either the *NPC1* or *NPC2* gene.[1,4] However, development of blood-based biochemical testing and genetic testing based on newer sequencing technologies are likely to make testing simpler and more widespread, and could lead to an increase in early infantile diagnoses of NPC.[5]

There are currently no therapies approved in the United States for treatment of NPC. However, Miglustat, which is approved for Gaucher's Disease in the United States and for NPC in several other countries, is considered a standard of care by some clinicians and patients with NPC and is commonly prescribed off-label for the treatment of NPC.[2]

Clinical trials for any rare disease population can be challenging due to small population size and a limited ability to fully characterize both clinical and laboratory-based aspects of disease progression. The extremely low incidence of NPC makes powering clinical trials for NPC particularly challenging. Clinical trials may take longer to complete due to limited enrollments. Like trials for other small populations, clinical trials for NPC products may need to engage patients from around the globe in order to ensure an adequate number of trial subjects. As NPC is a highly heterogenous disease, selected assessments of

symptoms and impacts may not reflect disease presentation or clinically meaningful improvements for all patients with NPC. Together, these challenges present significant hurdles to NPC therapeutic development.

The Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the US Food & Drug Administration, is hosting a workshop to support advancements in the selection and development of endpoints for NPC clinical trials. The workshop will discuss the current challenges to identifying clinically meaningful treatment effects in NPC trials and strategies to optimize NPC endpoint considerations to support successful therapeutic development for patients living with NPC.

This workshop will include the following:

- A review of endpoint considerations in NPC and discussion of challenges and opportunities to support product development.
- Consideration of functional assessments that could serve as clinical endpoints in NPC clinical trials.
- Discussions of innovative strategies to support product development, such as digital technologies and biomarkers.

Please note that while participants in this workshop will be discussing endpoints for NPC clinical trials, specific drugs or use of expanded access are not within the scope of this meeting. While this meeting is limited to discussions around endpoints, there are a number of other topics related to NPC clinical trials that warrant further discussion. Broader conversations will be needed to address the full range of challenges and opportunities for NPC therapeutic development.

Comments for this workshop may be submitted to Docket FDA-2021-N-1297. The Docket will be open until April 25, 2022. Comments in the Docket will be reviewed after closure.

Disclaimer

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Virtual Day 1 | Introduction and Overview of Endpoints for Niemann-Pick Type C (NPC)

Session 1: Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)

The original NPCCSS comprises 17 domains intended to capture and quantify disease progression. These NPC–specific domains were based on neurological impairments that allow for a calculation of a composite score to indicate disease severity. An abbreviated NPCCSS was created to focus on five domains identified by patients, caregivers, and NPC clinical experts as the most clinically relevant when assessing disease progression.[6] These five domains are ambulation, fine motor skills, swallowing, cognition, and speech, and are measured through clinician-reported outcomes (ClinROs).[7]

The 17-domain NPCCSS has been an important scale to support our understanding of NPC and the focus of this panel discussion will be on the use of the 5DNPCCSS in clinical trials. The ease of administration and interpretation of clinical severity scales such as the NPCCSS has made them appealing for use in clinical trials. The 17-domain NPCCSS has played a key role in the characterization of NPC's natural history and in the clinical management of NPC, including assessment of disease burden, response to therapy, and prognosis.[8] However, in the context of clinical trials there have been challenges identified with the NPCCSS and its streamlined version, the 5-domain NPCCSS. Specifically, there is a need for validity evidence indicating that the 5DNPCCSS adequately measures these critical domains. Additionally, there is a need for clear, standardized administration and scoring procedures to ensure that the NPCCSS is implemented and rated in the same way by all clinicians at all clinical trial sites. Finally, the 5DNPCCSS may not be sufficiently granular to capture small but meaningful changes in patient functioning in the context of clinical trials and functional measurements may be better suited. In this session, participants will review the five-domain NPCCSS and consider its strengths and limitations. In addition, participants will propose strategies to address identified limitations of the NPCCSS, suggest potential modifications to the scale, and consider strategies to use existing datasets to further evaluate its validity.

Discussion Questions:

1. What are key strengths and limitations of the five-domain NPCCSS in the context of clinical trials?
2. How do the measures included in the five-domain NPCCSS reflect the patient and caregiver experience of NPC?
3. As experience with the use of the abbreviated NPCCSS in clinical trials grows, are there specific modifications you would recommend for the NPCCSS to ensure it is sensitive to treatment effects in trials?
4. What are the barriers to standardizing administration of the NPCCSS? What recommendations would you make to ensure standardization of NPCCSS across clinical trial sites?
5. What are additional sources of evidence that could be used to bolster the validity of all or part of the NPCCSS?
6. What, if any, other modifications or considerations might help facilitate optimization of the NPCCSS for use in clinical trials?

Session 2: Functional Measures for Swallowing

Dysphagia, or impaired swallowing, can be seen in patients diagnosed with a variety of neurodegenerative conditions, including NPC. Across the age spectrum, patients with NPC often develop difficulties swallowing due to the impact of disease progression on sensory and motor coordination. The ability to swallow impacts both patient safety and quality of life. The presence of dysphagia can pose significant risks for choking, aspiration, and related pneumonia. Strategies to manage dysphagia can be challenging to implement and burdensome for patients and caregivers.[7]

Softening solid foods and thickening liquids are two approaches initially used to decrease the risk for aspiration in patients with dysphagia. However, as the dysphagia becomes more severe routine monitoring and evaluation may demonstrate a need for the use of a gastrostomy tube(g-tube).[9]

While swallowing has been identified as a key symptom of NPC, assessing dysphagia and its progression, and using swallowing as a clinical trial endpoint can be difficult. Some NPC programs have used the five-domain NPCCSS to assess dysphagia, as it includes a swallowing assessment based upon caregiver report. Functional swallow assessments may also be useful for measuring impairment in individuals with NPC. Which assessments are best suited to evaluate the progression of dysphagia in patients with NPC are unclear, making the selection of a specific tool for use in a clinical trial challenging.

In this session, participants will review potential swallowing assessment tools and consider their strengths and limitations as clinical trial endpoints.

Discussion Questions:

1. Are there aspects of swallowing that are more directly assessed by some instruments than others? What are the opportunities and challenges with using these different instruments?
2. Is there variability in tool administration or disease pathology that impacts interpretation across raters and over time? If so, what steps can be taken to mitigate these issues and determine interpretability of measurements on the individual level and of clinical trials?
3. What are the overall strengths and limitations of each assessment tool? What are the strengths and limitations of each assessment tool for use in NPC clinical trials specifically?
4. What challenges and opportunities exist with these different tools in relation to the patient and caregiver experience in clinical trials?

Session 3: Functional Measures for Ambulation, Speech, and Fine Motor

Ambulation, speech, and fine motor skills are part of the five-domain NPCCSS. NPC most commonly onsets during middle to late childhood. Neurological abnormalities may be the first apparent symptoms, specifically lack of muscle coordination, or cerebellar ataxia. Children with cerebellar ataxia often have difficulties with balance and trouble with walking. Ambulation was selected for the NPCCSS for its importance to patients' ability to move independently, and concerns about risks of falling or the greater health impacts associated with losing the ability to walk.

Affected children may also experience progressive difficulty speaking and may lose previously acquired speech skills. Speech was selected as part of the NPCCSS due to the importance communication has in everyday life, especially in expressing their needs or wants. Fine motor skills are significant for the

impact hand tremors or difficulty coordinating their hands had on their everyday activities like eating, writing, and caring for themselves.[7]

While these symptoms are key to understanding the progression of NPC, ambulation, speech, and fine motor skills can be difficult to assess for patients across the age spectrum, specifically for very young children (0-2 years) who would not be expected to have reached certain developmental milestones. Measurements based on alternative age-appropriate measurements can add further difficulties regarding standardization.[7]

Participants will review potential ambulation, speech, and fine motor assessment tools and consider their strengths and limitations as clinical trial endpoints.

Please note that while cognition is an essential aspect of NPC impacts and disease progression, *this session will not include a focus on the cognition domain*. Defining and measuring cognitive functioning across the developmental spectrum in patients with NPC and across countries and cultures is a complex challenge faced by most rare disease scientists and warrants its own focused discussion.

Discussion Questions:

1. In considering potential functional assessment tools, are there aspects for ambulation, speech, and fine motor that are more directly assessed by some instruments than others? What are the opportunities and challenges with using these different instruments?
2. Is there variability in tool administration or disease pathology that impacts interpretation across raters? If so, what steps can be taken to mitigate these issues and determine interpretability of measurements on the individual level and of clinical trials?
3. What are the overall strengths and limitations of each assessment tool? What are the strengths and limitations of each assessment tool for use in NPC clinical trials specifically?
4. What challenges and opportunities exist with these different tools in relation to the patient and caregiver experience in clinical trials?

Virtual Day 2 | Potential Innovative Endpoints and Strategies to Support NPC Product Development

Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

Clinical trials for patients with rare diseases can be particularly challenging due to small patient population size and poor disease characterization. Additionally, heterogeneity in age of onset and disease presentation, in NPC, can create further challenges for therapeutic development. Digital health technologies offer unique opportunities to ease the burden of clinical trial participation on patients and families. This may be especially beneficial for patients with rare diseases who may have to travel significant distances to reach participating clinical trial sites. Furthermore, digital health technologies offer opportunities to directly collect meaningful data from patients. Digital health technologies can also support the collection of continuous data, rather than snapshots, that may better reflect a disease course. However, digital health technologies are also associated with potential challenges, such as the ability to make reliable measurements and the ability to capture novel characteristics. Additionally, not all endpoints or measures are well suited for digital or remote collection. In this session, participants will discuss examples of digital health technologies and consider opportunities and challenges with their use to measure clinical endpoints.

Discussion Questions:

1. What functional aspects of NPC (e.g., ataxia) could be meaningfully and accurately measured by digital health technologies?
2. How would potential use of digital health technologies enhance your ability to participate in a clinical trial or run a clinical trial?
3. What are the opportunities and challenges with digital health technologies in patients with neurodegenerative disorders, in particular in progressive and heterogeneous diseases, such as NPC?
4. What considerations are important for ensuring that an endpoint measured using digital health technologies is clinically relevant to patients?

Session 5: Future Biomarker Considerations in NPC

The development of biomarkers is especially important in rare diseases such as NPC, as it can be challenging to establish clinical efficacy through standard clinical trials given small patient populations, widely variable clinical presentation, and slow rates of progression in some patients.[10] Biomarker testing is generally rapid, lower-cost, and less invasive than previous methods of NPC diagnosis and disease monitoring. Biomarkers can be used in various ways, such as to assist with the diagnosis and monitoring of a condition, and potentially to assess disease progression.

In NPC, research has identified several cholesterol oxidation products (oxysterols) that are detectable before the onset of symptoms and associated with disease progression. These oxysterols may be potential biomarkers for diagnosis and treatment of NPC, and as outcome measures to monitor response to therapy.[10,11] Other studies have identified additional potential biomarkers in NPC, such as Lyso-SM-509[12] and bile acid B.[13]

While these advances have been significant, there is currently no single biomarker specific for NPC. More understanding is needed regarding the utility of these biomarkers as measures of disease progression and treatment effectiveness.[14] Further, it can be challenging to meet regulatory standards to validate biomarkers as endpoints in prospectively defined clinical trials. Panelists will discuss how biomarkers help inform the evaluation of NPC and will discuss how biomarkers can characterize relevant outcome measures for clinical trials.

Discussion Questions:

1. What are the strengths and weaknesses of the various biomarkers being explored for NPC?
2. What is the role of blood biomarkers vs CNS biomarkers in assessing the severity of neurologic disease?
3. In the development of biomarkers for NPC, what are the advantages and disadvantages of animal models for biomarker discovery and development?
4. What are important considerations for the future of biomarker development in NPC?
5. Are there considerations related to biomarker development in other diseases that are relevant to biomarker considerations in NPC?
6. What are the challenges associated with validating biomarkers for NPC, and what approaches may support efficient biomarker validation?

Session 6: Closing Panel and Forward Looking

This session will address the next steps and stakeholder roles to support endpoint development and selection for NPC clinical trials. Participants will discuss feasible approaches to improving the quality and availability of functional measurements, and how new and existing data can best be used to support clinical trials. Participants may revisit discussions from earlier sessions and discuss how these considerations may impact NPC clinical trials moving forward. Participants will also discuss priorities, roles, and responsibilities for advancing biomarker development and validation. Finally, participants will discuss next steps for continued collaboration and advancement of NPC endpoints with the overall goal being the development of safe and effective treatments for NPC.

Discussion Questions:

1. Reflecting on the day, what are key strategies optimizing endpoints in NPC clinical trials?
2. What steps can be taken to make therapeutic development for NPC more efficient while ensuring the collection of robust clinical data to support regulatory and clinical decision making?
3. How can clinical trials be designed to best support patient access and ease burdens associated with trial participation?
4. Beyond endpoint selection, what are the other key considerations for supporting the approval of safe and effective treatments for NPC?
5. What are key strategies for facilitating collaboration between stakeholders, including patients and caregivers, with the overall goal of developing safe and effective treatments for NPC?

References

1. Mengel E, Bembi B, del Toro M, et al. Clinical disease progression and biomarkers in Niemann-Pick disease type C: a prospective cohort study. Orphanet Journal of Rare Diseases. 2020;15(1):328. doi:10.1186/s13023-020-01616-0
2. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet Journal of Rare Diseases. 2018;13(1):50. doi:10.1186/s13023-018-0785-7
3. Vanier MT. Niemann-Pick disease type C. Orphanet Journal of Rare Diseases. 2010;5(1):16. doi:10.1186/1750-1172-5-16
4. Imrie J, Heptinstall L, Knight S, Strong K. Observational cohort study of the natural history of Niemann-Pick disease type C in the UK: a 5-year update from the UK clinical database. BMC Neurol. 2015;15:257. doi:10.1186/s12883-015-0511-1
5. Thurm A, Chlebowski C, Joseph L, et al. Neurodevelopmental characterization of young children diagnosed with Niemann-Pick disease, type C1. J Dev Behav Pediatr. 2020;41(5):388-396. doi:10.1097/DBP.0000000000000785
6. Cortina-Borja M, te Vruchte D, Mengel E, et al. Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. Orphanet Journal of Rare Diseases. 2018;13(1):143. doi:10.1186/s13023-018-0880-9
7. Patterson MC, Lloyd-Price L, Guldberg C, et al. Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. Orphanet J Rare Dis. 2021;16(1):79. doi:10.1186/s13023-021-01719-2
8. Yanjanin NM, Velez JI, Gropman A, et al. Linear clinical progression, independent of age of onset, in Niemann-Pick disease, type C. *Am J Med Genet B Neuropsychiatr Genet.* 2010;153B(1):132-140.
9. Niemann-Pick disease type C. NORD (National Organization for Rare Disorders). Accessed January 12, 2022. https://rarediseases.org/rare-diseases/niemann-pick-disease-type-c/
10. Degtyareva AV, Proshlyakova TY, Gautier MS, et al. Oxysterol/chitotriosidase based selective screening for Niemann-Pick type C in infantile cholestasis syndrome patients. BMC Medical Genetics. 2019;20(1):123. doi:10.1186/s12881-019-0857-0
11. Porter FD, Scherrer DE, Lanier MH, et al. Cholesterol oxidation products are sensitive and specific blood-based biomarkers for Niemann-Pick C1 disease. Sci Transl Med. 2010;2(56):56ra81. doi:10.1126/scitranslmed.3001417
12. Sidhu R, Mondjinou Y, Qian M, et al. N-acyl-O-phosphocholineserines: structures of a novel class of lipids that are biomarkers for Niemann-Pick C1 disease. J Lipid Res. 2019;60(8):1410-1424. doi:10.1194/jlr.RA119000157
13. Jiang X, Sidhu R, Mydock L, et al. Development of a bile acid-based newborn screen for Niemann-Pick C disease. Sci Transl Med. 2016;8(337):337ra63. doi:10.1126/scitranslmed.aaf2326
14. Fog CK, Kirkegaard T. Animal models for Niemann-Pick type C: implications for drug discovery & development. Expert Opinion on Drug Discovery. 2019;14(5):499-509. doi:10.1080/17460441.2019.1588882