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

Key Themes and Future Directions from the January 2022 Public Workshop

August 4, 2022

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Overview

Mark McClellan

Director, Duke-Margolis Center for Health Policy

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Webinar Agenda

3:00 pm Welcome and Overview

3:05 pm Opening Remarks from FDA

3:10 pm Patient Community Perspective

3:20 pm Researcher Perspective

3:30 pm NPC Endpoint Considerations – Key Themes and Future Directions

3:45 pm Q&A

3:55 pm Closing Remarks

4:00 pm Adjournment

All times listed in ET

Opening Remarks from FDA

Patrizia Cavazzoni

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Patient Community Perspective

Justin Hopkin

National Niemann-Pick Disease Foundation

Patient Community Perspective

Sean Kassen

Ara Parseghian Medical Research Fund

Researcher Perspective

Forbes D. Porter

National Institute of Childhood Health and Human Development

National Institutes of Health

NPC Endpoint Considerations – Key Themes and Future Directions

Jacqueline Karp

Office of New Drugs

U.S. Food and Drug Administration

NPC Endpoint Considerations – Key Themes and Future Directions

August 4, 2022

Jackie Karp, MD

U.S. Food and Drug Administration (FDA)

Center for Drug Evaluation and Research

Division of Rare Diseases and Medical Genetics

Objective: Recap of Workshop Sessions

- Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)
- Functional Measures of Swallowing
- Functional Measures of Ambulation, Speech, and Fine Motor
- Exploring Digital Health Technology to Measure Functional Endpoints
- Future Biomarker Considerations in NPC
- Closing Panel and Forward Looking

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

Patient/caregiver perspective: "when someone tells you [that] you have five years left with your child, that's really not a slowly progressing disease."

Abbreviated five-domain NPCCSS (5DNPCCSS): 5 most clinically meaningful clinical functional areas (**ambulation, fine motor skills, swallowing, cognition, and speech**)

- Valuable resource for understanding disease progression
- Some challenges with interpreting results (especially for short clinical trials)
- Limitations in scale development/validity evidence interfere w/ score interpretation
- Cognition domain especially challenging (rate of decline does not align w/ trial durations)

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

Opportunities for addressing challenges

- **Ensure response options in each domain are clearly defined, do not overlap, consistently interpreted and relevant for all ages**
- **Ensure standardized implementation**
  - Harmonized training materials, standardization of assessments
- **NPC clinical trial measurement could be advanced by more precise assessments and new methods (e.g., biomarkers)**

Session 2: Functional Measures of Swallowing

Patient/caregiver perspective: "As a clinician and a parent, I feel strongly one can never replace what is observed on a day-to-day basis."

- **Swallowing a key symptom in NPC**

- **Difficulty in interpretation** due to disease heterogeneity, lack of standardization
  - Measures often do not reflect daily swallowing

- **Videofluoroscopic Swallowing Study**
  - Challenging for younger patients; impacted by patient compliance
  - Requires special training to administer, interpret

- **Fiberoptic Endoscopic Evaluation of Swallow**
  - Endoscope insertion difficult
  - Not available at many sites

- **Burdens make participation difficult**
  - Struggle w/ certain textures/tastes in assessments
  - Significant travel distances to specialized sites

Session 2: Functional Measures of Swallowing

Addressing Challenges

- **Patient/caregiver diaries**
  - Improve communication, longitudinal follow-up to fill in gaps between studies
- **New technologies** (e.g., audiovisual diaries)
  - Under study; may provide more consistent/standardized evaluations
- **Planning discussions** w/ patients/caregivers prior to assessments (e.g., types of foods, parts of swallowing process that are struggles)
- **Field of speech-language pathology becoming more standardized**
  - Improving accessibility/standardization of measures

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

Patient/caregiver perspective: "When these numbers show a slowing, or stalling of disease progression …, it's very important that these numbers and endpoints be interpreted as a massive success"

- **Measures (often categorical scales) may not be sufficiently sensitive** to detect meaningful changes
  - May not detect stabilization, slow improvement or slowed progression
  - May not reflect how patient functions in real world
  - May not capture progress if floor or ceiling of scale reached
  - Rely on episodic measurements, so may miss important events or mischaracterize trends
  - May lead to false negative results in clinical trials

- **Difficult to assess patients across age spectrum**
  - Certain developmental milestones (relevant to assessments) not met by very young
  - Age-appropriate measures can add further difficulties (e.g., standardization across population)

- **Assessments can be subjective and depend on patient's level of engagement**

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

- **Must define how multi-system impairments may impact assessments** (e.g., how cognitive issues can impact performance on fine motor assessment)

- **Assessments must be sufficiently sensitive** to detect stabilization/slowed progression meaningful to patients and families

- **Incorporation of multiple assessments, statistical analyses to optimize measurement**

Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

Patient/caregiver perspective: While patients and families are sharing successes and meaningful outcomes they see in their day-to-day lives with investigational interventions, they feel that information is not necessarily being adequately captured.

- **Digital health technologies could:**
  - Overcome challenges of functional assessments/rating scales (e.g., subjective, insensitive, episodic)
  - Foster use of novel measurements that may better reflect outcomes that matter to patients
  - Collect more frequent data from patients in clinical trials

  Via Telehealth, could also:
  - Expand patient access to clinical trials
  - Permit assessment in homes, which may reflect full range of patient's abilities rather than snapshot
  - Increase reliability by having same rater for all sites (e.g., w/ videographic analysis)
- **Concerns/limitations**: cybersecurity, data access/barriers, enormous amounts of data
- Digital health technologies **may be best used initially in complementary role to traditional clinical data collection** (rather than as a replacement)

Session 5: Future Biomarker Considerations in NPC

- **Biomarker development could support/enhance development**
  - Assist with diagnosis
  - Assess disease progression

- Compared to existing methods of diagnosis and disease monitoring, biomarker testing may be faster, lower-cost, and less invasive

- **Require analytical and clinical validation** for regulatory submissions
  - Biomarker that has been validated to predict a specific clinical benefit could be accepted as a surrogate endpoint for trials

- Robust biomarker data **could also be used as confirmatory evidence of effectiveness** alongside other data, such as data from clinical assessments

Session 5: Future Biomarker Considerations in NPC

- **Multiple biomarkers under investigation:** oxysterols, bile acids, 24-hydroxycholesterol, CSF proteins (CSF FABP3 and Calbindin D), eacylphosphocholineserine (APCS), grey matter volumes and comparison subcortical volume, and lysotracker staining
  - FDA recommends measuring as exploratory endpoints in all NPC trials
  - As evidence accumulates, may demonstrate that one or more can work as primary endpoints to speed development and approval of drugs

- **Challenges/limitations** w/ biomarkers:
  - May not capture full treatment effect
  - May have unknown prognostic value, relation to changes in timing of outcomes

- Many biomarkers under investigation **relevant to other neurological, lysosomal diseases** (e.g., neurofilament light chain for assessing neurodegeneration)
  - Opportunities for collaboration among researchers

Session 6: Closing Panel and Forward Looking

- **Patients and families must have a voice** in identifying meaningful clinical outcomes and in determining risk tolerance.

- Because neurodegenerative therapies may not improve disease symptoms, the **goal is to understand whether an intervention results in stabilization or attenuation in the rate of disease progression**.
  - **Endpoint development and selection must reflect this goal.**

- The **ultimate goal** is to **identify multiple safe and effective drugs that can impact the long-term course of disease across the NPC population**.

Session 6: Closing Panel and Forward Looking

- **Modifications to the 5DNPCCSS should be able to integrate w/ existing data**

- Existing **natural history data** invaluable, **may never be replicated**
  - Can serve a critical role in supporting future NPC research/development
  - **Bolstering** available data **rather than recreating** this dataset

- Potential **strategies for making development more efficient**
  - Mechanisms for **feedback between regulatory agencies**
  - More collaboration among all stakeholders; **data sharing**
  - **Learning from all submissions**, including unsuccessful ones
  - **Innovative trial designs that aggregate datasets** from multiple study populations, including combining placebo and experimental groups from different trials
  - **Continued engagement between regulators and patients/caregivers** to discuss meaningful measurements, acceptable levels of risk

Forward Looking

- **Collaboration is key to facilitating rare disease product development**
  - Important to continue and build on various rare disease efforts


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Q&A

Various Speakers

Q&A Respondents

- Katie Donohue, U.S. Food and Drug Administration
- Justin Hopkin, National Niemann-Pick Disease Foundation
- Jacqueline Karp, U.S. Food and Drug Administration
- Sean Kassen, Ara Parseghian Medical Research Fund
- Naomi Knoble, U.S. Food and Drug Administration
- Forbes D. Porter, National Institutes of Health

Closing Remarks

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Thank You!

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