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

Virtual Public Workshop

January 24-25, 2022

Workshop Docket Comment Summary

Workshop Docket Comment Description

In conjunction with the January 24-25, 2022 virtual public workshop entitled *Endpoint Considerations to Facilitate Drug Development for Niemann-Pick Type C*, a public docket[1] was open from January 21, 2022 until April 25, 2022 to collect further public input on the topic. As a supplement to the January workshop summary, this document provides a high-level summary of 15 submitted comments. Comments were submitted by parents and caregivers, health care providers, professional organizations, patient groups, and researchers. Comments received after the docket closed were also incorporated into this summary as applicable.

Docket submissions can be viewed in full here: Docket FDA-2021-N-1297

Summary of Comments

The below summary of docket submissions includes a number of key themes expressed in the comments provided by the various stakeholders.

Comments stressed that individuals with NPC have significant unmet treatment needs as there are no therapies currently approved in the United States for the treatment of NPC. For these patients, there is an urgent necessity for safe and effective therapies. It is important to consider input from patients, clinicians, and families when assessing the effectiveness of NPC investigational interventions to ensure meaningful improvements are captured.

The importance of regulatory flexibility for design, conduct, and analyses of NPC clinical trials was emphasized given the small patient population size and heterogeneity of disease presentation and progression. Comments acknowledged the complexity of this ultra-rare disease, and reiterated challenges discussed in the workshop including extremely heterogeneous disease presentation, the fact that NPC may cause degeneration in different areas and over different time-courses in each patient, and an acknowledgement that a one-year trial might be too short to demonstrate any meaningful change.

Comments described a strong patient preference for single-arm rather than placebo-controlled studies, use of existing natural history data, and acceptance of endpoint measures that are currently available and important to patients and their families. It was further noted that it is important to take into consideration invaluable information that has already been gathered through the natural history study at the National Institutes of Health (NIH) and the use of the NPC Clinical Severity Scale (NPCCSS).

[1] A docket is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

Building upon the discussion at the workshop around swallowing studies, it was noted that the Modified Barium Swallow (MBS) study may not be available in the European Union. Thus, it was stressed that it is important to consider whether an assessment tool will be available at all study sites as to prevent unnecessarily constricting the trial population size, which could make it harder to enroll and see statistically significant differences between study arms of NPC clinical trials

While not within the scope of this workshop, many stakeholders, including patients, therapists, and caregivers, stressed the importance of early and continued access to investigational products through the expanded access program. Stakeholders shared fears of what losing access to investigational products would mean for patients, especially for those who have been accessing these therapies for many years (such as arimoclomol and adrabetadex).

Letters that had been sent previously to the FDA on various investigational NPC therapies and detailing patient and caregiver perspectives on NPC and therapeutic development were also submitted to the docket. These letters echoed many of the experiences shared throughout the workshop on the successes patients and families have seen with investigational products and the urgent need to approve safe and effective treatments for patients with NPC. It was emphasized that clarity, collaboration, and action are needed immediately and that it is important for FDA to work with the NIH, industry, academia, health care providers, and the patient community to efficiently develop, approve, and ensure access to therapies.

Lastly, stakeholders submitted citations for published research articles on NPC that provided context on the topics under discussion during the workshop. Submitted references to publications included the following:

Studies Related to NPC Natural History

Bianconi, S. E., Hammond, D. I., Farhat, N. Y., Dang Do, A., Jenkins, K., Cougnoux, A., Martin, K., & Porter, F. D. (2019). Evaluation of age of death in niemann-pick disease, type C: Utility of disease support group websites to understand natural history. *Molecular Genetics and Metabolism*, *126*(4), 466–469. https://doi.org/10.1016/j.ymgme.2019.02.004

Imrie, J., Dasgupta, S., Besley, G. T., Harris, C., Heptinstall, L., Knight, S., Vanier, M. T., Fensom, A. H., Ward, C., Jacklin, E., Whitehouse, C., & Wraith, J. E. (2006). The natural history of Niemann–Pick Disease Type C in the UK. *Journal of Inherited Metabolic Disease*, *30*(1), 51–59. https://doi.org/10.1007/s10545-006-0384-7

Imrie, J., Heptinstall, L., Knight, S., & Strong, K. (2015). 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 Neurology*, *15*(1). https://doi.org/10.1186/s12883-015-0511-1

Shin, J., Epperson, K., Yanjanin, N. M., Albus, J., Borgenheimer, L., Bott, N., Brennan, E., Castellanos, D., Cheng, M., Clark, M., Devany, M., Ensslin, C., Farivari, N., Fernando, S., Gabriel, L., Gallardo, R., Castleman, M., Gutierrez, O., Herschel, A., … Haldar, K. (2011).

Defining natural history: Assessment of the ability of college students to aid in characterizing clinical progression of Niemann-Pick disease, type C. *PLoS ONE*, *6*(10). https://doi.org/10.1371/journal.pone.0023666

Thurm, A., Farmer, C., Farhat, N. Y., Wiggs, E., Black, D., & Porter, F. D. (2016). Cohort study of neurocognitive functioning and adaptive behaviour in children and adolescents with Niemann-Pick Disease Type C1. *Developmental Medicine & Child Neurology*, *58*(3), 262–269. https://doi.org/10.1111/dmcn.12970

Wraith, J. E., Guffon, N., Rohrbach, M., Hwu, W. L., Korenke, G. C., Bembi, B., Luzy, C., Giorgino, R., & Sedel, F. (2009). Natural history of Niemann-Pick Disease Type C in a multicentre observational retrospective cohort study. *Molecular Genetics and Metabolism*, *98*(3), 250–254. https://doi.org/10.1016/j.ymgme.2009.06.009

Yanjanin, N. M., Vélez, J. I., Gropman, A., King, K., Bianconi, S. E., Conley, S. K., Brewer, C. C., Solomon, B., Pavan, W. J., Arcos-Burgos, M., Patterson, M. C., & Porter, F. D. (2009). Linear Clinical Progression, independent of age of onset, in Niemann-Pick disease, type C. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *9999B*. https://doi.org/10.1002/ajmg.b.30969

Studies Related to the NPCCSS

Cortina-Borja, M., te Vruchte, D., Mengel, E., Amraoui, Y., Imrie, J., Jones, S. A., i Dali, C., Fineran, P., Kirkegaard, T., Runz, H., Lachmann, R., Bremova-Ertl, T., Strupp, M., & Platt, F. M. (2018). 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*, *13*(1). https://doi.org/10.1186/s13023-018-0880-9

Evans, W., Patterson, M., Platt, F., Guldberg, C., Mathieson, T., Pacey, J., Berry-Kravis, E., Farhat, N., Gascon, J., Geberhiwot, T., Gissen, P., Giugliani, R., Hastings, C., Héron, B., Imrie, J., Jones, S., Lachmann, R., Mengel, E., Patterson, M., … Walterfang, M. (2021). International consensus on clinical severity scale use in evaluating Niemann–Pick Disease Type C in paediatric and adult patients: Results from a Delphi Study. *Orphanet Journal of Rare Diseases*, *16*(1). https://doi.org/10.1186/s13023-021-02115-6

Farhat, N., Bailey, L., Friedmann, K., Bushnell, D. M., Rodriguez, D., Berry-Kravis, E., & Porter, F. D. (2022). Consistently high agreement between independent raters of Niemann-Pick Type C1 clinical severity scale in phase 2/3 trial. *Pediatric Neurology*, *127*, 32–38. https://doi.org/10.1016/j.pediatrneurol.2021.11.009

Mengel, E., Bembi, B., del Toro, M., Deodato, F., Gautschi, M., Grunewald, S., Grønborg, S., Héron, B., Maier, E. M., Roubertie, A., Santra, S., Tylki-Szymanska, A., Day, S., Symonds, T., Hudgens, S., Patterson, M. C., Guldberg, C., Ingemann, L., Petersen, N. H., … í Dali, C. (2020). Clinical disease progression and biomarkers in Niemann–Pick Disease Type C: A prospective cohort study. *Orphanet Journal of Rare Diseases*, *15*(1). https://doi.org/10.1186/s13023-020-01616-0

Mengel, E., Patterson, M. C., Chladek, M., Guldberg, C., í Dali, C., Symonds, T., Lloyd-Price, L., Mathieson, T., Crowe, J., & Burbridge, C. (2021). Impacts and burden of Niemann pick type-C: A patient and caregiver perspective. *Orphanet Journal of Rare Diseases*, *16*(1). https://doi.org/10.1186/s13023-021-02105-8

Patterson MC et al. Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium Rotterdam, Netherlands; 3–6 September 2019 available at https://www.clinoutsolutions.com/wp-content/uploads/2019/09/OR-REL-NPC-01-SSIEM-poster-v1.0.pdf

Patterson, M. C., Lloyd-Price, L., Guldberg, C., Doll, H., Burbridge, C., Chladek, M., íDali, C., Mengel, E., & Symonds, T. (2021). Validation of the 5-domain Niemann-Pick Type C Clinical Severity Scale. *Orphanet Journal of Rare Diseases*, *16*(1). https://doi.org/10.1186/s13023-021-01719-2

A white paper providing a background and perspective on regulatory approach to several NPC investigational products.

https://www.regulations.gov/comment/FDA-2021-N-1297-0007

Workshop Disclaimer

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