Mucopolysaccharidosis Type III (Sanfilippo Syndrome): Developing Drugs for Treatment
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Patroula Smpokou at 240-402-9651 or (CBER) Office of Communication, Outreach, and Development at 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2020
Clinical/Medical

Mucopolysaccharidosis Type III (Sanfilippo Syndrome): Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2020
Clinical/Medical

TABLE OF CONTENTS

Mucopolysaccharidosis Type III (Sanfilippo Syndrome): Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors regarding eligibility criteria, trial design considerations, and efficacy endpoints to enhance clinical trial data quality and foster greater efficiency in development programs for drugs[2] to treat mucopolysaccharidosis type III (MPS III; also called Sanfilippo syndrome).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

MPS III is a rare, autosomal recessive, inborn error of glycosaminoglycan (GAG) metabolism with an estimated incidence of 0.28–4.1 per 100,000 live births. It belongs to a group of genetic disorders called mucopolysaccharidoses, which are caused by different single enzyme defects affecting lysosomal GAG breakdown. MPS III is caused by deficient activity of any one of four enzymes involved in the breakdown of the GAG heparan sulfate (HS) in lysosomes. The disease is divided into four distinct subtypes based on the gene defect and corresponding enzyme deficiency as follows: MPS IIIA (*SGSH* (N-sulfoglucosamine sulfohydrolase) gene; heparan *N*-

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research and by the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For purposes of this guidance, unless otherwise specified, references to *drugs* include drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and biological products licensed under section 351 of the Public Health Service Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

sulfatase deficiency), MPS IIIB (*NAGLU* (N-acetyl-alpha-glucosaminidase) gene; *N*-acetyl-α-glucosaminidase deficiency), MPS IIIC (*HGSNAT* (heparan-α-glucosaminide N-acetyltransferase) gene; acetyl CoA:α-glucosaminide *N*-acetyltransferase deficiency), and MPS IIID (*GNS* (N-acetylglucosamine-6-sulfatase) gene; *N*-acetylglucosamine 6-sulfatase deficiency) (Valstar et al. 2008). These enzymatic defects result in progressive intralysosomal accumulation of HS, which is believed to lead to or initiate a cascade of events leading to cellular damage and progressive tissue and organ dysfunction. Currently, there are no approved disease-modifying therapies for MPS III.

The central nervous system is the organ primarily affected in MPS III. The natural history and rate of progression of the neurologic manifestations are not well characterized in any of the four MPS III subtypes. Some limited natural history information is available in MPS IIIA. In general, genotype alone does not appear to be a reliable sole predictor of disease severity or rate of neurological progression in MPS III (Valstar et al. 2008; Valstar et al. 2011). However, in MPS IIIA, patients with onset of signs and symptoms in early childhood may have a more rapidly progressive course (*severe* MPS IIIA) compared to patients diagnosed later in childhood or adolescence (*attenuated* MPS IIIA). In severe MPS IIIA, clinical symptoms manifest in early childhood (2–6 years of age) and include developmental delay (primarily of speech and language) and behavioral problems (e.g., hyperactivity, inattention, anxiety, autistic features, aggression, lack of fear). Other symptoms variably include the following: disturbance of the normal sleep cycle, frequent upper respiratory and ear infections, hearing and visual impairment, and motor deficits. Hepatomegaly is found in some patients (splenomegaly is rare), but it is generally much less common and less severe in MPS III compared to other mucopolysaccharidoses.

The following describes the general disease trajectory in severely affected patients (also called rapid progressors) with MPS IIIA (Shapiro et al. 2016). Typically, a patient's initial period of normal or near normal development (up to 2 years of age) is followed by a period of slowing in developmental progression (between 2 and 4 years of age). Development appears to arrest around 4 years of age in severely affected patients with MPS IIIA. Subsequently, patients enter a phase of progressive neurocognitive decline characterized by developmental regression and loss of previously acquired skills, which eventually leads to complete loss of cognitive, language, and motor abilities culminating in dementia. Motor abilities are usually not affected until later in the disease course. Median age at death in MPS IIIA is reported as 15 years of age, ranging between 8.5 and 25.5 years of age (Valstar et al. 2008). There is insufficient information regarding the general disease trajectory and natural history of manifestations in patients with MPS IIIB, IIIC, and IIID.

III. IMPORTANT CONSIDERATIONS FOR CLINICAL TRIALS

A. Eligibility Criteria and Baseline Assessments

All eligible patients should have clinical signs and symptoms consistent with a diagnosis of MPS III, which should be confirmed by both biochemical testing (HS concentration) and molecular genetic testing. Ideally, enrolled patients should be in the early stages of the disease (i.e., before

irreversible neurological damage has occurred). For gene/enzyme-specific therapies targeting a specific MPS III subtype, enrolled patients should have the same MPS III subtype. If appropriate, (depending on the drug's mechanism of action) sponsors can enroll in the same trial patients of different ages, patients with different MPS subtypes and/or patients who are at different stages of the disease. Baseline laboratory assessments should include, at a minimum, genotyping (if not already available) and assessment of HS concentration in relevant tissues (blood, urine, and/or cerebrospinal fluid (CSF)). As part of baseline laboratory assessments in enzyme replacement therapy and gene therapy trials, sponsors should collect and store blood (or other relevant tissues) for use in the assessment of cross-reactive immunologic material (CRIM) status. Baseline clinical assessments should include standard evaluations of hearing, vision, cognition, and adaptive behavior to ensure that enrolled patients are able to sufficiently complete trial assessments.

B. Trial Design

Because of the current paucity of natural history knowledge and the clinical heterogeneity of MPS III, appropriately designed and executed natural history studies could provide crucial information to help guide and inform essential aspects of a clinical development program.[3]

Given the rarity of MPS III, a single adequate and well-controlled trial (as described in 21 CFR 314.126), showing a clinically meaningful treatment effect on core disease manifestations, accompanied by additional confirmatory evidence can be used to support approval. Such confirmatory evidence could be based on different lines of evidence (e.g., data showing a treatment effect on disease-specific biochemical markers (e.g., CSF HS) in treated patients; nonclinical data showing biochemical and functional treatment effects in a well-characterized MPS III animal model).[4]

If a large treatment effect and/or an effect on objective clinical measures (e.g., survival) are not expected within a specified trial duration, FDA strongly recommends a randomized, parallel-group trial design with an appropriate concurrent control group. Because of the uncertainties related to the lack of a well-characterized natural history, the variable rate of neurologic disease progression among patients, and the nonlinear developmental trajectory observed in many MPS III patients (Ghosh et al. 2017), such randomized, concurrently controlled trial design would provide the most informative and reliable data for an evaluation of efficacy in the most efficient and expedient way. Given the small patient population, sponsors should use randomization as early as in the first clinical trial involving MPS III patients to allow for maximal and most efficient use of efficacy data for regulatory purposes.

---

[3] See the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

When natural history information becomes available and can reliably predict the disease course in a given patient cohort, and when a large treatment effect size is anticipated based on preliminary information, an externally controlled clinical trial may be acceptable. Sponsors can consider innovative and adaptive trial designs and should discuss these early in development with the appropriate review division.[5, 6]

A patient's symptomatic treatment regimen (e.g., concomitant drugs, physical and occupational therapy, other interventions) should be optimized in advance of trial entry, and efforts should be made to maintain the stability of these background treatments during the trial. Any changes in the patient's background treatment regimen made during the trial should be carefully documented.

As most drugs would be intended to slow or arrest the neurological disease progression rather than to reverse it, a clinical trial should be of sufficient duration, at least 2–3 years to observe an effect on neurological disease aspects. In addition, patients with different disease severity would be expected to have different rates of neurocognitive decline, which would necessitate different durations of observation to assess treatment effects on selected endpoints. For gene therapy products, sponsors should be aware of special considerations regarding the length of long-term follow-up.[7]

C. Pharmacodynamic Endpoints

Assessment of changes in HS concentration in CSF could provide evidence of *in vivo* biological activity of the drug, demonstrate proof-of-concept, and help characterize the dose-response relationship in early phase trials. Changes in plasma or urine HS should be considered of limited utility given the neurologic nature of MPS III. Assessment of changes in organ volume (e.g., liver, spleen) should be considered of limited utility given that organomegaly is not a common finding in MPS III patients and that changes in organ volume are of unclear clinical significance in a disease that is fundamentally neurologic. Quantitation of pharmacodynamic biomarkers (e.g., HS, HS derivatives, enzyme activity) should be conducted at a central laboratory using appropriately validated methods to ensure reliability of the results. Understanding the variability of the test(s) used is fundamental to the interpretation of any treatment effects on those biomarkers.

[5] For sponsors interested in discussing complex innovative trial designs, see also the FDA Complex Innovative Trial Design pilot meeting program web page available at https://www.fda.gov/drugs/development-resources/complex-innovative-trial-designs-pilot-program.

[6] See the draft guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[7] See the draft guidance for industry *Long Term Follow-Up After Administration of Human Gene Therapy Products* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

D. Efficacy Endpoints

Demonstration of a clinically meaningful treatment effect on neurological disease manifestations that are important to patients and their families can form the basis for traditional approval. Sponsors should assess multiple, distinct clinical endpoints in trials to provide a global characterization of treatment effects on disease manifestations. At this time, additional evidence should be provided to support the use of HS reduction in CSF or other tissues (blood or urine) as a surrogate endpoint reasonably likely to predict clinical benefit to support accelerated approval.[8]

The selection and prioritization of efficacy endpoints should take into consideration patients' and parents'/caregivers' preferences to ensure that sponsors assess outcomes that are clinically meaningful to patients and their families. The selection of efficacy endpoint(s) should also consider the mechanism of action and anticipated clinical effects of the drug on the different disease manifestations. Furthermore, given the multiple clinical manifestations of MPS III, which may differentially affect patients' daily functioning, sponsors can consider the use of a multiple-endpoint strategy.[9] FDA strongly encourages sponsors to engage in early and continuous discussions with the appropriate review division regarding the selection of the most informative and clinically meaningful endpoint(s) for demonstration of efficacy.[10]

Standardized clinical outcome assessment (COA) instruments should be used to evaluate treatment effects on major neurological disease aspects (e.g., cognition, behavior) (Janzen et al. 2017). Appropriate standardized tests of cognitive performance should be selected based on patients' baseline level of functioning. When selecting COA instruments to evaluate cognitive performance, sponsors should also consider whether there may be anticipated floor effects of the particular instrument in the enrolled population as this could affect interpretability of the data. Sponsors should also consider that the selection of particular COA tests may also inform the frequency of the corresponding assessments (Van der Lee et al. 2017).

All COA instruments should be administered by trained personnel who are familiar with the instruments and with the special challenges of MPS III patients as they relate to patients' behavioral problems, inattention, hyperactivity, sensory impairment (hearing, vision), speech and language deficits, fatiguability, and motor impairment as those can interfere with test administration and interpretation of test results. Instructions, training materials, and case report forms should include detailed information on all specific methods that should be utilized when administering these tests. Assessments can be divided into multiple short sessions, and the trained personnel should allow adequate time for the completion of each assessment. In addition, assessments should be administered in an environment familiar to the patient, and the testing environment should be free of items that may cause distraction.

[8] See section 506(c) of the FD&C Act; 21 CFR part 314, subpart H; and 21 CFR part 601, subpart E.

[9] See the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[10] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic.

195 The amount of time used and other contextual features of performance-based assessments should
196 be recorded and accounted for in data analyses. Other factors that may affect patients'
197 behavioral and cognitive performances, such as uncontrolled or insufficiently controlled seizures
198 (which can be part of the underlying disease), should be carefully assessed and documented
199 throughout the trial and should be considered in the interpretation of treatment effects. FDA
200 strongly encourages sponsors to discuss all proposed COAs with the appropriate review division
201 early in development (i.e., pre-investigational new drug application phase).
202

REFERENCES

Ghosh A, Shapiro E, Rust S, et al., 2017, Recommendations on Clinical Trial Design for Treatment of Mucopolysaccharidosis Type III, Orphanet J Rare Dis, 12(1):117–131.

Janzen D, Delaney KA, and Shapiro EG, 2017, Cognitive and Adaptive Measurement Endpoints for Clinical Trials in Mucopolysaccharidoses Types I, II, and III: A Review of the Literature, Mol Genet Metab, 121(2):57–69.

Shapiro EG, Nestrasil I, Delaney KA, et al., 2016, A Prospective Natural History Study of Mucopolysaccharidosis Type IIIA, J Pediatr, 170:278–287.

Valstar MJ, Marchal JP, Grootenhuis M, Colland V, Wijburg FA, 2011, Cognitive Development in Patients with Mucopolysaccharidosis Type III (Sanfilippo Syndrome), Orphanet J Rare Dis, 6:43–48.

Valstar MJ, Ruijter GJ, Van Diggelen OP, Poorthuis BJ, Wijburg FA, 2008, Sanfilippo Syndrome: A Mini-Review, J Inherit Metab Dis, , 31(2):240–252.

Van der Lee JH, Morton J, Adams HR, et al., 2017, Cognitive Endpoints for Therapy Development for Neuronopathic Mucopolysaccharidoses: Results of a Consensus Procedure, Mol Genet Metab, 121(2):70–79.