Fabry Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 clinical trial design features that can support approval of drugs and biological products intended for the treatment of Fabry disease (FD).[2]

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

FD is a rare, X-linked, slowly progressive, lysosomal storage disorder caused by pathogenic variants (disease-causing mutations) in the galactosidase alpha (*GLA*) gene resulting in absent or deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal A). The α-Gal A enzyme breaks down glycosphingolipids within lysosomes. α-Gal A deficient activity leads to progressive intralysosomal accumulation of the undegraded substrate globotriaosylceramide (GL-3, also known as Gb3), a glycosphingolipid. FD is characterized by chronic symptomatology (e.g., gastrointestinal symptoms, neuropathic symptoms including pain, hypohidrosis or anhidrosis), slowly progressive organ damage eventually leading to chronic renal disease and renal failure, cardiovascular disease (e.g., hypertrophic cardiomyopathy, heart

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research in cooperation with 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 submitted for licensure or 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)).

failure, myocardial infarction, arrhythmias), cerebrovascular disease (strokes), and early mortality.[3]

FD is divided into two subtypes based on age of symptom onset and extent of organ involvement:[4]

- Classic FD presents in patients with absent or minimal residual α-Gal A enzyme activity (less than 1 percent of mean normal). Childhood-onset clinical manifestations in classic FD include chronic gastrointestinal symptoms (e.g., diarrhea, abdominal pain, constipation), neuropathic pain crises involving the extremities (acroparesthesias), proteinuria, and hypohidrosis or anhidrosis leading to heat and exercise intolerance. Angiokeratomas on the skin and cornea verticillata (corneal *whorls*) on ophthalmologic slit lamp exam, both asymptomatic, are also sometimes observed. Adult-onset manifestations in classic FD include progressive renal failure, cardiac disease (e.g., hypertrophic cardiomyopathy, heart failure, myocardial infarction, arrhythmias), and stroke, which cause chronic morbidity and early mortality. The highest concentrations in tissues and plasma of the substrate GL-3 and of its degradation product, globotriaosylsphingosine (lyso-GL-3), are typically seen in patients with classic FD.

- Nonclassic (late-onset) FD is more prevalent than classic FD.[5] Patients with late-onset FD have some residual α-Gal A enzyme activity, which is highly variable (greater than 1 percent of mean normal). Late-onset FD presents clinically in adulthood with renal, cardiac, and/or cerebrovascular disease; has a highly variable age-of-symptom onset; and follows a highly variable rate of progression.[6] Within the late-onset subtype, patients may have only single organ involvement.[7] Patients with late-onset FD (and female patients) show variable levels in tissues and plasma of the substrate GL-3 and its degradation product, lyso-GL-3.

Despite its X-linked inheritance, FD affects both males and females, although to different degrees. In general, male patients with the classic subtype experience the most severe clinical manifestations, multi-organ disease, faster disease progression, and an earlier age of symptom onset compared to male patients with the late-onset subtype and to female patients. In female

[3] Germain, DP, 2010, Fabry Disease, Orphanet J Rare Dis, 5:30, doi: 10.1186/1750-1172-5-30.

[4] Germain, DP, 2010, Fabry Disease, Orphanet J Rare Dis, 5:30, doi: 10.1186/1750-1172-5-30; Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, and Desnick RJ, 2006, High Incidence of Later-Onset Fabry Disease Revealed by Newborn Screening, Am J Hum Genet, 79(1):31–40; and Ortiz A, Germain DP, Desnick RJ, et al., 2018, Fabry Disease Revisited: Management and Treatment Recommendations for Adult Patients, Mol Genet Metab,123(4):416–427.

[5] Ortiz A, Germain DP, Desnick RJ, et al., 2018, Fabry Disease Revisited: Management and Treatment Recommendations for Adult Patients, Mol Genet Metab, 123(4):416–427.

[6] Ortiz A, Germain DP, Desnick RJ, et al., 2018, Fabry Disease Revisited: Management and Treatment Recommendations for Adult Patients, Mol Genet Metab, 123(4):416–427.

[7] Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick RJ, 2006, High Incidence of Later-Onset Fabry Disease Revealed by Newborn Screening, Am J Hum Genet, 79(1):31–40.

patients, disease severity and age of symptom onset depend, at least partly, on tissue-specific X chromosome inactivation. The spectrum of organ involvement and disease severity in female patients with FD can range from completely asymptomatic to the severe phenotype seen in male patients with classic FD. Overall, the rate of disease progression is highly variable in male patients with late-onset FD and in female patients.

III. KEY CONSIDERATIONS FOR CLINICAL TRIALS

A. Eligibility Criteria

All eligible patients should have a confirmed diagnosis of FD based on both biochemical testing and molecular genetic testing (as outlined below). Of note, both plasma and leukocyte α-Gal A activity should be assayed given that some pathogenic *GLA* variants affect intracellular trafficking and secretion of α-Gal A such that the reduction in α-Gal A enzyme activity in plasma may be more pronounced than within leukocytes. Clinical trials should allow enrollment of both male and female patients. As early as feasible, sponsors should consider enrolling pediatric patients with FD in clinical trials.

Criteria for confirming the diagnosis of FD should include, at a minimum, the following:[8]

- In symptomatic male patients:
  - Absent or minimal α-Gal A enzyme activity (i.e., less than 1 percent of the mean normal) in both plasma and isolated peripheral leukocytes.
  - When α-Gal A enzyme activity is low but not absent (i.e., greater than 1 percent of the mean normal), identification of a clinically significant[9] *GLA* variant (mutation).

[8] Mehta A and Hughes DA, 2017, Fabry Disease. In: Adam MP, Ardinger HH, Pagon RA, et al., editors, GeneReviews, Seattle (WA): University of Washington, Seattle, accessed July 30, 2018, https://www.ncbi.nlm.nih.gov/books/NBK1292/; and Arends M, Wanner C, Hughes D, et al., 2017, Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study, J Am Soc Nephrol, 28(5):1631–1641.

[9] Richards S, Aziz N, Bale S, et al., 2015, Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet Med, 17(5):405–424. Laboratory reports of genetic testing results may include the terms *likely pathogenic* or *pathogenic* to characterize whether a given *GLA* variant (mutation) causes FD. For the purposes of this guidance, the term *clinically significant* includes variants considered either pathogenic or likely pathogenic.

- In symptomatic female patients:

  – Identification of a clinically significant[10] *GLA* variant. This is needed as α-Gal A enzyme activity may range from normal to absent because of the presence of both normal and abnormal copies of the *GLA* gene in tissues.

In cases where the *GLA* variant is considered a "variant of uncertain significance,"[11] additional biochemical and/or histopathological evidence should be used to establish the diagnosis of FD (e.g., elevated plasma lyso-GL-3, demonstration of tissue GL-3 inclusions or other).

B. Trial Design and Efficacy Endpoints

1. Trial Design

Given the rarity of FD, sponsors can use a single adequate and well-controlled trial (as described in 21 CFR 314.126), showing a clinically meaningful treatment effect on core clinical aspects of FD, as the basis for drug approval when accompanied by confirmatory evidence. A parallel-group design should be used with an appropriate concurrent control group (placebo or active treatment). Sponsors should consider stratifying at randomization by known prognostic factors, such as sex and age. If the drug is intended to slow or arrest disease progression but not reverse it, the trial should be of sufficient duration to observe disease progression in the control group. There are special considerations regarding the length of long-term follow up for gene therapy products.[12]

Importantly, all laboratory tests conducted in a clinical development program should be performed using appropriately validated methods to ensure reliability of the results and should be conducted at a central laboratory.

[10] Richards S, Aziz N, Bale S, et al., 2015, Standards and Guidelines for the Interpretation of Sequence Variants: a Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet Med, 17(5):405–424. See footnote 9.

[11] Richards S, Aziz N, Bale S, et al., 2015, Standards and Guidelines for the Interpretation of Sequence Variants: a Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet Med, 17(5):405–424.

[12] 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. 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.

2. General Considerations for Efficacy Endpoints

Demonstration of clinical benefit on any core disease manifestation (e.g., renal disease, cardiovascular disease, cerebrovascular disease, gastrointestinal symptoms, neuropathic symptoms, pain) can be the basis for traditional approval.[13] When selecting efficacy endpoints, the sponsor should consider the natural history and time course of the selected disease manifestation(s) assessed, the drug's mechanism of action and the target organ(s), and the target FD patient population or subpopulation. For instance, certain clinical outcome assessments may not be appropriate for use in pediatric FD patients based on their age or symptom presence or absence or severity. Similarly, classic FD and late-onset FD patients often have differences both in the presence of disease manifestations (some late-onset FD patients may only have renal disease or only cardiac disease) and in the rate of disease progression. Given the multisystemic nature of FD, the highly variable rate of disease progression (especially in late-onset FD patients and in female patients), and the heterogeneity of clinical manifestations, sponsors could consider combining multiple clinical outcomes for assessment in clinical trials. Specifically, sponsors could consider the use of a composite endpoint such that changes in symptoms and/or functional outcomes could be captured across a variety of FD manifestations. The choice of such endpoints could be based on baseline symptom presence and severity in enrolled patients. FDA strongly encourages sponsors to engage in early discussions (as early as the pre-investigational new drug application phase) with the appropriate review division regarding the selection of efficacy endpoints and when considering combining efficacy outcomes for demonstration of efficacy.

3. Specific Considerations for Efficacy Endpoints

a. Neuropathic and gastrointestinal symptoms

Sponsors can establish drug effectiveness with the demonstration of clinically meaningful improvement in neuropathic symptoms, including pain, or gastrointestinal symptoms (abdominal pain, diarrhea, constipation). Sponsors should select well-defined and reliable instruments for assessments of changes in such symptoms in accordance with the recommendations of the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009). FDA strongly encourages sponsors to engage early with the appropriate review division for selection of the most appropriate clinical outcome assessment instruments. FDA encourages the development of publicly available, fit-for-purpose, patient-reported outcome instruments that can be used across multiple drug development programs in FD to facilitate and accelerate drug development in this disease.[14]

[13] The term *traditional approval* denotes the longstanding route of drug approval based on the demonstration of clinical benefit or an effect on a surrogate endpoint known to predict clinical benefit. That term is distinguished from accelerated approval, which is associated with use of a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit to support drug approval.

[14] See the draft guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (January 2014). 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.

b. Renal disease

Sponsors could use the demonstration of a sustained treatment effect on a specified magnitude of loss of renal function (e.g., a 30 percent decline in glomerular filtration rate (GFR), assessed via a widely accepted estimating equation for GFR or measured GFR) or on the rate of loss of renal function as the basis for traditional drug approval. In general, sponsors of trials using rate of loss of renal function as an endpoint (e.g., a comparison of the annualized change in estimated GFR (eGFR) between the treatment arms) should assess whether the treatment effect continues to accrue across the various stages of renal disease by enrolling patients with different levels of renal function at baseline. In addition, the trial duration should be sufficient (generally at least 24 months) to evaluate for long-term effectiveness and to obtain a more reliable estimate of the treatment effect on the rate of change in eGFR.

In general, programs should collect information on progression to end-stage renal disease requiring chronic dialysis or renal transplantation while acknowledging that such events are likely to be uncommon in clinical trials of early-stage renal disease in FD given the slowly progressive nature of FD.

Sponsors can use histological reduction of GL-3 inclusion burden in biopsied kidney interstitial capillaries (KIC) as a surrogate endpoint reasonably likely to predict clinical benefit to support accelerated approval. If a sponsor plans to use a surrogate endpoint based on histological assessment of GL-3 inclusions, FDA encourages the sponsor to engage in early discussion with the appropriate review division to more precisely define such an endpoint (including the magnitude of change in that endpoint) that would be reasonably likely to predict clinical benefit. When assessing (counting) KIC GL-3 inclusions in histology specimens, the sponsor should use validated and standardized assay methodologies, and scoring of KIC GL-3 inclusions should be conducted by experienced pathologists in a blinded and systematic fashion. In general, postmarketing studies to verify and describe the clinical benefit should already be underway at the time of submission of a marketing application. FDA encourages sponsors to engage in early discussion with the appropriate review division regarding trial design features of such postmarketing studies.

Patients' concomitant therapies that could affect renal function or the measurement of renal function (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers) should be optimized before trial enrollment, and doses of such therapies should remain stable for the duration of the trial.

Although proteinuria is an important prognostic marker in patients with renal diseases in general, including FD, it is not clear whether treatment effects on proteinuria predict treatment effects on important renal outcomes in FD. At this time, additional evidence is needed to support the use of proteinuria as a validated or reasonably likely surrogate endpoint for clinical benefit in FD.

c. Cardiac disease

Endpoints that assess treatment effects on cardiovascular hospitalization, functional capacity (e.g., exercise capacity), and/or cardiovascular symptoms can be used to provide evidence of

effectiveness in treating the cardiac manifestations of FD. At this time, additional evidence is needed to support the use of left ventricular mass index and global longitudinal strain as validated or reasonably likely surrogate endpoints for clinical benefit in FD.