Pediatric Rare Diseases — A Collaborative Approach for Drug Development Using Gaucher Disease as a Model

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Hong Vu at 301-796-7401.

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

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Rare Diseases

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Pediatric Rare Diseases — A Collaborative Approach for Drug Development Using Gaucher Disease as a Model Guidance for Industry[1]

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I. INTRODUCTION

The emergence of concomitant trials for multiple investigational drug products for the treatment of rare diseases can pose significant challenges to effective drug development due to the limited number of patients worldwide with any given rare condition. The purpose of this guidance is to facilitate drug development in pediatric rare diseases. In particular, it discusses a new possible approach to enhance the efficiency of drug development in pediatric rare diseases using Gaucher disease as an example. This new approach consists of a controlled, multi-arm, multi-company clinical trial, which aims to facilitate the development of multiple drug products in a time-efficient manner while minimizing the number of patients necessary to be treated with placebo. The general principles presented should be viewed as a proposal only, and the principles underlying the proposal may be extended to other areas of drug development in rare diseases. Of note, the specific recommendations regarding drug development for Gaucher Disease apply only to systemic (i.e., non-neurological) manifestations of Gaucher disease in treatment-naïve patients with Type I and Type III phenotypes, across all the pediatric ages (i.e., up to 18 years of age).

Modified approaches may be proposed, but the sponsor should justify the specific choice of each new strategy. Given that rare disease drug development tends to require global involvement, and the potential differences in requirement between the FDA and other regulatory agencies, sponsors are advised to consult the appropriate regulatory agency(ies) prior to initiation of such trials.

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products in the Center for Drug Evaluation and Research at the Food and Drug Administration. This guidance adapts with minor modifications the 2017 update of the 2014 Food and Drug Administration – European Medicines Agency Collaborative Approach document titled "Gaucher Disease — A Strategic Collaborative Approach From EMA and FDA."

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

A. Disease Characteristics and Response to Treatment

Gaucher disease is one of the most common lysosomal storage disorders, estimated to affect 6,000 individuals in the United States.[2] It meets the U.S. regulatory definition of an orphan disease (i.e., fewer than 200,000 affected individuals).

Historically, Gaucher disease has been classified into three phenotypes. Although nowadays many view Gaucher disease as a spectrum of manifestations, and alternative classifications have been proposed on the basis of absence or presence of neurological symptoms (the latter further subdivided into acute or chronic forms), the following phenotypes continue to be commonly referenced:

- Type I refers to the somatic, non-neurological form (the most prevalent)
- Type II refers to the acute, infantile neuronopathic form, usually lethal in infancy
- Type III refers to the chronic, neuronopathic form (it may have somatic manifestations as well)

In Gaucher disease, the age at onset of symptoms tends to correlate with clinical severity and subsequent outcomes. A lower residual level of enzyme activity generally results in earlier onset and greater severity of disease manifestations.

The underlying biology of Gaucher disease is the same in adults and children. However, clinical manifestations in children differ from those seen in adults, both in presentation and disease course. Disease-modifying factors such as type of genetic mutation, residual enzyme activity, and epigenetic factors may further influence disease presentation and rates of clinical progression.

The current standard of care in the pediatric Gaucher population in the United States consists of enzyme replacement therapy (ERT), which is used to treat the non-neurological (i.e., somatic) manifestations of the disease in patients with Type I and Type III phenotype. Despite the availability of ERT, other therapies with different mechanisms of action may still offer complementary or additive clinical benefit.

Given that ERT is the current standard of care, placebo-controlled trials of new generation ERTs in pediatric patients with Type I Gaucher disease are not considered ethical because of

[2] https://rarediseases.org/rare-diseases/gaucher-disease/

demonstrated clinical improvements with the currently available ERT. However, new non-ERT investigational drug products may be studied using a placebo add-on design while continuing current ERT management.

B. Unmet Needs in Pediatric Gaucher Disease

Studies conducted thus far have not adequately addressed all the major medical needs across all pediatric age groups. For example, few patients younger than 2 years of age have been enrolled in clinical trials. Additionally, the disease's impact on growth rate, bone, and pulmonary manifestations has not been fully studied with available ERT therapy. Another unmet medical need is that of drug products with more practical routes of administration. Developing age-appropriate oral pharmaceutical drug products (e.g., substrate reduction therapies) could be beneficial across all pediatric ages and may add benefit to the existing ERTs. Finally, although not addressed by this guidance, there is an unmet clinical therapeutic need for pediatric patients with neurological involvement (Types II and III), because current ERT therapy does not impact neurologic manifestations of Gaucher disease.

III. NONCLINICAL AND CLINICAL CONSIDERATIONS

A. Nonclinical Models of Gaucher Disease

Animal models of Gaucher disease are available to test preliminarily the effect of new drug products prior to initiating human studies (Farfel-Becker et al. 2011). However, the Gaucher disease phenotypes in many disease models have little or no similarity to the human Gaucher phenotypes. The selection of an animal Gaucher disease model to support pediatric drug development should be based on the relationship with efficacy endpoints to be evaluated in pediatric studies, or the need to measure or develop pharmacodynamic (PD) markers of drug product activity. Because toxicity may result from the sudden release and accumulation of metabolites resulting from the enzymatic degradation of the accumulated substrate, it may be appropriate to include toxicity endpoints in the pharmacology studies conducted in animal models of the disease.

For ERTs, the need for juvenile animal toxicology studies should be decided on a case-by-case basis, depending on the age of the patient population to be treated. Toxicology studies in juvenile animals of appropriate age should be conducted when considered necessary.

Small molecules also should be assessed on a case-by-case basis to determine the need for juvenile animal toxicity studies. Factors to consider are described in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.[3] It should be noted that the assessment for small molecules may be more complex than for ERTs, because the on- and off-target effects

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

of small molecules are less predictable, and the development programs (clinical and nonclinical) for small molecules differ from ERT development programs.

B. Endpoint Assessments in Gaucher Disease

Previous approval of ERT for Gaucher disease in adult patients has been based upon demonstrated clinical improvements in hepatosplenomegaly and improvements in biochemical endpoints (hemoglobin and platelet levels).

For drug development programs in pediatric rare diseases, it may be necessary to develop, validate, and employ age-specific endpoints. The relevant endpoints and outcome measures for the pediatric population should be identified as early as possible. It is important to include protocol design features that allow pediatric patients to contribute directly in these measures when possible (e.g., patient-reported outcome measures). Where relevant, it may also be reasonable to assess, in the adult drug development program, endpoints that can be potentially used in pediatric clinical trials.

Because the quality of available clinical outcome assessments (COAs) can vary, qualification and standardization is strongly recommended. Developers are encouraged to discuss the selected COA for the outcomes of interest with the FDA; involvement of relevant stakeholders, including patients is encouraged.

If for any reason studies cannot be blinded, biases should be addressed. The issue of assay sensitivity should be considered if the trial uses a noninferiority margin.

With specific relevance to Gaucher disease, the following should also be considered when planning studies:

- Disease-modifying factors (e.g., mutation, residual enzyme activity, age) and epigenetic factors contribute to different disease presentations. Enrolling pediatric patients who are as homogenous as possible will increase the probability of detecting a treatment effect. The need for a study to be conducted in a homogeneous population should not delay the timely access to a drug product for age subgroups that are inherently harder to study because of intrinsic heterogeneity.

- Exploratory biomarkers, such as markers of lung and bone disease, and measurement of bone mineral density or bone marrow disease burden should be assessed.

- Neurological assessments should be included in studies as exploratory endpoints to inform further studies for neuronopathic manifestations of Type III Gaucher disease. Inclusion of a pharmacogenomics perspective in the drug development program, to evaluate and explore the different modifiers of the genotype-phenotype relationship, is also recommended.

C. Long-Term Clinical Aspects

Long-term follow-up in a prospective study is necessary to evaluate the long-term safety and efficacy of treatment on disease manifestations in pediatric patients.

Throughout many parts of the world, children with Gaucher disease are often managed at specialized centers where enrollment into clinical trials can be facilitated. Follow-up of patients from such centers should be encouraged to evaluate long-term safety and long-term maintenance dosing.

Hematological and/or visceral endpoints have been standardized, and are most commonly evaluated in the pediatric trials.

Improved documentation of other significant measurements (e.g., growth and developmental changes, bone disease, pulmonary function, and neurological manifestations) should be implemented to facilitate understanding of the long-term effects of treatment.

Patient registries are an adjunctive tool for monitoring efficacy and safety. When registries are set up individually per drug product, the burden on all stakeholders is increased and comparative analyses between patient groups or across drug products cannot be easily conducted. The FDA recommends across-registry agreement on a uniform set of core data elements to be collected by all existing or future Gaucher disease registries. This may include information on key pediatric manifestations such as growth rate and bone disease, relationship between treatment and outcomes, collection of adverse events, etc. All children born to treated mothers should also be evaluated long term.

D. The Use of Extrapolation of Efficacy for Pediatric Gaucher Disease

Extrapolation of efficacy can be considered when the course of the disease and the expected response to a drug product would be sufficiently similar in the pediatric and reference population (i.e., adult or other pediatric age population). In the case of pediatric Gaucher disease, the impact of the different mechanisms of action and disease-modifying factors (e.g., type of mutation, residual enzyme activity, age) and epigenetic factors resulting in different presentations of the disease should be carefully considered. When characteristics of different patient populations are able to be identified, extrapolation can be considered. The use of extrapolation of efficacy in pediatric Gaucher disease can avoid unnecessary studies, increase efficiency, reduce testing burden to patients, and better allocate resources to address relevant questions. An extrapolation plan could be formulated early during drug development, with the recognition that the plan may not address all aspects necessary in the development of emerging drug products across all ages of pediatric patients. Ultimately, additional clinical studies may be necessary for determination of efficacy across all age groups.

Pediatric extrapolation of efficacy from adults to children can be considered for the somatic manifestations of both Type I and Type III Gaucher disease, such as visceral, hematologic, and pulmonary disease. In contrast, effects of therapy on specific pediatric manifestations (e.g.,

growth rate, onset of puberty and progression of pubertal development) are not amenable to extrapolation.

These characteristics should be specifically addressed in pediatric studies. In such studies safety data should be collected to identify unexpected (age-specific) safety concerns.

Existing knowledge generated from adult Gaucher disease programs (such as nonclinical data, data about related compounds, effect of treatment on specific disease subgroups) can inform specific aspects of the pediatric program. Data from the adult Gaucher disease programs may support conclusions of efficacy and safety. Such data could be used in exploring differences in pharmacokinetic (PK), PK/PD, treatment-induced changes in different disease manifestations, and clinical response to treatment in the pediatric population. A mechanism-based approach (e.g., physiologically based PK modeling, mechanistic disease PK/PD) should play a key role for dose characterization. Whenever new studies in children are deemed necessary, modeling and simulation should be used to optimize pediatric studies (e.g., design, sample size, starting doses, timing of sampling, and number of samples) and particularly to inform the dosing rationale.

Safety and risk considerations based on the existing knowledge should guide the decision of whether specific mitigation, such as staggered enrollment based on age group, is necessary. However, any uncertainties related to the use of existing knowledge should be identified early in the pediatric drug development and managed prospectively (e.g., potential issues such as differences in drug product quality/manufacturing, immunogenicity, pharmacokinetics).

IV. PROPOSED MULTI-ARM, MULTI-COMPANY TRIAL FOR PEDIATRIC GAUCHER DISEASE

The proposal in this guidance covers the principal features necessary to demonstrate efficacy and safety in treatment-naïve pediatric patients with Gaucher disease Type I. It also applies to the systemic non-neurological manifestations in Type III Gaucher disease. The proposal provides a strategy for designing a multi-arm, multi-company drug development program. It includes a description of the main inclusion criteria, relevant age groups, suggested efficacy endpoints, and study duration. Although such a program can be very challenging, the aim of the strategic plan is not only to facilitate agreement on individual applications, but also to address the feasibility of developing multiple drug products for a rare disease in a time-efficient manner.

While recognizing the inherent limitations and challenges in conducting simultaneous drug development programs in pediatric Gaucher disease, this guidance proposes a multi-arm, multi-company, as presented in Table 1. If this approach is to be undertaken, each individual new drug product should demonstrate both safety and efficacy.

This approach may allow for a reduction in the total number of children to be enrolled, as compared to conducting separate controlled trials, because a single control arm can be used to assess the effects of more than one drug product. The proposal applies only to systemic (i.e., non-neurological) manifestations of Gaucher disease in treatment-naïve patients with Type I and

Type III phenotypes, across all the pediatric ages. It is not intended for the neurological manifestations of Gaucher disease for which there are no approved drug products at this time.

Table 1. Proposed Double-Blind, Controlled, Randomized, Multi-Center, Multi-Arm, Multi-Company Noninferiority or Superiority ERT Trial for Non-Neurological Manifestations of Gaucher Disease

Study Identifier(s)	Strategic Collaborative Pediatric Approach for Gaucher Disease
Study design features	• Double-blind, controlled, randomized, multi-center, multi-arm, multi-company noninferiority or superiority trial to evaluate the efficacy and safety of "product A," "product B," "product C," etc., compared to a single ERT drug product in pediatric patients with Gaucher disease Type I and Type III. • Equal allocation to each arm: e.g., 1:1:1:1; an unequal 2:1 allocation (new drug product:ERT drug product) may be considered. • Randomization should ensure that at any point in time, patients can be randomized to control as well as a new active drug product • Centralized randomization stratified for type and age group • Centralized assessment (laboratory and radiographic) may be considered.
Main objective(s)	To evaluate noninferiority or superiority of new drug product(s) to an approved ERT treatment.
Study population and subset definition	Male and female pediatric patients, from birth to younger than 18 years with Type I and Type III phenotypes with non-neurological manifestations of Gaucher disease.[a]
Number of study patients by pediatric subset (e.g., age, sex, severity or stage)	• The calculated sample size should be sufficient to detect noninferiority in the proposed primary endpoint with at least 80% power and a type I error rate of 0.025 for each investigational drug product in the trial. Superiority trials are also acceptable. The noninferiority margin should be carefully chosen and prespecified. This is particularly crucial because the assay sensitivity of the trial cannot be assessed in the usual way due to lack of a placebo control group. Consulting regulatory bodies for scientific advice about this issue before study start is therefore highly recommended. • The sample size is determined by the predefined noninferiority margin and the assumed variability of the primary endpoint. The most precise information available at the time of study planning should be thoroughly considered and be supported by data and/or literature references.
Main inclusion criteria	• Clinical diagnosis of Gaucher disease, with documented deficiency of acid beta-glucosidase activity by enzyme assay. • Gaucher Type I and Type III with non-neurological manifestations. • Genotyping for Gaucher disease. • Treatment-naïve patients. • Birth to younger than 18 years of age.[a]

continued

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Study Identifier(s)	Strategic Collaborative Pediatric Approach for Gaucher Disease
Main exclusion criteria	• Clinical symptoms predominantly indicative of neurological disease (i.e., Type II disease; Type III patients with neurological manifestations can be enrolled as long as the efficacy measures somatic disease).
Study duration for patients	• Two years of treatment for the analysis of the primary endpoint. • Long-term monitoring of primary and secondary endpoints and safety in an extension study. This extension should cover at least 3 years; however, at least 5 years is recommended.
Dosage, treatment regimen, route of administration	• ERT drug products: doses should be defined. • Substrate reduction therapy drug products: doses should be defined.[b] • Other therapies: doses should be defined.
Control(s)	• Active control group — ERT administered at the approved dose. The dose should be adjusted by weight at least every 6 months, in line with growth, as reflective of current standard of care. • An add-on placebo-controlled design can be considered when evaluating study drugs with different mechanisms of action.
Endpoint(s) with time(s) of assessment	The relevant endpoints should be chosen based on the mechanisms of action of the selected drug products. Such selection should also take into consideration the heterogeneity of the pediatric Gaucher population. Consider the following suggestions: • Change in hemoglobin relative to baseline, stratified by background hematinic usage. • Growth rate as measured by Z-score; bone age, height change, weight and body mass index at baseline and subsequent time points (e.g., every 6 months and yearly thereafter). • Age at pubertal onset (Tanner Stage II) and Tanner staging at baseline and at least every 6 months between Tanner Stage I and Stage IV for the duration of the trial. • Platelet count at baseline and at least every 6 months. • Liver and spleen size as multiples of normal (measured with magnetic resonance imaging) at baseline and subsequent time points. • Bone manifestations; including pain intensity and duration and fractures, at least every 6 months. • Pulmonary function, measured at baseline and appropriate time intervals (e.g., every 6 months). • Safety and tolerability, including infusion-related reactions. • Antibody levels (including neutralizing antibodies) for each ERT drug product — the specific schedule should be discussed with the regulatory agencies. Assays should be validated at the time of trial initiation.

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Table 1, continued

Study Identifier(s)	Strategic Collaborative Pediatric Approach for Gaucher Disease
Statistical plan including study conduct and analysis	• Primary analysis of the primary endpoint: noninferiority comparison of each individual investigational drug product to control, respectively, by means of a 95% confidence interval method, in both the per-protocol and intent-to-treat population.[c] • After data freeze, the main analysis of the multi-company study should be performed by therapy-blinded, independent statisticians. It is recommended that the long-term monitoring results be analyzed in the same way. • All statistical analyses should be prespecified in detail in a statistical analysis plan. • The potential impact of missing values should be addressed with sensitivity analyses. Various approaches should be performed and their results should be compared and critically discussed, in particular with respect to the noninferiority design of the trial.[d]
Measures to minimize pain and distress	Topical anaesthesia should be offered for all venous access procedures with documentation of usage.
External independent data safety monitoring board	• External independent data safety monitoring boards should be used during trials. • Early stopping of a treatment arm for clinical decline should be considered

[a] Although pediatric age is defined per FDA regulation from birth to 16 years (21 CFR 201.57(c)(9)(iv)(A)), studying patients up to 18 years of age is appropriate because other definitions of pediatric age used in clinical practice apply to children up to 18 years.
[b] For a substrate reduction therapy or "other therapies" trial, a placebo, add-on design may be more appropriate. The FDA should be consulted.
[c] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.
[d] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* for detailed recommendations.

GENERAL REFERENCES AND GUIDELINES

Literature

Dunne, J, WJ Rodriguez, MD Murphy, et al., 2011, Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs, Pediatrics, 128:e1242–e1249.

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Guidances for Industry

Draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*[4]

Guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

Guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*

ICH guidance for industry *E9 Statistical Principles for Clinical Trials*

EMA Documents[5]

Concept Paper on Extrapolation of Efficacy and Safety in Medicine Development

Guideline on the Choice of the Non-Inferiority Margin

Guideline on Clinical Trials in Small Populations

[4] When final, this guidance will represent the FDA's current thinking on this topic.

[5] EMA documents can be found on the Search the Document Library web page at http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/document_library_search.jsp.

Guideline on Missing Data in Confirmatory Clinical Trials

Patient Registries Workshop, 28 October 2016

Preliminary Meeting Report: Workshop on Methodological Aspects of Clinical Trials for Efficacy Evaluation in Small Populations

Press Release: Orphan Drug and Paediatric Clinical Trials — EMEA Workshop on Methodological Aspects of Clinical Trials for Efficacy Evaluation in Small Populations

Points to Consider on Switching Between Superiority and Non-Inferiority