



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 July 2017
EMA/237265/2017

Paediatric Gaucher disease

A strategic collaborative approach from EMA and FDA

Draft presented at EMA Workshop with European Working Group on Gaucher disease (EWGGD) and European Gaucher Alliance (EGA)	October 2011
Comments from FDA, Health Canada and Japan	April 2012
Comments from Paediatric Review Committee (FDA)	July 2012
Joint workshop with FDA to consult industry, experts and patient organisations	17-18 September 2012
Comments from Scientific Advice Working Party (EMA)	September 2012
Comments from FDA	July 2013
Adopted by Scientific Advice and Committee for Human Medicinal Products (EMA) for release for consultation	March 2014
Adopted by FDA and Paediatric Committee (EMA) for release for consultation	May 2014
Start of public consultation	14 May 2014
End of consultation (deadline for comments)	31 August 2014
Adopted by Committee for Human Medicinal Products (EMA)	22 June 2017



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Executive summary

This Strategic Collaborative Approach document is not a formal guidance; the purpose of this document is to facilitate paediatric drug development particularly in the field of Gaucher disease. The general principles presented should be viewed as suggestions only. This proposal is not meant to be exhaustive; it is intended instead to further stimulate exploration of new approaches for various situations in the drug development of new Gaucher disease therapies. The specifics should be determined following discussions with the individual regulatory agencies as deemed appropriate and feasible by both drug manufacturers and regulatory agency(ies).

The emergence of multiple candidate drug products for the treatment of Gaucher disease can pose significant challenges to effective drug development, given the limited number of patients worldwide with this condition. This document discusses two possible approaches to facilitate investigations of products intended for the treatment in Gaucher disease:

1. extrapolation across age groups within a single drug development program
2. a multi-arm, multi-company clinical trial, which addresses the feasibility of developing multiple drug products in a time-efficient manner.

This proposal applies only to systemic (i.e., non-neurological) manifestations of Gaucher disease in treatment-naïve patients with Type I and III phenotypes, across all the paediatric ages.

In this document, Gaucher disease is being used as a disease model. However, the principles underlying this proposal may be extended to other areas of drug development in rare diseases. In addition, different approaches may be proposed and the applicant should justify the specific choice of each new strategy. Due to differences in the regulatory requirements of both Europe and the United States, particularly regarding extrapolation of efficacy from adults to children, additional trials may be required to support an application for approval.

1. Background information

1.1. Disease characteristics

- As one of the most common lysosomal storage disorders, Gaucher disease is estimated to affect less than 0.6 in 10,000 people in the European Union (EU). This is equivalent to a total of fewer than 23,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. In the US, an estimated 20,000 people are affected by Gaucher type I disease, which meets the US regulatory definition of orphan disease (fewer than 200,000 people in the US).
- Historically, Gaucher disease has been classified into three types. Although many now prefer to view it as a disease spectrum, with a medical classification based on the absence or presence of neurological symptoms (later further sub-divided into acute or chronic), the following types continue to be commonly referred to:
 - Type I, refers to the 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. Type II and Type III account for 8% and 22% of the cases, respectively.

- 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 more severe 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. These differences can affect the disease's impact on growth rate and bone disease presentation and severity.

1.2. Current paediatric practice

- The current standard treatment is enzyme replacement therapy (ERT). A product for substrate-reduction therapy (SRT) is currently approved for paediatric patients in the EU and Canada (but not in the US).
- ERT is currently the standard of care for treatment of non-neurological manifestations in patients with Type I and Type III disease. However, other therapies with different mechanisms of action may still offer potential for clinical benefit.
- Given that ERT is currently the standard of care, placebo-controlled trials of new medicinal products as monotherapy in paediatric patients with Type I and Type III (non-neurological manifestations only) Gaucher disease are not considered ethical. Therefore either an active controlled or a placebo-add-on to current ERT study should be used to evaluate benefits and risks of new (non-ERT) investigational products.

1.3. Unmet needs

- Studies conducted thus far have not adequately addressed the major medical needs in Gaucher disease. For example, few patients below 2 years of age have been enrolled in clinical trials, or improvement of the psychological and social well-being of children have not been sufficiently considered.
- There is an unmet clinical therapeutic need for paediatric patients with neurological involvement (Types II and III), as current ERT therapy only impacts visceral disease pathology and not neurologic manifestations. Additionally, the disease's impact on growth rate, bone and pulmonary manifestations has not been fully studied with available ERT therapy.
- Another unmet clinical need is that of drug products with more practical routes of administration. Developing age-appropriate oral pharmaceutical products (e.g., substrate reduction therapies) could be beneficial across all paediatric ages and may add benefit to the existing ERTs. Some paediatric patients, in particular, find the frequency of ERT administration to be burdensome.

2. General considerations for study population, practicalities in the design and execution of paediatric trials

2.1. Patient selection

As the paediatric Gaucher population is heterogeneous, it is important to consider disease modifying factors (mutation, residual enzyme activity, age etc.) and epigenetic factors contribute to different disease presentations. Enrolled paediatric patient populations should be as homogenous as possible to

enhance the probability of detecting a treatment effect if there is one. The need for a study to be conducted in a homogeneous population should be balanced against the need for timely access to a medicinal product even for the youngest age groups of the paediatric population.

Additionally patients with milder presentations may be diagnosed late (e.g., adolescents). Adolescent patients may still require paediatric expertise for assessments of growth and puberty and should have access to an institution where appropriate means to measure growth and development are readily available.

Due to a small number of eligible children and limited paediatric specific resources at research centres, consideration should be given to available centres throughout many parts of the world because children with Gaucher disease are often managed at specialised centres where enrolment into clinical trials can be facilitated.

Resources at these centres should be encouraged, specifically to conduct clinical trials to evaluate long-term safety and long-term maintenance dosing.

2.2. Non-clinical models

- Animal models of Gaucher disease are available to test efficacy of new drug products, as described by Farfel-Becker *et al* (2011). However, the Gaucher disease phenotypes in many of the disease models have little or no similarity to any of the human Gaucher phenotypes. Therefore, the selection of an animal Gaucher disease model to support paediatric drug development should be based on the relationship with efficacy endpoints to be evaluated in paediatric studies, or the need to measure or develop pharmacodynamic markers of drug activity. As 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.
- Small molecules also require a case-by-case assessment for determining the need for juvenile animal toxicity studies. Factors to consider are described in the EMA *Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications* (EMA/CHMP/SWP/169215/2005) and the ICH guidance *M3(R2)*. It should be noted that the assessment for small molecules may be more complex than for ERTs, because the on- and off-target effects of small molecules are less predictable and the development programs (clinical and nonclinical) for small molecules differ from ERT development programs.

2.3. Endpoint assessments

- As stated in the ICH E11 (2000) Section 2.4.2, it may be necessary to develop, validate, and employ age specific endpoints. The relevant endpoints and outcome measures for the paediatric population should be identified as early as possible. It is important to include protocol design features that allow paediatric participants to contribute directly to these measures when possible (e.g., patient reported outcome measures). Where relevant, it may also be reasonable in the adult development program to assess endpoints that potentially can be used in paediatric clinical trials.
- As the quality of available Outcome Measurement Instruments (OMI)/Clinical Outcome Assessments (COA) can vary, standardisation is strongly recommended. Developers are encouraged to discuss the selected OMI/COA for the outcomes of interest with the regulatory agencies; involvement of relevant stakeholders, including patients, is encouraged.
- If for any reason studies cannot be blinded, biases will need to be addressed. The issue of assay sensitivity will need to be considered if the trial uses a non-inferiority margin.

- With specific relevance for the Gaucher disease, the following should be considered when planning studies:
 - Haematological and/or visceral endpoints have been standardised, and are most commonly evaluated in the paediatric trials.
 - The relevant pharmacodynamic endpoints should be chosen based on the mechanism of action of the selected products. Such selection should also take into consideration the heterogeneity of the paediatric Gaucher population.
 - For the clinical evaluation the following endpoints should be considered: change in haemoglobin; growth rate; platelet count; liver- and spleen size.
 - Exploratory biomarkers, such as markers of lung and bone disease, and measurement of bone mineral density or bone marrow burden should be assessed.
 - Neurological assessments should be included in studies as exploratory endpoints to inform further studies for neuropathic manifestations of Type III Gaucher disease.
 - The inclusion of a pharmacogenomics perspective in the development program, to evaluate and explore the different modifiers of the genotype-phenotype relationship.

2.4. Long term clinical aspects, including safety

- Long-term follow-up in a prospective study is necessary to evaluate the long-term safety and efficacy of treatment on disease manifestations in paediatric patients.
- Other long-term clinical manifestations such as growth and developmental changes, bone disease, pulmonary function, and neurological manifestations, are not uniformly measured and documented but improved documentation would allow for analyses 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 product, the burden on all stakeholders is increased and comparative analyses between patient groups or across products cannot be easily conducted. The EMA and FDA strongly recommend across-registry agreement on a uniform set of core data elements to be collected by all existing or future Gaucher disease registries. These might include, for example, information on key paediatric manifestations such as growth rate, bone disease, treatments and their outcomes and adverse events as well as data related to disease modifying and epigenetic factors. Other information could be collected depending on registry holder capacity or to meet additional needs relating to evaluation of a particular treatment.
- The effect of treatment during pregnancy is not fully understood. Therefore, pregnant women receiving therapy for Gaucher disease should be monitored as high risk pregnancies. All children born to treated mothers should also be evaluated long term.

3. A strategic collaborative paediatric approach

This proposal covers the principal features necessary to demonstrate efficacy and safety in treatment-naïve paediatric patients with Gaucher disease Type I. It also applies to the systemic non-neurological manifestations in Type III Gaucher disease. This proposal provides examples of approaches to optimise paediatric drug development such as the use of extrapolation of data from adults to children and extrapolation of data between paediatric age groups, and a strategy for designing a multi-arm, multi-company development programme. These approaches may provide opportunities to address challenges in conducting paediatric studies when structured and integrated in the development program.

It includes the use of existing knowledge to inform the design of a paediatric study, a description of the main inclusion criteria, relevant age groups, suggested efficacy endpoints and study duration. Although such a programme 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 products for a rare disease in a time-efficient manner.

3.1. The use of extrapolation of efficacy for paediatric Gaucher disease

Extrapolation of efficacy can be considered when the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric and reference population (i.e., adult or other paediatric age population). In the case of paediatric Gaucher disease, the impact of the different mechanisms of action and disease modifying factors (type of mutation, residual enzyme activity, age etc.) and epigenetic factors resulting in different presentations of the disease must be carefully considered. When it is possible to identify specific characteristics of different patient populations, extrapolation can be considered. The EMA and FDA recognise that the use of extrapolation of efficacy in paediatric 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 products across all ages of paediatric patients.

Ultimately, additional clinical studies may be necessary for determination of efficacy across all age groups.

According to the EMA, the development of an extrapolation concept for paediatric Gaucher disease should be built upon all available data (in vitro, preclinical, clinical), and include the use of modelling and simulation approaches. The aim is to develop a clear quantitative hypothesis regarding the similarity of the disease subgroups and the similarity of response to intervention between the initial population studied and the new target populations, as described in the recent [paper on extrapolation of efficacy and safety in medicine development released by the EMA](#).

Extrapolation of efficacy from adults to children may 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 paediatric manifestations (e.g. growth rate, puberty and development) are not amenable to extrapolation.

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

Existing knowledge generated from adult Gaucher disease programmes (such as nonclinical data, data about related compounds, effect of treatment on specific disease subgroups) can inform specific aspects of the paediatric programme. It is considered important to further inform on and learn about the causal genotype-phenotype relationships for disease traits that manifests differently between adults and children; the data collection should be planned from this perspective and opportunities for addition of informative endpoints should be considered. The use of data from the adult Gaucher disease programmes should be maximised since this may reduce paediatric data requirements and it may support conclusions of efficacy and safety. Such knowledge could be used in predicting differences in PK, PK/PD, treatment-induced changes in different disease manifestations, and clinical response to treatment in the paediatric population. Mechanism-based approaches (PBPK modelling, mechanistic disease and PK/PD, etc.) will play a key role for this purpose. Whenever new studies in children are deemed necessary, modelling and simulation should be used to optimise paediatric 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 enrolment based on age group, is necessary. However, any uncertainties related to the use of existing knowledge must be identified early in the paediatric development and managed prospectively (e.g., potential issues such as differences in product quality/manufacturing, immunogenicity, PK).

3.2. Proposed multi-arm, multi-company trial for paediatric Gaucher disease

While recognising inherent limitations and challenges in conducting simultaneous drug development programs in paediatric Gaucher disease, this document proposes a multi-company, multi-arm trial, as presented in Table 1. If this type of approach is to be undertaken, EMA and FDA established regulatory pathways (e.g., parallel scientific advice) should be used to facilitate such a study. This approach may allow for a reduction in the total number of children to be enrolled as compared to separate controlled trials, because a single control arm can be used to assess the effects of more than one drug product. This proposal applies only to systemic (i.e., non-neurological) manifestations of Gaucher disease in treatment-naïve patients with Type I and III phenotypes, across all the paediatric ages.

Disclaimer: The multi-arm, multi-company study suggested in Table 1 is a proposal only, and the specifics should be determined following discussions with the respective regulatory agencies.

Table 1. Proposed multi-arm, multi-company trial for non-neurological manifestations of Gaucher disease

Study identifier(s)	Strategic collaborative paediatric approach for Gaucher disease
Study design features	<ul style="list-style-type: none"> • Double blind, controlled, randomised, multicentre, multi-arm, multi-company non-inferiority trial to evaluate the efficacy and safety of <product A>, <product B>, <product C>, etc. compared to a single ERT product in paediatric* patients with Gaucher disease Type I and/or Type III. • Equal allocation to each arm: e.g., 1:1:1:1; an unequal 2:1 allocation (new product: ERT product) may be considered. • Patients can be randomised at different points in time. • Centralised randomisation stratified for type and age group • Centralised assessment (laboratory and radiographic) may be considered.
Study population and subset definition	Male and female paediatric patients from birth to less than 18 years with Type I and Type III phenotypes with non-neurological manifestations of Gaucher disease. ^a
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	<ul style="list-style-type: none"> • Specific discussions with different regulatory agencies are encouraged before reaching an agreement on the statistical plan.
Main inclusion criteria	<ul style="list-style-type: none"> • Clinical diagnosis of Gaucher disease, with documented deficiency of acid beta-glucosidase activity by enzyme assay. • Gaucher type I and III with non-neurological manifestations. • Genotyping for Gaucher disease.

Study identifier(s)	Strategic collaborative paediatric approach for Gaucher disease
	<ul style="list-style-type: none"> • Treatment-naïve patients. • Birth to less than 18 years of age.^a
Main exclusion criteria	<ul style="list-style-type: none"> • Clinical symptoms predominantly indicative of neurological disease (i.e., Type II disease; for type III, patients with neurological manifestations may be enrolled as long as the efficacy evaluation measures somatic disease).
Study duration for participants	<ul style="list-style-type: none"> • 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 three years; however, at least 5 years is recommended.
Dosage, treatment regimen, route of administration	<ul style="list-style-type: none"> • ERT products: doses to be defined. • SRT products: doses to be defined. • Other therapies: doses to be defined.¹
Control(s)	<ul style="list-style-type: none"> • <Active control group – ERT administered at the approved dose. The dose must 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 may be considered when evaluating study drugs with different mechanisms of action>.
Endpoint(s) with time(s) of assessment	<p>The relevant endpoints should be chosen based on the mechanism of action of the selected products. Such selection should also take into consideration the heterogeneity of the paediatric Gaucher population. Consider the following concepts:</p> <ul style="list-style-type: none"> • Change in haemoglobin at two years relative to baseline, stratified by background hematinic usage; • Growth rate as measured by Z-score, bone age, height change, weight and BMI at baseline, 1, 2, 3 and 5 years; • Age at pubertal onset (Tanner Stage II) and Tanner staging at baseline and at least every 6 months between Tanner stage I and 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 (MN) (measured with ultrasound scan/MRI scan) at baseline, 1, 2, 3, and 5 years; • 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., 1, 2, 3, and 5 years); • Safety and tolerability - including infusion related reactions; • Antibody levels for each ERT product – the specific schedule to be discussed with the regulatory agencies.
Statistical plan (SAP) including study conduct and analysis	<ul style="list-style-type: none"> • For active controlled studies: primary analysis, primary endpoint: non-inferiority comparison of each individual investigational medicinal product to control, respectively, using 95% confidence intervals, in both the Per-Protocol and Intention-To-Treat population (see EMA guidelines for non-inferiority trials).

¹ For an SRT or “other therapies” trial, a placebo, add-on design may be more appropriate. Consult with regulatory agencies first.

Study identifier(s)	Strategic collaborative paediatric approach for Gaucher disease
	<ul style="list-style-type: none"> • After data freeze, the main analysis of the multi-company study has to be performed by therapy-blinded, independent statisticians. It is recommended that the long-term monitoring results be analysed in the same way. • All statistical analyses should be pre-specified in detail in a SAP. • 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 non-inferiority design of the trial (see EMA Guideline on Missing Data in Confirmatory Clinical Trials).
Measures to minimise pain and distress	Topical anaesthesia should be offered for all venous access procedures with documentation of usage.
External Independent Data Safety Monitoring Board	Yes Early stopping of a treatment arm for clinical decline should be considered

^a Paediatric age defined as birth to 16 as per FDA regulation (21 CFR 201.57(F)(9)(i))

4. General guidelines and reference

- [EMA reflection paper on extrapolation of efficacy and safety in medicine development](#)
- [ICH E11\(R1\) guideline on clinical investigation of medicinal products in the pediatric population](#)
- [EMA Guideline on clinical trials in small populations](#)
- [Meeting report: EMA public workshop on extrapolation of efficacy and safety in medicine development across age groups](#)
- [Preliminary meeting report: EMEA workshop on methodological aspects of clinical trials for efficacy evaluation in small populations](#)
- [Orphan drug and paediatric clinical trials - EMEA workshop on methodological aspects of clinical trials for efficacy evaluation in small populations](#)
- [ICH Topic E 9: Statistical Principles for Clinical Trials](#)
- [EMA Guideline on the choice of the non-inferiority margin](#)
- [EMA Points to consider on switching between superiority and non-inferiority](#)
- [EMA Guideline on Missing Data in Confirmatory Clinical Trials](#)
- [FDA guidance on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product](#)
- [FDA guidance on Non-Inferiority Clinical Trials](#)
- [FDA guidance on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims](#)
- [FDA guidance on General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products](#)
- [EMA Patient Registries Workshop, 28 October 2016; Observations and recommendations arising from the workshop](#)

- Farfel-Becker, T. et al. Animal models for Gaucher disease research *Dis. Model. Mech.* 4, 746–752 (2011)
- Gaucher Disease (Hardback) – CRC Press Edited by Futerman A.H and Zimran, A (2007)
- Mistry et al (*PNAS*, 107, 19473-19478, 2010)
- Pastores et.al (*Semin Hematol* 41 (suppl 5):4-14, 2004)
- Dunne, J. et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics* 128, e1242–e1249 (2011).
- Orphanet Report Series, June 2013