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Gaucher disease

A strategic collaborative approach from EMA and FDA

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Executive summary

The emergence of many candidate products for the treatment of Gaucher disease is positive and challenging at the same time.

The purpose of this Collaborative Approach document is to increase - the chances of rapid and smooth agreement of the Paediatric Investigation Plan (EMA) / Pediatric Study Plan (FDA). In addition, this document discusses the possibility of a multi-arm, multi-company clinical trial for the treatment of Gaucher disease, as one approach to address the feasibility of developing multiple products for a rare disease in a limited timeframe.

Specifically, two complementary approaches are discussed:

1. Extrapolation of efficacy and modelling-based approaches;
2. A multi-arm, multi-company development programme, to determine the safety and efficacy of each emerging product.

Based on these discussions and the regulatory framework in place in Europe, this Collaborative Approach document is proposed to inform development of both Pediatric Investigational Plans (PIPs -) and Pediatric Study Plans (PSPs). Due to differences in regulatory requirements in Europe and the United States, notably regarding extrapolation of efficacy from adults to children, additional trials may be required to support an application for approval in the US.

1. Background information

1.1. Disease characteristics and response to treatment

- 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.
- 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. These differences include growth rate and bone disease (presentation and severity).
- Overall, age at onset of symptoms correlates with symptom severity, with a poorer outcome in those who are symptomatic at a very young age. This is primarily linked to a lower residual level of enzyme activity resulting in a greater severity in childhood.

- Current paediatric practice:
 - The current standard treatment is enzyme replacement therapy (ERT). A product for substrate-reduction therapy (SRT) is currently approved in the EU and Canada (but not in the US), for use in adults who cannot receive ERT.
 - While ERT has provided significant advances in patients with Type I and Type III disease, other therapies with different mechanism of actions may still offer great potential.
 - Placebo-controlled studies of ERTs are not considered ethical, because of clearly improved functioning and survival since the introduction of ERT.
 - The dosing of ERT is highly debated and individualised. Throughout Europe, and globally, children with Gaucher disease are managed at specialised centres, which renders them relatively easy to access for clinical trials.

1.2. Unmet needs

- There is a high unmet clinical therapeutic need for paediatric patients with neurological involvement (Types II and III). Additionally, growth rate, bone and pulmonary manifestations remain high on the list of unmet needs.
- Studies conducted so far have not addressed all paediatric age ranges.
- Another unmet clinical need is that of more practical routes of administration. Developing age-appropriate oral pharmaceutical products (e.g., oral SRT products) is considered beneficial for all paediatric age ranges. Some paediatric patients, in particular, find the two weekly infusions of ERT to be painful, and overall the treatment burden is challenging.

1.3. Non-clinical models

- Animal models of Gaucher disease are available to test efficacy, 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 efficacy endpoints to be evaluated in paediatric studies, or the need to develop pharmacodynamic markers of drug activity.
- For ERTs, the need for juvenile animal toxicology studies should be decided on a case-by-case basis. For example, when paediatric patients are included in the first-in-human study, a juvenile animal toxicology study may be requested instead of (but not in addition to) an adult animal toxicology study.
- 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.

1.4. Long term clinical aspects

- Patient registries are an important means of monitoring long-term safety and efficacy. When registries are set up individually per product, it increases the burden on all stakeholders, and does not allow comparative analysis across products. EMA and FDA recommend use of the existing International Collaborative Gaucher Group (ICGG) Gaucher Registry; with expansion of the database to collect information on key paediatric manifestations such as growth rate, and bone disease.
- Haematological and/or visceral endpoints have been standardised and normalised, and are most commonly evaluated in the paediatric trials.
- Other long-term clinical manifestations such as growth and developmental changes, growth rate, bone disease, pulmonary function, and neurological manifestations are not uniformly measured and documented.
- Long-term follow up in a prospective study is considered necessary to demonstrate the long-term effects of treatment on these disease manifestations in paediatric patients.

2. A Strategic Collaborative Paediatric Approach

This proposal covers the principal features considered necessary for demonstrating efficacy and safety in treatment-naïve paediatric patients with Gaucher disease Types I and III, across all the paediatric age strata. The proposal contains inclusion criteria, age groups, endpoints (including secondary long term efficacy endpoints) and proposed minimal duration of studies.

It is appreciated that the concept of a multi-arm, multi-company development programme can be very challenging. However, 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 limited timeframe.

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

The EMA and FDA consider that the primary rationale for extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency, for reducing burden to patients, and to allocate resources to areas where studies are the most needed. An extrapolation study approach could be implemented to strengthen and maximise development plans, with the recognition that the plan will not address all aspects necessary for the assessment of new and emerging products. Ultimately, supportive clinical studies are considered necessary. The development of an extrapolation concept for paediatric Gaucher disease would build on a systematic synthesis of available data (in vitro, preclinical, clinical), and include the use of modelling and simulation approaches. The aim is to develop an explicit (quantitative) hypothesis regarding the similarity of the disease (its subtypes), and the similarity of response to intervention between source and target populations, as described in the recent [Concept paper on extrapolation of efficacy and safety in medicine development](#) released by the EMA.

According to the FDA definitions ([Dunne et al, 2011](#)), partial extrapolation of efficacy can be used when there is uncertainty about one or more of the assumptions underlying complete extrapolation. The paediatric evidence required to support partial extrapolation ranges from a single adequate, controlled trial to confirm efficacy, to only a PK/PD (exposure-response) study to confirm response in the paediatric population.

Given the experience obtained with enzyme replacement therapies to date (as reported from sponsor data and published literature), extrapolation of efficacy from adults to children can be considered applicable to visceral and haematological endpoints, within Type I Gaucher disease. Extrapolation of efficacy between similar products is more complex within the context of a drug development aimed at marketing authorisation. However, data from medicinal products with the same mechanism of action could provide a useful source of information for designing an optimal clinical development programme, despite obvious potential issues such as differences in product quality/manufacturing, immunogenicity, PK, etc.

Some characteristics of Gaucher disease for which treatment efficacy (particularly in the long term defined as beyond 2 years) is not considered amenable to extrapolation from the adult to the paediatric population, are the following:

- Growth rate;
- pubertal onset and development;
- prevention of bone disease;
- preservation of pulmonary function;
- maintenance of long term efficacy.

Treatment effects on the above characteristics of Gaucher disease should therefore be specifically addressed in paediatric studies. Some of these characteristics can potentially be studied post-marketing, in the context of the Risk Management Plan, and consequently would not need to be included in the strategic plan. The safety of treatments for Gaucher disease cannot be extrapolated from adult to paediatric patients.

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

In view of some of the feasibility concerns and challenges in conducting several simultaneous development plans in a rare disease, the possibility of conducting a multi-company, multi-arm trial, as presented in Table 1, is proposed. Such a complete study would be considered scientifically and ethically suitable to demonstrate efficacy and safety of each individual new product.

A reduction in the total number of children to be included would be achieved, compared to separate controlled trials, as a single control arm would be needed to compare the effects of more than one product.

To date there is a lack of validated clinical endpoints to monitor bone and lung disease manifestations in Gaucher disease across the paediatric age spectrum. As a result, the currently utilised haematological parameters are still considered to be of greater utility in designing a trial. It is encouraged that potentially relevant clinical biomarkers, such as biomarkers for bone or pulmonary disease, be studied as exploratory markers within the trial, to identify appropriate markers that could be validated for use as surrogate endpoints to support efficacy.

Table 1. Proposed double-blind, controlled, randomised, multicentre, multi-arm, multi-company non-inferiority trial

Study identifier(s)	Strategic collaborative pediatric approach for Gaucher disease
Study design features	• 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> compared to imiglucerase in paediatric patients with Gaucher disease Type I and III. • Equal allocation to each arm for multi-arm study: e.g., 1:1:1:1; in the case of a two-arm study an unequal 2:1 allocation (new product:imiglucerase) may be considered • Centralised randomisation stratified for type and age group • Centralised, independent, blinded assessment of radiological imaging. • Centralised, independent, blinded assessment of biomarkers. • Centralised independent data management and auditing
Main objective(s)	To evaluate non-inferiority of new product(s) to treatment with imiglucerase.
Study population and subset definition	Male and female paediatric patients, from birth to less than 18 years with Type I and Type III.
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	• The calculated sample size should be sufficient to detect non-inferiority in the proposed primary endpoint with at least 80% power and a (multiple) Type I error rate of 0.025 (one-sided). • <u>The non-inferiority</u> margin has to be carefully chosen (see according EMA guideline). This is particularly crucial as the assay sensitivity of the trial cannot be assessed in the usual way due to lack of a placebo control group for ethical reasons. Consulting regulatory bodies for scientific advice about this issue before study start is therefore highly recommended. • The required sample size will primarily depend on 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 III • Genotyping for Gaucher disease. • Treatment naïve patients • Birth to less than 18 years of age
Main exclusion criteria	• Clinical symptoms indicative of Type II/acute-neurological disease. • Allergic and anaphylactic response antibodies or failed ERT in past.
Study duration for participants	• Two years of treatment for primary endpoint. • Long term monitoring of primary and secondary endpoints and safety. This extension should cover at least three years however at least 5 years is recommended.
Dosage, treatment regimen, route of administration	• ERT products: doses to be defined. • SRT products: doses to be defined. • Other therapies: doses to be defined.
Control(s)	Active control group - imiglucerase administered at 60iu/kg. The dose must be adjusted by weight at least every 6 months, in line with growth

Study identifier(s)	Strategic collaborative pediatric approach for Gaucher disease
Primary endpoint(s) with time point(s) of assessment	• <u>Treatment naïve patients</u>: Change in normalised haemoglobin measurement between baseline and two years
Main secondary endpoint(s) with time(s) of assessment	• Growth rate, as measured by Z score of height, 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); • Platelet count at baseline and at least every 6 months; • Liver and spleen mass (measured with US/ CT/ MRI) 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 with lung function tests at baseline, 1, 2, 3, and 5 years; • Safety and tolerability - including infusion related reactions; • Antibody levels for each ERT product - at each infusion (every 2 weeks) for 3 months and then every 3 months; antibody levels should also be measured at the time of a hypersensitivity event.
Statistical plan including study conduct and analysis	• Primary analysis primary endpoint: Non-inferiority comparison of each individual investigational medicinal product to control, respectively, by means of 95% confidence interval method, in both the Per-Protocol and Intention-To-Treat population (see EMA guidelines for non-inferiority trials). • 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
External Independent Data Safety Monitoring Board	Yes Early stopping of a treatment arm for inferiority reasons should be considered
Deferral	Yes
Date of completion	Not later than 2 years after Marketing Authorisation in adults

Non-binding elements / Recommendations:

Applicants should consider, and discuss in their applications:

- The need for stratified randomisation (and analysis) for region;

- The need to include assessment of exploratory biomarkers, such as surrogate markers of lung and bone disease, and measurement of Bone Mineral Density or Bone Marrow Burden.
- The inclusion of a pharmacogenomics approach in the development program, to evaluate/explore the different modifiers of the genotype-phenotype (subgroup) relationship.

3. General guidelines and reference

[EMA Guideline on clinical trials in small populations](#);

[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](#);

[EMA Concept paper on extrapolation of efficacy and safety in medicine development](#)

[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](#);

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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).

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