EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 September 2012
EMA/754506/2012
Human Medicines Development and Evaluation

An alternative approach to drug development in children with Gaucher disease

A collaborative proposal from EMA and FDA

Table of contents

Executive summary

The last few years have witnessed a surge of medicinal product intended to treat this orphan designated disease. After more than a decade of having only one treatment option, there are now currently three enzyme replacement therapies (ERT) and a substrate reduction therapy (SRT) available with a second one on the horizon. While the emergence of so many products is advantageous on many levels it also presents challenges – particularly that of ensuring that the level of data to support safe and efficacious use of each one is generated.

The purpose of this document is to initiate exploring the perspectives of stakeholders that are currently involved in the development of medicinal products for Gaucher disease. With the aim to ensure that studies conducted in this field are maximized in design to provide the necessary high quality data – specifically in paediatrics. Data that will enable an informed choice by patient, family and practitioner alike.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

This discussion was triggered by the number of new products being submitted to the Paediatric Committee (PDCO) for evaluation of Paediatric Investigation Plans (PIP). This raised concern about the feasibility of performing all the studies in what is a rare disease; the difficulty for key opinion leaders to choose which study to participate in, and the difficulties for patients and their families in understanding and choosing between trials and treatment options. Crucially, there was a noted concern that some of the significant clinical needs were still not being addressed.

Focusing efforts in this area is considered to be a means of ensuring comparable data and addressing unmet needs in the paediatric Gaucher population, while potentially reducing the overall economic burden linked to conducting studies.

As a result, three different approaches are proposed for consideration in order to make progress towards this goal:

1. creating a standard paediatric clinical development plan (e.g Paediatric Investigation Plan (PIP) and a template Written Request);
2. utilising extrapolation and a modelling based approach;
3. designing a multi-product, multi-company development programme to examine the safety and efficacy of each emerging product.

Status of this document

Status	**Date**
Drafting started	1 May 2011
Initial discussion at Paediatric committee (PDCO)	August 2011
Workshop arranged by Paediatric task force at EMA, including European Working Group on Gaucher disease (EWGGD) and European Gaucher Alliance (EGA)	11 October 2011
Draft presented to the FDA, Health Canada and Japan	21 February 2012
Comments sought from FDA, Health Canada and Japan	8 April 2012
Discussion at PERC (FDA)	July 2012
Workshop to consult industry, experts and patient organisations	17-18 September 2012
Discussion at SAWP (CHMP)	24 September 2012

1. Background information

1.1. Disease characteristics and response to treatment

- As one of the most common lysosomal storage disorder, Gaucher disease has estimates of prevalence ranging from 1:640 through to 1:3969. It is classified as an orphan disease however.
- Gaucher disease has been classified into three types:
  - Type I, refers to the traditionally referred to non-neurological involvement form.
  - Type II, refers to the acute, infantile neuronopathic form.
  - Type III, refers to the chronic, neuronopathic form.

    Type I is most prevalent.

    Type II and III account for between 8 and 22%.

Type II is a paediatric only disease which results in death, while still in infancy.

- The disease is very heterogeneous, overall and within types.
- The underlying biology of Gaucher disease overall and within the respective Gaucher subtypes is the same in adults and children. However, clinical manifestations in children differ from those seen in adults, on presentation and through disease course. These differences include growth and the severity of bone disease in children compared to adults.
- Overall, age at onset of symptoms correlates with symptom severity, with a poorer outcome expected with those who are symptomatic at a young age. This is primarily linked to a lower residual level of enzyme activity resulting in the greater severity in childhood.
- Current paediatric practice:
  - The current 'gold-standard' treatment is enzyme replacement therapy (ERT).
  - Placebo controlled studies are not considered ethical, because of improved survival since the introduction of ERT. A comparator treatment generally has to be applied.
  - Dosing of ERT is highly debated and individualised. Not all clinicians increase dose incrementally to weight gain. Dosing is not always individualised based on clinical parameters either.
  - It is recognised throughout Europe, and globally, that children with Gaucher disease are being managed at specialised centres, therefore leading to the possibility of a multi-centre trial(s) involving all.

1.2. Unmet needs

- There is a high unmet clinical therapeutic need for patients with neurological involvement. Additionally growth, bone and pulmonary manifestations remain high on the list of unmet needs.
- Combination therapy (for example ERT and SRT) could be explored as a potential approach for difficult to manage visceral manifestations.
- The complete age range for which the medicine is eventually used has not been included in studies conducted this far. Furthermore, a waiver for the less than 24 months has been granted by the PDCO at European level to date.
- Another unmet clinical need is that of a different route of administration. Some patients, paediatrics in particular find the two weekly infusion to be painful, difficult and challenging. An alternate route/ frequency of administration could be considered advantageous, acknowledging that choice of preferred pharmaceutical form may vary according to age.
- Developing age-appropriate oral pharmaceutical forms would be considered beneficial for all paediatric age ranges.

1.3. Non-clinical

- Animal models of Gaucher disease are available for efficacy testing, as described by Farfel-Becker et al (Disease Models & Mechanisms, 4, 746-752, 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. For example, abnormalities in skeletal development are a major manifestation of type 1 Gaucher

disease in paediatric patients. Focal osteonecrosis and osteopenia were observed in the mouse Gaucher disease model described by Mistry et al (PNAS, 107, 19473-19478, 2010). Based on the similarity in phenotypes of this animal disease model and paediatric Gaucher disease, the selection of this disease model can be justified for the evaluation of efficacy in preventing development of skeletal defects associated with paediatric Gaucher disease.

- Animal models of Gaucher disease can enable the development of pharmacodynamic markers of drug activity. For this purpose, selection of the animal disease model should be based on the paediatric Gaucher phenotype of interest, or the specific paediatric Gaucher disease manifestation(s) of interest.

1.4. Clinical

- Data registries are acknowledged to be an important means of monitoring patient's long term; however such data registries have several limitations. Such limitations in particular limit the ability to compare across products.
- After the haematological and/or visceral endpoints have normalised, as most commonly evaluated in the paediatric trials, other long-term clinical manifestations such as maturation, growth, bone disease, pulmonary function, and neurological manifestations remain a challenge.
- Long term follow up, in a prospective study is necessary to demonstrate long term effect on bone, growth and pulmonary disease in paediatrics.

2. General note on creating a Paediatric Clinical Development Plan

Developing a standard paediatric clinical development plan would allow a core set of principles to be agreed upon by clinicians, industry, patient representatives and regulators; with the expectation that each applicant developing a medicinal product in this field would adopt the development plan in order to evaluate the efficacy and safety of each individual medicinal product.

This standard paediatric clinical development plan would cover the principal features considered necessary, focusing on the inclusion criteria in order to define the disease severity and symptomatology, and sample size across all the paediatric age strata. The chosen end-points would be standardised, including secondary long term efficacy endpoints and duration of study. The scope of any potential waiver would be defined consistently throughout. The type of study[ies] to be conducted would be presented logically, with emphasis given to the unmet clinical needs as currently reported by clinicians and patients. Such an outline would align all new and emerging development, ensuring the generation of data that is comparable across products.

A potential limitation with this approach is that this still leaves a high number of different studies being conducted in parallel, and in essence competing for the same centres/patients. Furthermore, the most likely study design in this case being a single-arm uncontrolled study. The lack of randomisation would also hinder the likelihood of patient characteristic data being comparable across each individual product due to the vast clinical heterogeneity observed in this disease area, with major difficulties in predicting patient phenotypes from genotypes, along with different clinical presentations across ethnic backgrounds and continents (Hruska et al 2007).

Furthermore, as many of the studies in question have now been instigated by industry, a complete revision of those studies may not be feasible on a scientific or ethical basis. Therefore alternative options to that of creating a Paediatric Clinical Development Plan are considered necessary.

3. General note on potential use of extrapolation for Gaucher disease

In line with the FDA decision tree, (Dunne et al, 2011) extrapolation can be considered possible when fundamental assumptions are met. These are that there are similar disease progressions and similar responses to intervention in adult and paediatrics. A third assumption is that the two populations have similar exposure-response relationships.

The PDCO sees a necessity to go beyond FDA paediatric decision tree and develop an expanded and refined algorithm for extrapolation for paediatric drug development. A recent Concept paper on extrapolation of efficacy and safety in medicine development released by the EMA proposed a preliminary concept for this algorithm. Further development of this is now underway with the aim of identifying a process that generates a set of accepted rules put down in a guidance document for industry and to harmonize regulatory decisions across committees.

According to the FDA definitions, partial extrapolation of efficacy is 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, well-controlled trial to confirm efficacy to a PK/PD (exposure-response) study to confirm response in the paediatric population. The supportive evidence required from paediatric studies being dependent on whether the aim of extrapolation is to confirm efficacy, confirm responses, or to confirm doses.

Under the FDA assumptions, extrapolation of adult efficacy data could potentially be considered suitable for the assessment of visceral and haematological manifestations of Gaucher disease given the experience obtained with the enzyme replacement therapies to date as reported from sponsor data and published literature findings. This is important when considering the developmental needs of new and emerging products, particularly those with the same/similar mechanism of action as the original enzyme replacement.

Extrapolation of efficacy would reduce the number and complexity of paediatric trials necessary to achieve paediatric labelling, although some supportive paediatric data may still be required (e.g. PK and safety). As previously stated, extrapolation of adult data for the visceral and haematological manifestations of the disease could be considered acceptable in new emerging products. However given that there are many other visceral manifestations to be considered with a distinct difference in children compared to that seen in adults, it may not be sufficient to utilise complete extrapolation as a "stand-alone" approach.

Aspects of Gaucher disease that may not be considered amenable to extrapolation from the adult to the paediatric population, particularly in relation to long term efficacy, are as follows:

- growth;
- prevention of bone disease;
- assessment of pulmonary efficacy;
- maintenance of long term efficacy;
- long term safety.

These long term efficacy endpoints have also been noted to be of high therapeutic needs, not currently being addressed.

Nonetheless an extrapolation approach, as that presented in Table 1 could be implemented to strengthen and maximise development plans considered necessary for the assessment of new and emerging products, especially those with the same mechanism of action.

With three ERT now available or potentially available, consideration should also be given to whether data can be extrapolated across ERTs, based on the concept that they all work through a similar mechanism of action. This may support the notion of completing just confirmatory PK/PD and safety studies if the extrapolation approach was adopted.

Table 1. Extrapolation Approach of Efficacy to the paediatric population

Identifier	**Measure to extrapolate efficacy of haematological and visceral disease from adult to the paediatric population**
Extrapolation approach	Analysis of sponsor data and published literature on currently available <enzyme replacement therapies> across all age groups and <all Gaucher types>
Extrapolation objective(s)	To examine assumptions of partial extrapolation from adults to the paediatric population. To examine assumptions of partial extrapolation from one enzyme replacement to another.
Methodology	To examine the assumption that the outcome of treatment with <medicine> is likely to be similar in paediatric subsets by age and by disease type compared to adults To examine the assumption/position that <medicine A> is expected to have the treatment outcome as <medicine B> in all paediatric subsets and disease type To define how the assumptions are to be confirmed and the pharmacokinetic, pharmacodynamic, and safety data considered necessary to support the assumptions. To agree on the format and presentation of adult data and currently available paediatric data (including maturational profile parameters) needed to support a physiology-based population pharmacokinetics model. To compare adult and paediatric data with respect to pharmacodynamic effect size by exposure, by age, type and genotype. To agree on the data/studies eventually required to support such assumptions (e.g PK/PD/ safety)
Study population and subset definition (incl. stratification)	Gaucher disease - Type I (non-neurologic) and Type III (chronic neuronopathic). Children aged from [birth] / [2 years] to less than 18 years of age e.g. from 2 to less than 4 years, from 4 years to less than 12 year, from 12 to 18 years.

4. General note on multi-product, multi-company trial for Gaucher disease

In view of some of the concerns and challenges with creating a creating a Paediatric Clinical Development Plan, and some of the potential limitations identified with extrapolation, consideration has to be given to conducting a complete study to demonstrate efficacy and safety. One option considered to be scientifically and ethically suitable would be to conduct a multi-company, multi-product trial, as presented in Table 2.

Such an approach would focus on the long-term efficacy data that are specific to the paediatric population. Additionally, potentially relevant clinical biomarkers (e.g., chitotriosidase, CCL18/PARC)

could be evaluated as exploratory value within the trial for further validation; as they are not currently considered as validated efficacy endpoints at this point. The study is proposed as an opening point of discussion for all stakeholders to have their input in order to ensure that the study is designed to the most robust clinical and scientifically level.

Table 2. Double blind, randomised, multicentre, multi-product, multi-company trial

Study identifier(s)	**Double blind, randomised, multicentre, multi-product, multi-company trial**
Study design features	Double blind, randomised, multicentre, multi-product, multi-company non-inferiority trial to evaluate the efficacy and safety of velaglucerase (VPRIV), taliglucerase (Protalix), eliglustat compared to imiglucerase (Cerezyme), in managing haematological, visceral, bone and pulmonary disease in paediatric Gaucher patients. Allocation: 1:1:1:1 central randomisation. Randomisation stratified for <genotype><disease subset><region> Blinding of: <participant><caregiver><investigator><treating physician><assessor>. Independent, blinded, assessment of haematological samples used for primary endpoint. Independent, blinded, assessment of radiological imaging. Centralised assessment of biomarkers.
Main objective(s)	To evaluate non-inferiority of all products
Study population and subset definition	Male and female paediatric patients from <2>/ <6> 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)	Per group sample size 40: non-inferiority margin 1.2 g/dL change from baseline
Main inclusion criteria	A clinical diagnosis of Gaucher disease with documented deficiency of acid beta-glucosidase activity by enzyme assay. Genotyping for Gaucher disease and chitotriosidase. No previous exposure to ERT.
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	<Three>/<four> years treatment to monitor primary endpoint. Extension for on-going safety and impact on growth, bone, pulmonary.
Dosage, treatment regimen, route of administration	All ERT prescribed at 60iu/kg/ two weekly, administered intravenously. Dose must be increased incrementally in line with growth. [eliglustat dose to be defined]
Control(s)	Active controlled
Primary endpoint(s) with time point(s) of assessment	Normalisation in haemoglobin measurement between baseline and <three> /<four> year time point.
Main secondary endpoint(s) with time(s) of assessment	Liver and spleen mass. Bone manifestations; including pain intensity and duration Bone manifestations; number of fractures Bone Mineral Density

Study identifier(s)	**Double blind, randomised, multicentre, multi-product, multi-company trial**
	Growth (height/ weight/ BMI). Pulmonary function measured with lung function test and evaluation of chest x-ray Biomarkers - chitotriosidase, CCL18/PARC [further potential lung and bone] Safety and tolerability assessments. Antibody titers for each product and effect on efficacy and safety.
Statistical plan including study conduct and analysis	Primary analysis of primary endpoint: Per group sample size 40: non-inferiority margin 1.2 g/dL change from baseline. Data should be analysed by independent assessors
Measures to minimise pain and distress	Topical anaesthesia should be made available for all canulation/ access of port-a-cath as per patient choice
External Data Safety Monitoring Board	Yes

5. General guidelines and reference

- EMA scientific guidelines for small populations:
  - 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 metholigical aspects of clinical trials for efficacy evaluation in small populations.
- Gaucher Disease Edited by Futerman A.H and Zimran, A (2007)