16 June 2017
EMA/752905/2016

Overview of comments received on 'Gaucher disease: a strategic collaborative approach from EMA and FDA' (EMA/44410/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Biotechnology Industry Organization (BIO)
2	European Federation of Pharmaceutical Industries and Associations (EFPIA)
3	Inherited NeuroMetabolic Disease Information Network (InNerMeD-I-Network)
4	NIHR Clinical Research Network (CRN): Children's Theme
5	Shire plc

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1.	The Biotechnology Industry Organization (BIO) appreciates the work of both the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) on this Strategic Collaborative Approach initiative to improve the efficiency of drug development for Gaucher disease. BIO represents more than 1,000 biotechnology companies, state biotechnology centers, academic institutions, and related organizations both in the United States and abroad. BIO members are critical contributors to the research and development of innovative health care, agricultural, industrial, and environmental biotechnology products. BIO believes that the focus on rare diseases is appropriate for this novel initiative, given the vast unmet medical need in the rare diseases space and that the complexity and duration of drug development programs in general are exacerbated by the inherently small patient populations with rare diseases. Furthermore, we would like to express our appreciation for the opportunity for meaningful stakeholder input both during the Joint Workshop in September 2012 and the ongoing comment period. It is crucial that regulatory agencies on both sides of the Atlantic continue to engage with a diversity of stakeholders to further reduce barriers to the research and development of rare disease drugs and biologics. We hope that the process used for the Strategic Collaborative Approach to Gaucher disease is a model for, at minimum, the level of public engagement we can expect from such initiatives in the future. BIO requests that, moving forward, the EMA and FDA engage with the industry around potential therapeutic areas for inclusion in the Strategic Collaborative Approach in the future. Further, BIO believes that the Agencies should also offer opportunities for stakeholders to present potential therapeutic area candidates for consideration and provide comments on those conditions suggested for inclusion. Allowing for such public comment earlier in the process better ensures that regulatory science is keeping up with the pace of scientific discovery and trends in research and development. BIO urges the Agencies to detail how each public comment received is incorporated through the process (e.g., into draft documents), and if a comment is not incorporated,	Accepted.

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	the rationale for its exclusion. This "best practice" often is required of U.S. agencies when releasing regulation and allows stakeholders to better understand the thinking of the Agencies, which can help inform comments submitted in the future. BIO recommends that the Agencies identify a mechanism to track the impact of this initiative. One way to do this is to request relevant Sponsor feedback after the submission of study plans and throughout the regulatory process for therapies covered by a Strategic Collaborative Approach. Another method could be to survey—or to contract with an independent vendor to survey—various stakeholders (e.g., industry, patient organizations, professional societies) that have completed a collaboration or are in the midst of collaborating. Alternatively, the Agencies should consider including details on upcoming Strategic Collaborative Approach documents in their annual work plans (to the extent that such plans are published publicly), as well as the number of submitted applications that utilize the guidance produced by this initiative annually. The Agencies should invite additional thoughts on how the impact of this initiative can be evaluated.	
1.	BIO requests that EMA clarify that the final Strategic Collaborative Approach document should be interpreted as formal guidance and, in the case of applications submitted to EMA, whether deviations from the document therefore should be explicitly justified. BIO also encourages FDA to publish the strategic Collaboration Approach document in the Federal Register for public comment so that it may be formally considered as FDA guidance. In doing so, FDA should enumerate how this, and future, Strategic Collaborative Approach documents take into account the differences in regulatory requirements between the U.S. and E.U. BIO requests that FDA specifically address how the Strategic Collaborative Approach impacts Written Requests (WR) in the U.S., as the draft document only addresses the intersection with Paediatric Study Plans (PSPs).	The Strategic Collaborative Approach document is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency. The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.

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1.	One of the primary issues the Agencies are attempting to address through the Strategic Collaborative Approach is the limited patient population available for clinical trials for rare diseases. In this regard, BIO recommends that FDA and EMA consider including more discussion in each Strategic Collaborative Approach document—where relevant and appropriate—around the potential role that innovative trial design and post-approval real-world data collection can play in improving the time-to-market for therapies that meet unmet medical needs, especially in the rare disease space. Additionally, we specifically request that the Agencies allow Sponsors sufficient flexibility in decisions around enrolling treatment-naïve participants versus those who have been treated. While this issue impacts every rare disease population to a degree, it is acutely relevant for those diseases where a standard of care for treatment exists and in which the majority of patients is likely to have been treated soon after an initial diagnosis. BIO cautions that rigid requirements may increase the duration of trial recruitment and/or the cost of the trial prohibitively, or may make it infeasible to design a trial with sufficient statistical power.	Accepted. Flexibility has been incorporated in the Strategic Collaborative approach.
1.	Because it may not be feasible—for reasons discussed in the immediately preceding comment—to rely on paediatric studies alone to meet regulatory requirements for approval in rare disease populations, BIO supports population extrapolation between adults and children because establishing efficacy in other age groups through pivotal trial comparability data (using a surrogate marker if available) can provide a strong presumption for efficacy in paediatric populations. Employing population extrapolation in this manner can improve the efficiency of paediatric drug development, especially in the case of rare diseases, although it must take into account potential differences in the pharmacokinetic, pharmacodynamic, and pharmacogenomic profile of the drug across different age groups. In reference to the document's section on The use of extrapolation of efficacy, we appreciate that the Agencies generally note the potential utility of modelling and simulation approaches when used to inform data analyses. BIO agrees that the ability to employ these approaches is particularly important due to the small (sometimes extremely small) patient populations affected by a rare disease. However, we believe it	The Strategic Collaborative Approach document should be read in conjunction with the ICH guidelines and other regional guidance of relevance such as the EMA reflection paper on extrapolation of efficacy and safety in paediatric medicine development.

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	would be appropriate for the Agencies specifically to note in this and future Strategic Collaborative Approach documents that any modelling must take into account potential differences in the pharmacokinetic, pharmacodynamic, and pharmacogenomic profile of the drug across different age groups. Additionally, BIO recommends that this and future Strategic Collaborative Approach documents cross-reference existing resources for Sponsors—such as guidance from the International Conference on Harmonization (e.g., on evaluating the impact of ethnic factors on a therapy's effect)—that address additional factors that must be taken into account in extrapolation and modelling efforts.	
1.	BIO strongly agrees with, and appreciates, the Agencies' recognition of the "very challenging" nature of multi-arm, multi-company development programs (p. 5, Section 2, second paragraph). As the Strategic Collaborative Approach initiative develops, we urge FDA and EMA to engage industry in collaborative discussion of ways to establish and leverage the utility of registration studies, since, in the case of many if not most rare diseases, an active comparator study is either not possible or infeasible.	Not accepted. Out of scope.
1.	BIO asks that the Agencies clarify certain aspects of the proposed multi-product, multi-company study, including: The application of existing requirements governing "sponsorship" (especially if there are three or more products in the study), taking into account the resulting implications for other aspects of drug development; Eligibility of individual products for specific designations (e.g., orphan designation) and timelines for such; and, The sufficiency of the Strategic Collaborative Approach to fulfill EMA's Paediatric Investigation Plan (PIP) requirements and/or FDA's PSP and WR requirements and to entitle companies to paediatric rewards. BIO strongly supports the voluntary publication of clinical trial data among its members. In this case, we recommend that the consortia exercise caution on the publication method for clinical trial data until ownership/custodianship of such collaborative measures are clearly identified. To that end, we urge the Agencies to consider implementing a pilot program or propose language in the guidance that clarifies how such issues might be managed.	The Strategic Collaborative Approach document is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.

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	In the case of multi-company, multi-arm (product) studies, BIO recommends that the Agencies state that they plan to concurrently establish and align study timelines among the collaborating Sponsors, as well as the primary and secondary endpoints, such that a standard protocol is applied across all included products. BIO requests that the Agencies clarify that, in the case of a multi-product, multi-company study, individual participating Sponsors would not need to conduct additional studies.	
1.	In consideration of secondary endpoints, BIO recommends that the Agencies consider including endpoints that measure quality of life and relevant patient-reported outcomes, as well as identify mechanisms to validate measurement tools for these outcomes.	Accepted. Section 1.4 outcome assessments have been added.
2.	It is not clear on whether this Collaborative Approach document is intended to be released as an 'EMA Guidance'. At a recent public meeting (DIA North America 2014), a representative from the FDA noted in a Session Q&A that FDA & EMA would not be releasing 'joint guidance' for paediatrics because the burden was too high to address all of the perceived needs with the current resource within the agency. Therefore, is this 'collaborative approach' a suggestion from EMA & FDA or intended as EMA Guidance? It should also be clarified if the Collaborative Approach document is to be deemed a formal EMA guidance document and if it is expected that deviations need to be justified. The (regulatory) status of the Collaborative Approach document needs to be better explained versus a so-called Standard PIP. As this 'collaborative approach' is a "new" entity, will an option for parallel advice or common commentary be considered as routine for sponsors early in the development of a Gaucher program? Per the 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-*	The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.

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	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." As this is intended to enhance 'the chances of rapid and smooth agreement' on an EU PIP and US PSP, is there also alignment within the EMA that this approach would also be sufficient for marketing authorisation in pediatric Gaucher's Disease? The impact on currently agreed PIPs for Gaucher disease needs to be clarified. Specifically it needs to be clarified if the approaches in the Collaborative Approach document are expected to be incorporated in currently agreed upon PIPs, for example at the time that a Request for Modification is submitted (for any reason). The concern around the relatively large number of clinical studies required by PDCO in paediatric Gaucher patients is shared. Gaucher is an ultra-rare disease, and companies may effectively compete for the same group of (ERT-naïve) patients. There is a risk that individual trials may fail due to lack of eligible patients. It can be argued that similar to the regulatory situation in the US, a formal PIP requirement should be waived for orphan designated products. Paediatric (ERT-naïve) patients eligible and willing to participate in clinical studies are rare and therefore should be directed to relevant studies that clearly address unmet medical need, e.g. an oral product with a novel mechanism of action. Furth ermore, because the large majority of current paediatric Gaucher patients are treated, flexibility should also be afforded in the study-population (naïve vs. maintenance patients). A requirement to study naïve patients makes it almost impossible to enrol patients in reasonable time, especially in the higher paediatric age cohorts where fewer patients may be newly diagnosed. The Collaborative Approach document proposes studies covering Gaucher disease Type I and III. It must be recognized that study design and endpoints suitable for Gaucher disease Type I, may not be optimal for establishing efficacy and safety in Type III disease (including neurological symptoms), and flexibility should be afforded taking into account the target population of interest. As a disease program, the ICGG Registry captures data from patients independent of treatment status and type of treatment. No safety data is collected in the ICGG registry.	

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	Physicians report adverse events in patients on a certain treatment to the respective MAH/ pharmacovigilance database, irrespective of whether the patient is in the Registry.	
2.	Extrapolation of efficacy While extrapolation from adult to paediatric data may be a valid approach for some outcome parameters for an individual product, monitoring growth and prevention of bone disease may not be amenable to extrapolation as discussed in the Collaborative Approach document. It should be clarified, when adopting an extrapolation approach, whether the PIP applicant will be expected to develop additional clinical studies in paediatric patients. Extrapolation between different (ERT) products may be considered if products have been demonstrated to be biosimilar. The efficacy and safety (immunogenicity) profiles of biological products may vary substantially. Differences in manufacturing processes and platforms have been shown to impact protein structure including post-translational and other modifications (amino-acid sequence, glycosylation) and consequently biological activity and immuno-chemical properties. A modelling-based approach may be challenging if the pharmacokinetic profile of the drug potentially varies between different age groups. For example, a drug product that is metabolized via the CYP450-system, which is known to be immature in during early childhood.	The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.
2.	Multi-arm-multi company trial A multi-product, multi-company development program raises regulatory/legal questions, including governance and funding of such a study ('sponsorship'), eligibility for paediatric reward/incentives and at which time, potential for a PIP for a new product being submitted during the course of such program, etc. Together with individual product characteristics (incl. route of administration), these must be taken into account in determining whether a multi-arm-multi company trial may be the optimal approach for a new compound, on a case by case basis. A multi-product, multi-company development programme may take away some of the constraints around multiple studies competing for the same pool of eligible paediatric patients. However, in itself such a design does not address most areas of unmet medical	The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.

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	need as mentioned in the Collaborative Approach document (patients with neurological involvement, paediatric age ranges, more practical routes of administration). When adopting a multi-product, multi-company study, would the PIP applicant be expected to develop additional clinical studies in paediatric patients depending on the specific medicinal product/mechanism of action, or would the PDCO not require/waive additional studies?	
2.	<u>Paediatric dosage form</u> Expectations for paediatric dosage form development efforts should match up with the number of paediatric patients to be treated. Gaucher is an ultra-rare disease, and the feasibility of developing multiple paediatric formulations - liquid as well as multiple lower strength capsule dosage forms - should be weighed against commercial viability.	The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.
3.	Generally, the document has been drafted on robust basis, with a strong methodological rationale and in consideration of internationally-recognised ethical principles for research in paediatrics.	Accepted.
4.	We value the opportunity to comment on this consultation which we believe proposes an important step forward for a collaborative approach to the development of new treatments for people with rare conditions. We have consulted colleagues within the NIHR CRN Children's Theme Clinical Studies Groups (CSG), and particularly those from the Inherited Metabolic Diseases CSG when collating our comments. The guidance states that there are new products that need to be evaluated. It is agreed that a multi-product trial is the way to go but it is also important to measure within this trial the acceptability by patients and their families of the new medicines to ensure that these have good compliance within the target patient population For the neuronopathic GD community there are many products on the horizon (Ambroxol, Genzyme small molecule, gene therapy), therefore it would be helpful if the EMA/FDA help support the development of a joint thinking approach to research within these areas.	Partly accepted. In the revised 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.

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	We recommend that orphan drug databases for post marketing follow up need to be adopted to become "disease registries" where all patients are monitored on the same database, with the same end-points, improving the ability to monitor. If this joint collaborative approach could also be applied to the development and maintenance of registries it would be beneficial for the patients as well as the scientific/clinical community. The collaboration between the FDA and EMA to address this issue is a key step forward as it is essential that regulators on different continents agree on the requirements of orphan diseases in order to make multi centres, multi-country trials possible. We would strongly recommend that this approach is replicated in order to encourage the pharmaceutical industry collaborate in such multi product multi company initiatives, as this will allow physicians to generate the best evidence for prescribing treatment, and particularly orphan drugs, for people with rare conditions. A number of other conditions would benefit from such an approach including Hepatitis C and Duchenne Muscular Dystrophy. In addition, this way of working would be relevant for Fabry Disease and Pompe's Disease where a number of new treatments are on the horizon.	
5.	Even though the proposal under consideration has many merits, Shire concludes that there are fundamental challenges related to the design, governance and execution of such a study, and on following pages in this document Shire has provided specific comments to the existing proposal. Furthermore, as an alternative to the existing proposal, Shire would like to put forward the following for consideration: A workshop, under the auspices of FDA and EMA, with the aim to discuss and agree on format for QoL and other PRO instruments as well as methods and procedures for assessment of disease activity/clinical trial endpoints. An agreement around such key elements would provide valuable guidelines and facilitate data pooling and data comparison and as such ensure quality and standards for future studies in Gaucher disease, specifically in the pediatric population.	Partly accepted. Section 1.4 outcome assessments have been added.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 3, Section 1.1, *1st bullet*	2	Comment: The quoted incidence of Gaucher of less than 0.6 per 10,000 is not in line with estimates mentioned in COMP/EC Orphan drug Designations (i.e. less than 0.3 per 10,000) Proposed change: As one of the most common lysosomal storage disorders, Gaucher disease is estimated to affect less than 0.3 ~~0.6~~ in 10,000 people in the European Union (EU).	Not accepted, out of scope. The purpose of this document is intended to further stimulate exploration of new approaches for various situations in the drug development of new Gaucher disease therapies.
Page 3, Section 1.1, *2nd bullet*	3	Comment: The three most known subtypes of Gaucher disease are listed. However, six different subtypes have been identified: Proposed change: 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. Type IIIC, refers to the cardiovascular form. Perinatal Lethal, the most severe type of Gaucher disease Atypical, refers to the form due to Saposin C deficiency.	Not accepted, out of scope. The purpose of this document is intended to further stimulate exploration of new approaches for various situations in the drug development of new Gaucher disease therapies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 3, Section 1.1, *2nd bullet*, *Point 1*	5	Comment: These numbers are very high as compared to most published data (see eg. Charrow J, et al, Arch Intern Med. 2000;160:2835–2843 and Tylki-Szymanska A, et al, J Inherit Metab Dis. 2010;33:339–346).	Not accepted, out of scope. The purpose of this document is intended to further stimulate exploration of new approaches for various situations in the drug development of new Gaucher disease therapies.
Page 4, Section 1.1, *4th bullet, Point 1*	3	Comment: It should be stated that SRT can be used not only in patients who cannot receive ERT, but also on stable patients (COX TM et al Orphanet. Journal 2012, 7,12).	Not accepted. Zavesca is not approved for pediatric use in the US and the section relates pediatric use.
Page 4, Section 1.1, *4th bullet, Point 1*	2,5	Comment: Regarding "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." Actelion has an approved SRT. ZAVESCA (miglustat) that was approved by FDA in 2003. Proposed change: "A product for substrate-reduction therapy (SRT) is currently approved in the EU, US and Canada (but not in the US), for use in adults who cannot receive ERT." **Comment:** If the SRT product refers to Miglustat (Zavesca), it is currently approved in the US (since July 2003) for the treatment of mild to moderate T1GD in adults for whom ERT is not a therapeutic option. Eliglustat (Cerdelga) is another recently approved SRT.	Accepted. The sentence has been clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 4, Section 1.1, *4th bullet, Point 1*	2	Comment: It is not appropriate to refer to Zavesca ('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.') under the heading 'Current paediatric practice', as it would seem to endorse off-label use Proposed change: Please, would it be possible to remove sentence?	Accepted.
Page 4, Section 1.1, *4th bullet, Point 2*	2,3,5	Comment: Regarding '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.' For Type III it should be noted the advances of ERT are in treating the non-neurological symptoms of the disease. Proposed change: While ERT has provided significant advances as long-term treatment in patients with Gaucher Type I and Type III (non-neurological manifestations) disease… Comment: The document highlights the therapeutic need that is particularly relevant for patients affected by Gaucher disease type II and III (with neurological involvement). In fact, it is also stated that "ERT has provided significant advances in patients with Type I and Type III disease". It should be added that in the case of Gaucher type III the amelioration are confined only to the peripheral symptoms while the CNS involvement is not benefitting from the treatment.	Partly accepted. The text has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: It may be pointed out that there is no benefit of ERT on neurological symptoms, therefore placebo controlled trials targeting in particular neurological symptoms in T3 GD maybe considered on background ERT therapy.	
Page 4, Section 1.1, *4th bullet, Point 3*	2	Comment: The third bullet point on 'Placebo controlled studies…' should not appear on the heading 'Current paediatric practice' as this refers to clinical studies. Comment: As noted, placebo-controlled studies of ERTs are not considered ethical. When new approved treatment modalities, such as SRTs, with demonstrated efficacy and safety become commercially available, these should also no longer need to be studied in placebo-controlled studies.	Accepted.
Page 4, Section 1.1, *4th bullet, Point 4*	2	Comment: Regarding "Throughout Europe, and globally, children with Gaucher disease are managed at specialised centres, which renders them relatively easy to access for clinical trials." The original statement is not true in much of the US and in many other countries. Proposed change: "Throughout Europe, and globally, and many parts of the world, children with Gaucher disease are managed at specialised centres, which renders them relatively easy to access for clinical trials."	Accepted. The sentence have been clarified and moved under 1.5 Long-term clinical aspects
Page 4, Section 1.2, *2nd bullet*	2,5	Comment: As to paediatric age ranges not studied, clarify that this specifically refers to patients below 2 years of age	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: Please consider revising to: "Studies conducted so far, have not adequately addressed the major medical needs in all pediatric age ranges."	
Page 4, Section 1.3, *3rd bullet*	2	Comment: Referring to: '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.' it should be clarified to which extend the replacement of the adult animal toxicology study by a juvenile study is to be seen in the context of the PIP, or that this also refers to e.g. Clinical Trial Applications and/or the MAA.	Not accepted. The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.
Page 5, Section 1.4, *1st bullet*	2	Comment: As a disease program, the ICGG Registry captures data from patients independent of treatment status and type of treatment. No safety data is collected in the ICGG registry. Proposed change: Please, would it be possible to remove 'long-term safety and'	Partly accepted. The comment is no longer applicable to the revised document.
Page 5, Section 1.4, *1st bullet*	3	Comment: Importantly, the document recommends the use of an existing international registry (ICGG), and in particular its extension for the collection of information about paediatric clinical manifestations (e.g. growth rate). Proposed change: EMA and FDA strongly recommend use of the existing International Collaborative Gaucher Group (ICGG) Gaucher Registry; with expansion of the database to	Partly accepted. The comment is no longer applicable to the revised document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		collect information on key paediatric manifestations such as growth rate, and bone disease.	
Page 5, Section 1.4, *1st bullet*	5	**Comment:** The International Collaborative Gaucher Group (ICGG) is a Sanofi/Genzyme sponsored database and as such not open for other companies which might also have their own registries. It is strongly suggested to ensure that any database utilized in conjunction with this initiative is independent of any commercial interests. Another option for collaboration would be for the Regulatory Agencies and the participating companies to agree on common research hypothesis and align on common data collection tools for specific topics, i.e.: PRO and QoL questionnaires in which data collected would be exactly the same. In that way, pooling data for analysis, reports or publications would be much easier, quicker and cheaper than trying to match different databases for the same purposes. In such a scenario, agreement on methods and procedures for assessment of disease related clinical trial endpoints would also be very useful, and should be sought.	Accepted.
Page 5, Section 1.4, *4th bullet*	2,5	Comment: Since product RMPs often have 'long term safety' as missing information, this is an opportunity to be more overt about the need to gather long term safety information. Proposed change: "Long-term follow up in a prospective study is considered necessary to demonstrate the long-term safety and efficacy of treatment on these disease manifestations in paediatric patients."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: It is highly desirable that a consensus for assessment of other long-term clinical manifestations such as growth rate, developmental changes, bone disease, pulmonary function, and neurological manifestations are established.	
Page 5, Section 2, *1st paragraph*	2,5	Comment: It should be clarified that for Gaucher disease Type III this refers to the effect on non-neurological symptoms of the disease. Comment: In fact, it is also stated that "ERT has provided significant advances in patients with Type I and Type III disease". It should be added that in the case of Gaucher type III the amelioration are confined only to the peripheral symptoms while the CNS involvement is not benefitting from the treatment. Nevertheless, the proposed clinical trial described in Section 2.2 concerns the forms of Gaucher I and III. Type II Gaucher (one of the most serious forms and fatal in childhood) is still an "unmet need". Therefore, it should be clarified the decision of considering or not the subtype II in the development of this initiative.	Accepted.
Page 5, Section 2.1	5	**Comment:** It should be pointed out in this section that such extrapolation unfortunately does not cover the major medical needs in the pediatrics population. It is proposed that for any modeling approach, a broad and unbiased view is initially taken. In this context it is important to include the possibility for any new treatment modality to have a different efficacy profile as compared to ERT, e.g.	Not accepted. The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.

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		good effort on neurological symptoms but less so on hematological parameters.	
Page 6, Section 2.1, *4th bullet*	2	Comment: It is difficult to see why infiltrative lung disease, as well as maintenance of long term efficacy, would not be amenable to extrapolation from adult to paediatric patients, as the mechanism of action is expected to be similar. It is understood that that ERT has not shown to be optimally effective in lung in all populations.	Accepted.
Page 6, Section 2.1, *final paragraph*	5	**Proposed Change:** Please consider revising to: "Treatment effects on the above characteristics, representing major medical needs in the pediatric population, should therefore be specifically…"	Accepted.
Page 6, Section 2.1, *final paragraph*	1,2	Comment: BIO requests that the Agencies clarify what the "strategic plan" is, as referenced in: '…and consequently would not need to be included in the strategic plan.' Comment: Reference is made to a strategic plan: '…and consequently would not need to be included in the strategic plan.' It is unclear what strategic plan is meant here. It is not defined elsewhere in the document.	Accepted.
Page 6, Section 2.2	1	Comment: BIO requests that the Agencies clarify that the multi-arm, multi-company study laid out in Table 1 is a proposal only, and that Sponsors should work with FDA and EMA on the details of parameters for any such study if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change: BIO requests that the Agencies revise to read: "…presented in Table 1, is proposed. If this type of study is to be undertaken, FDA and EMA intend to work directly with Sponsors to determine the parameters of such a study, pursuant to the specific products proposed for inclusion and the target population. Such a complete study would be considered scientifically and…"	
Page 6, Section 2.2	2, 3	Comment: It would be relevant to understand if the FDA and EMA have identified a third-party convener who will bring companies together to develop and agree on the protocol design. Also, what is EMAs understanding how companies that may be in discovery and not yet ready for development could be involved in the protocol design considerations, or would these companies be relegated to accept the protocol as designed by its predecessors even if science has evolved rendering this protocol now out-dated. Comment: The proposed trial is widely described in its methodological aspects. However, it is quite unclear what does "multi-company trial" refers to. Proposed change: It might be useful to add a definition or reference explaining the concept of "multi-company trial".	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.
Page 6, Section 2.2	2	Comment: This is in regards to the statement, "As a result, the currently utilised haematological parameters are still considered to be of greater utility in designing a trial."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		FDA currently has concerns about the value of this parameter in the context of varying background hematinic treatment. An alternative is to look at spleen volume. Proposed change: "As a result, the currently utilised haematological parameters are still considered to be of greater utility in designing a trial, notwithstanding the confounding issues of background hematinic treatment."	
Page 7, Table 1, *Study Design Features*	2	Comment: Age group will need to be further defined to avoid too much heterogeneity in the target population, and to account for the endpoints and mechanism of action of compounds other than ERTs.	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.
Page 7, Table 1, *Main inclusion criteria*	2	Comment: Inclusion criteria are broad which will lead to too much population heterogeneity to be analysed. Inclusion criteria will need to be more specific i.e. reflecting haemoglobin level, platelets, organ volume, severity of neurological involvement, etc. At the same time, it will be challenging to find sufficient number of naïve paediatric patients with the same baseline to participate in the proposed multi-arm multi-product study with 3 or 4 arms. Inclusion of naïve patients is limited by small patient numbers. Random sequential treatment-sequence periods would minimize inter-patient variability.	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.
Page 7, Table 1, *Main inclusion criteria*	2,5	Comment: Would there be any stratification by paediatric age range? 0-23 months; 2-11 years; 12-18 years? Proposed change: Please clarify.	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: There is, most likely, a strong need to consider stratification of patient inclusion based on key criteria.	
Page 7, Table 1, *Main inclusion/ exclusion criteria*	2	Comment: Inclusion / exclusion criteria may differ between products, for example depending on the mechanism of action. This will limit patient enrolment for all treatment groups if patients are randomized.	Accepted. The Strategic Collaborative Approach document is not a formal guidance; the general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.
Page 7, Table 1, *Main exclusion criteria*	2,5	Comment: This section states allergic and anaphylactic response antibodies or failed ERT in the past, but at the same time an inclusion criterion is treatment naïve patients, so the exclusion criterion (or otherwise the inclusion criterion) seems superfluous. **Comment:** Would this be compatible with inclusion criteria "treatment naïve patients?"	Accepted.
Page 7, Table 1, *Main exclusion criteria*	4	Comment: If a child has severe thrombocytopaenia/active bleeding disorder at presentation, would it be an exclusion criterion?	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.
Page 7, Table 1, *Study duration for participants*	2	Comment: First sentence should be rephrased for clarity i.e. 'Two years of treatment for primary analysis period primary endpoint'	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 7, Table 1, *Study duration for Participants*	5	**Comment:** Please confirm that the proposed duration of the extension is at least 3 years from first administration in the main study.	Partly accepted. The comment is no longer applicable to the revised document.
Page 7, Table 1, *Dosage, treatment regimen, route of administration*	4	Comment: Children with Gaucher's I/III are started on treatment @ 60IU/kg. Careful consideration would be required in relation to criteria and timing of discontinuation within the treatment arm. The approach for ERT in adult Gaucher's in England is to use 30 units/Kg body weight and then increase or reduce the dose depending on the target goals. In certain situations 60 units/Kg body weight can be used. Use of maximum does in the control arm will have effect on the outcomes. Dose: 30iu vs 60iu debate needs evaluating so that a standardised dose is set. The current product used orally in adults is a tablet therefore there is work required to determine what formulation strategy is appropriate for children – both in terms of acceptability of the medicine (e.g. taste if it is a liquid) and the ability to dose adjust to enable accurate therapy for paediatric populations. Proposed change: It is therefore requested that the FDA/EMA include a PKPD model in this proposal to evaluate the 30iu vs 60iu debate, and to allow for the standardisation of dose. A standard dose could then be established as a control arm for the conduct of this study.	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.

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		Oral formulations will be offered in age-appropriate preparations to ensure ability to adjust dose.	
Page 7, Table 1, *Control(s)*	2	Comment: Typo -> 60 U/kg and not 60iu/kg	Partly accepted. The comment is no longer applicable to the revised document.
Page 7, Table 1, *Control(s)*	2	Comment: It should be noted that Cerezyme® (imiglucerase) which is requested as active comparator in the proposed multi-arm non-inferiority study is not approved for use in the US in the treatment of paediatric subjects with Gaucher disease Type III.	Accepted.
Page 7, Table 1, *Control(s)*	5	**Comment:** We strongly suggest that the study design is not biased to a single ERT. Velaglucerase is a widely approved ERT for GD and should be considered as an additional reference compound in this study. With the availability of two dominating ERTs, it seems inadequate to select one of these as the sole comparator.	Accepted.
Page 8, Table 1, *Primary endpoint(s) with time point(s) of assessment*	2	Comment: This does not take into account background treatment for anaemia. Additionally, some of these are stated as secondary endpoints when they could be suitable primary endpoints. An example of an endpoint that could be a primary endpoint is liver and spleen mass. If stratification is added to the primary endpoint(s), the sample size and power calculation should also consider stratification. As a result, the definition of background hematinic usage strata and the haemoglobin information for each stratum will be required for the calculation. Proposed change:	Accepted.

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		In the section 'Primary endpoint(s) with time point(s) of assessment,' suggest changing the text to say the following: "Treatment naïve patients: Change in normalised haemoglobin measurement between baseline and two years, stratified by background hematinic usage."	
Page 8, Table 1, *Primary endpoint(s) with time point(s) of assessment*	4	Comment: Haemoglobin is not considered to be the most appropriate primary outcome as it is not sensitive enough Proposed change: Platelets would be a more appropriate outcome	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.
Page 8, Table 1, *Primary endpoint(s) with time point(s) of assessment*	5	**Comment:** Please see comments above. ERTs are highly efficacious on Hb and novel compounds may have different efficacy profile.	Accepted.
Page 8, Table 1, *Main secondary endpoints with time of assessments*	2, 4	Comment: Liver and spleen size are usually expressed as multiples of normal (MN), which allows for adjustment of (changes in) body weight, and in children of linear growth. Proposed change: Liver and spleen volume (MN) mass… Comment: MRI would be ideal however USS would be acceptable and is more widely available.	Accepted.
Page 8, Table 1,	2	Comment: Assessments of Quality of Life/convenience should be	Accepted. Addressed in 1.4 outcome assessment

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Main secondary endpoints with time of assessments		included, and recommended instruments should be identified.	
Page 8, Table 1, *Statistical Plan*	2	Comment: It should be clarified if it is proposed for the study to remain blinded for the entire 5 year duration. This point is unclear based on the statement: "It is recommended that the long-term monitoring results be analysed in the same way."	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.
Page 8, Table 1, *Measures to minimise pain and distress*	2	Comment: Topical anaesthesia might obscure observations such as infusion site pain. Therefore its use should be recorded in the case report form (CRF). There is no statement regarding the acceptability of pre-medication Proposed change: "Topical anaesthesia should be offered for all venous access procedures and its use documented".	Accepted.
Page 8, Table 1, *External independent data safety monitoring board*	2	Comment: Instead of 'inferiority reasons' is it recommended to refer to 'clinical decline' Proposed change: Early stopping of a treatment arm for clinical decline inferiority reasons should be considered	Accepted.
Page 8, Table 1, *Date of completion*	1, 2	Comment: BIO requests that the Agencies set a more feasible date of study completion in this, and future, Strategic Collaborative Approach documents. We believe that "not	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		later than 2 years after Marketing Authorization in adults" does not accurately account for the time it will take to conduct a paediatric study with the required 2-year study period (primary analysis period). Additionally, this proposed completion timeline underestimates the time it will take to address the complexity (scientific, legal, and logistical) of designing and conducting a multi-company, multi-product study based on the parameters laid out in this Strategic Collaborative Approach (which we believe are likely to be the foundation for future proposals). Proposed change: BIO requests that the Agencies remove the phrase: "Not later than 2 years after Marketing Authorisation in adults" Comment: Taking into account that it may be prudent to defer initiation of a paediatric study until demonstration of adult safety and efficacy and until after obtaining regulatory approval, and further taking into account the requested study duration of 2 years (primary analysis period), it will not be feasible to complete such study within 2 years of Marketing Authorisation in adults. Further, in the framework of a multi-company multi-product study it is assumed that the development timelines of all those products are aligned, which is most probably not the case. With various Marketing Authorisation submission dates for the various products, this means that most probably some companies will not be able to meet the requirement to submit the results of the uniform study on time in relation to their product's MA	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approval. A non-inferiority study with 3 or more treatment arms in a treatment naïve population (especially one with a very limited eligible patient population) poses significant statistical, sample size, and feasibility challenges. It's difficult to reconcile these challenges against the proposed time frame (i.e. 2 years post-MA in adults). Proposed change: Remove 'Not later than 2 years after Marketing Authorisation in adults'	
Page 8, Non-binding elements, *1st bullet*	2	Comment: As to 'The need for stratified randomisation (and analysis) for region' it must be clarified that this depends on the regions/countries involved and if there is a specific regulatory need to be met, for example in the case of Japan. Stratified randomisation by region should not be mandatory.	Not accepted. The multi-arm, multi-company study laid out in Table 1 is a proposal only, and the specifics should be determined following discussions with the individual regulatory agencies if it is deemed appropriate and feasible by both the Sponsors and the regulatory agency.