Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for taliglucerase alfa rpc

Proprietary Product Name: Elelyso

Sponsor: Pfizer Australia Pty Ltd

October 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory committee on prescription medicines
ADA	Antidrug antibodies
AE	Adverse event
AUC	Area under the concentration-time curve
CER	Clinical evaluation report
C_{max}	Maximum concentration
ERT	Enzyme replacement therapy
EU	European Union
GD	Gaucher disease
h	hour/s
ICH	International Conference on Harmonisation of registration requirements for pharmaceuticals for human use (ICH)
IgG	Immunoglobulin G
IV	Intravenous or intravenously
PK	Pharmacokinetic/s
PSC	Pharmaceutical subcommittee
rpc	Recombinant plant carrot
SAE	Serious adverse event
SD	Standard deviation
T_{max}	Time to achieve maximum concentration

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	13 May 2014
Active ingredient:	Taliglucerase alfa rpc[1]
Product name:	Elelyso
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose form:	Powder for injection
Strength:	200 units
Container:	Vial
Pack size:	1
Approved therapeutic use:	*Elelyso is indicated for long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of Type 1 Gaucher disease associated with at least one of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia.*
Route of administration:	Intravenous infusion
Dosage (abbreviated):	Due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage must be individualised to each patient. (see Product Information for full *Dosage and Administration*)
ARTG number:	207695

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Elelyso powder for intravenous (IV) infusion, containing taliglucerase alfa rpc 200 units, for the following indication:

> *Elelyso is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopaenia, bone disease.*

[1] rpc = recombinant plant carrot

Gaucher disease (GD) is a rare genetic disorder that is the most common glycosphingolipid storage disease. It is due to an inherited deficiency of the lysosomal enzyme, β-glucocerebrosidase, which catalyses the hydrolysis of glucocerebroside to glucose and cerebroside (ceramide). Thus in GD there is an accumulation of glucocerebroside within macrophages and subsequent tissue and organ damage in the liver, spleen, bone marrow, skeleton, lungs and occasionally lymph nodes. There is no alternative metabolic pathway. The clinical manifestations include organomegaly, growth retardation, anaemia, thrombocytopaenia and sometimes neurological decline. Untreated, it leads to premature death from bleeding complications, liver disease, sepsis, lung disease, pulmonary hypertension and bone disease.

Taliglucerase alfa acts as an enzyme replacement therapy (ERT) for the lysosomal enzyme, β-glucocerebrosidase.

Taliglucerase alfa (Elelyso) *for long term enzyme replacement therapy for the treatment of Gaucher disease* received orphan drug status by the TGA on 21 March 2011.

Application background

The application to register taliglucerase alfa was first submitted to the TGA in May 2011 (submission number PM-2011-00478-3-3). The sponsor withdrew that application prior to completion of the evaluation phase to allow time to address questions raised by TGA.

The sponsor re-submitted the application (number PM-2013-00303-1-3; the current application) with a new, complete set of quality data and additional, new clinical data. All of the clinical and nonclinical data provided for the first submission (PM-2011-00478-3-3) remained applicable to the current application (also called resubmission) and have been taken into account for this AusPAR.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 21 May 2014.

At the time the TGA considered this application, a similar application had been approved in 8 countries including the USA (1 May 2012), and was under evaluation in 5 countries. Market authorisation for taliglucerase alfa rpc in the European Union (EU) was refused in October 2012 *"due to orphan drug legislation on market exclusivity grounds"*.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

Drug substance (active ingredient)

Taliglucerase alfa is a recombinant form of the human lysosomal enzyme, β-glucocerebrosidase, which catalyses the hydrolysis of glycolipid glucocerebroside to glucose and ceramide. It is a glycosylated protein of 506 amino acids with approximately 7% of its molecular mass of 60496-60882 Dalton (Da) contributed by N-glycans. The amino acid sequence contains 5 potential N-linked glycosylation consensus sites, but only

4 are occupied by glycan chains. There are seven cysteine residues that form two disulfide bonds between the first four cysteine residues and three free sulphydryls (thiols).

This product has the same core amino acid sequence as the registered products Cerezyme (imiglucerase rch) and Vpriv (velaglucerase alfa–ghu) but has different N- and C-terminal sequences and significantly different glycosylation due to the differing cell lines.

Manufacture

The substance is manufactured by a unique process involving propagation of the carrot root cell line. Assurance has been obtained that the manufacturing process is controlled and the drug product is consistent. In-process controls are adequate. Cell banking processes are satisfactory. All viral and prion safety issues have been addressed, including potential use of animal-derived excipients, supplements in the cell culture process and in cell banking.

The purification steps are adequately controlled with respect to loading, washing, elution, regeneration and storage.

During development, a number of manufacturing process changes were made, some of which had (limited) effects on the composition of the product. The accumulated difference in glycosylation meant that batches made by the final commercial process, which have been used in Phase III trials, have different levels of certain glycans to those used in the early stages of the Phase III clinical trials. Analysis of antidrug antibodies (ADA) in patients in the clinical trials indicated the difference was sufficient to trigger a mild if transient immune response in one patient. This issue was brought to the attention of the clinical evaluator.

Physical and chemical properties

The amino acid sequence was confirmed and secondary, tertiary and quaternary structure supported with evidence. Disulphide bonding and N-glycosylation sites were demonstrated. The oligosaccharides were comprehensively profiled and the commercial product shown to be consistently glycosylated. The drug substance was shown to have full enzyme activity and to be taken up into rat alveolar macrophages. Process- and product-related impurities were analysed and either shown to be adequately cleared or adequately controlled by specifications.

The major glycan will direct the product to the lysosome without modification but the xylose and α(1,3) linked fucose are plant-specific sugars reported to be immunogenic in humans and animals. This issue was brought to the attention of the clinical evaluator.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, are satisfactory. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time conditions to characterise the stability profile of the drug substance and to establish a shelf life.

Drug product

Formulation

The drug product is supplied a carton with a single use vial containing 200 U of the enzyme. The powder is reconstituted with water for injection, diluted into saline and infused intravenously over a period of 1-2 h once every two weeks.

Manufacture

The product is manufactured by: thawing of the drug substance; dilution and addition of the formulation components; sterilisation by filtration; aseptic filling into vials; lyophilisation; capping and crimping; visual inspection; storage and labelling.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, are satisfactory.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

The proposed shelf life is two years when stored at 2-8°C. A single thermal cycling study on a single batch was conducted but gave equivocal results. A further study is recommended, as is a temporary registration provision that storage should be maintained at 2-8°C including maintaining a cold chain during transport with an excursion of no more than 96 h at no more than 27°C. No validation studies to Australia have been done. However similar studies of shipping from USA to Brazil and from Germany to Israel have shown that the use of containers with active heating and cooling can maintain 2-8°C for 7-8 days. As it is projected that transit from USA to Australia should be about 5 days, the thermal capacity of the containers would appear to be adequate. It is recommended that at least the initial batches include temperature loggers to confirm these studies are applicable in shipping to Australia.

In-use stability data have also been submitted. Finally approved storage conditions are shown in the PI at Attachment 1.

Biopharmaceutics

Biopharmaceutic data are not required for this product because it is administered intravenously (IV).

Advisory committee considerations

This application was submitted for advice from the September 2013 meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC recommended (in part):

1. The PSC endorsed all the issues raised by the TGA in relation to the quality and pharmaceutic aspects of the submission by Pfizer Australia Pty Ltd to register Elelyso powder for injection containing 200 Units of the new biological entity, taliglucerase alfa (rpc). In particular, the PSC supported the evaluator's questions in relation to the

specification for the mean enzyme activity, the stability of the product and the recommendations regarding storage conditions.

2. The PSC:
   - Agreed that validation batches do not appear to be consecutive batches and advised that the sponsor should be asked to address this [as part of the review of the original submission].
   - Advised that the observed progressive decrease in mean activity of the drug substance over the repeat harvesting of the cell culture is unlikely to have an impact on the drug product.
   - Expressed concern at the lack of Australia-specific validation data on shipping conditions.
3. The PSC considered that clear differences in the levels of some glycoforms between the drug substance in the formulation used in clinical trials and the drug substance in the formulation proposed for registration were such that clinical trial data, specifically on immunogenicity, were no longer relevant given that these were generated using drug product with lower concentrations of fucosylated and xylylated $mannose_3$ glycan.
4. The PSC considered that their concerns in relation to immunogenicity / the action of pre-existing antibodies on the product still remained. The PSC advised that to unequivocally address their concerns, the sponsor should be asked to provide data on antibody status in subjects at baseline and then after treatment with the proposed formulation.
5. The PSC considered the data on transport conditions and, critically, on immunogenicity and the effects of differences in levels of some glycoforms between the clinical trial formulation and the formulation proposed for registration to be inadequate and render the submission unacceptable.

The above recommendations were addressed in subsequent questions from the TGA to the sponsor and follow-up evaluation reports (not shown here).

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. The following evaluations were undertaken:

- Primary
- Genetic development
- Endotoxin safety
- Viral and transmissible spongiform encephalopathies (TSE) safety
- Container safety
- Sterility

The Module 3 (quality) evaluators have no objection to the approval of Elelyso (taliglucerase alfa rpc) 200 units powder for infusion.

In addition to conditions noted above under *Product Stability*, specific conditions of registration regarding batch release testing by the TGA and Certified Product Details (CPDs) were recommended. Details of these are beyond the scope of the AusPAR.

III. Nonclinical findings

Introduction

General comments

The nonclinical data submitted in support of the safety and efficacy of taliglucerase alfa were of high quality and were performed by reputable laboratories. The pivotal, nonclinical safety data were performed according to good laboratory practice (GLP) standards. One shortcoming of the dossier was the absence of any studies demonstrating that taliglucerase alfa was able to reverse the symptoms of β-glucocerebrosidase deficiency in an animal model of GD. Similarly, the toxicity studies were all performed using animals with normal β-glucocerebrosidase activity and did not include studies with an animal model of GD.

Pharmacology

Primary pharmacology

Uptake of taliglucerase alfa by human peripheral blood macrophages, under in vitro culture conditions, was compared with imiglucerase (a mammalian cell line produced form of human β-glucocerebrosidase). The two products showed comparable, dose dependent uptake, which was approximately halved in the presence of mannan (mannose polymer), suggesting that a large component of uptake was attributable to the mannose receptor. Similar experiments were also performed with peripheral blood macrophages from rabbits and cynomolgus monkeys, and with a rat macrophage cell line (the choice of these species reflected their use in the repeat-dose and reproductive toxicity studies). Again, taliglucerase alfa showed dose-dependent uptake into these cells that was substantially inhibited by the presence of mannan.

No pharmacology studies were performed in an animal model of GD.

Secondary pharmacodynamics and safety pharmacology

Specific secondary pharmacodynamics and safety pharmacology studies were not performed. Electrocardiograms recorded prior to and during dosing in marmoset 29 day and cynomolgus monkey 4 and 39 week repeat dose toxicity studies were unremarkable. No clinical signs indicative of central nervous system (CNS) effects were observed in toxicity studies. The lack of specific safety pharmacology studies appears reasonable given the history of successful use of analogues of human β-glucocerebrosidase for ERT of GD and findings in acute and repeat dose toxicity studies at high doses.

Pharmacokinetics

Plasma pharmacokinetics (PK) of taliglucerase alfa were studied as part of repeat dose toxicity studies in marmosets and cynomolgus monkeys. These species were chosen based on the assumption that they would show similar PK to humans. Plasma concentrations of taliglucerase alfa were measured using an enzyme linked immunosorbent assay (ELISA)

that was validated within the quantification range of 3.9 to 250 ng/mL. In both marmosets and cynomolgus monkeys, dosing at supratherapeutic levels (see Table 1) produced greater than dose proportional increases in AUC values suggesting saturation of clearance and/or cellular uptake mechanisms. Terminal half-life values for marmosets ranged from approximately 12 to 50 minutes dependent on taliglucerase alfa dose. Such values are comparable with those reported from human studies (according to the sponsor's nonclinical overview). Repeat dosing with taliglucerase alfa, in both marmosets and cynomolgus monkeys, had no marked effect on PK parameters, although some results suggested induction of clearance mechanisms. For both monkey species, the PK parameters of taliglucerase alfa showed no gender differences.

No tissue distribution, metabolism, or excretion studies were conducted. It is expected that taliglucerase alfa is taken up by cells (such as macrophages) expressing the mannose receptor. It is reasonable to expect that taliglucerase alfa would be degraded to peptides and amino acids. Protein clearance mechanisms are well understood.

Pharmacokinetic drug interactions

Taliglucerase alfa is a protein and would not be expected to interact with co-administered drugs via effects on cytochrome P450 dependent metabolism or xenobiotic transporters.

Toxicology

Acute toxicity

Mice and cynomolgus monkeys were given IV doses of taliglucerase alfa up to 18 mg/kg without significant adverse findings. No acute effects were observed in the repeat dose studies at up to 55 mg/kg in marmosets or at up to 27.8 mg/kg in cynomolgus monkeys.

Repeat-dose toxicity

These studies used marmoset (daily dosing up to 29 days) and cynomolgus monkeys (daily dosing up to 4 weeks and fortnightly dosing up to 39 weeks), of both sexes, given IV infusions of taliglucerase alfa up to 55 mg/kg. The pivotal studies were GLP compliant and consistent with relevant International Conference on Harmonisation of registration requirements for pharmaceuticals for human use (ICH) guidelines. There were no adverse findings that could be attributed to the test article in either species. Both male marmosets and male cynomolgus monkeys showed an increase in spleen weight at the high dose, which reached statistical significance for marmosets. These weight increases were not, however, correlated with histopathological change and were not considered to be of toxicological significance. Repeat dose reproductive toxicity studies in rats showed transient swelling of limbs and/or face at the high dose (see below).

Table 1: Relative exposure for repeat-dose toxicity studies

Species	Study duration	IV Dose (mg/kg)	$AUC_{(0-t)}$ (µg·h/mL) [a]	Exposure ratio (AUC)[b]	Exposure ratio (mg/m^2)[c]
Marmoset	29 days	11[d]	183	334	14
		55[d]	1714	3131	69
Cynomolgus monkey	4 weeks	5.6[d]	61	111	14
		27.8[d]	2050	3,744	70

Species	Study duration	IV Dose (mg/kg)	$AUC_{(0-t)}$ (µg·h/mL) [a]	Exposure ratio (AUC)[b]	Exposure ratio (mg/m^2)[c]
	39 weeks	5.6[e]	76	10	1
		27.8[e]	1783	233	5
Human (patients)	9 months	1.8[d] (60 units/kg)	7.665	–	-

[a]: Average area under the concentration-time curve (calculated from time 0 to final time point) during the study; b: ratios are relative to mean AUC0-t value from Week 38 measurement of trial in patients with GD (protocol no. PB-06-001)- AUC values from daily-dosing monkey studies were multiplied by 14 for comparison with fortnightly dosing in human study; c: ratios are relative to human dose of 1.8 mg/kg/fortnight, adjusted for differences in dosing interval between studies (marmoset and cynomolgus monkey (4 weeks) doses were multiplied by 14 to equate with human dosing interval), and converted from mg/kg to mg/m2 using scaling factors of 6 (marmoset), 12 (cynomolgus monkey), and 37 (human-70 kg); d: mg/kg/day; e: mg/kg/fortnight

Relative exposure

The suggested maximum clinical dose of taliglucerase alfa is 60 units/kg, corresponding to approximately 1.8 mg/kg, to be administered fortnightly by IV infusion. Using the standard human surface area conversion factor of 37, this represents a dose of 66 mg/m^2. A dose of 11 mg/kg in marmosets (using the marmoset conversion factor of 6) or 5.6 mg/kg in cynomolgus monkeys (using a conversion factor of 12) represents a dose of approximately 66 mg/m^2. Calculations of exposure ratios for taliglucerase alfa (molecular weight of approximately 60,800 Da) using mg/m^2 values, rather than mg/kg, are consistent with FDA recommendations (2005[2]).

Comparison of exposure ratios calculated using scaling of dose for body surface area with ratios based on measurements of plasma taliglucerase alfa concentrations, shows that the two values (for both marmoset and cynomolgus monkey data) are markedly discordant (12 to 80 fold differences) (Table 1 above). The high exposure ratio values for the marmoset and cynomolgus monkey four-weeks studies are partly related to the use of daily dosing (compared with fortnightly dosing for humans). Another factor contributing to high exposure in the monkey studies is the apparent saturation of clearance mechanisms at the high doses used.

Genotoxicity and carcinogenicity

Possible genotoxic or carcinogenic action by taliglucerase alfa was not examined by the sponsor. Given taliglucerase alfa's mode of action (that is, breakdown of lysosomal glucocerebroside) and the products of its enzymic action (glucose and ceramide), it appears unlikely that it would have direct genotoxic or carcinogenic activity.

Reproductive toxicity

Possible effects of taliglucerase alfa on fertility and embryofetal development were studied using rats and rabbits. These studies were GLP compliant and used appropriate animal numbers, test article doses, and dosing intervals. The high dose in the rat studies (55 mg/kg; nominal exposure ratio of 20 to 25; see Table 2 below) had no effect on male and female reproductive performance, fertility of both sexes, reproductive indices, or fetal

[2] FDA (2005) Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. <http://www.fda.gov/cder/guidance/index.htm>

development. The high dose of taliglucerase alfa did, however, produce transient swelling of limbs and/or face in rats of both sexes. The occurrence of this response after the first dose in some rats suggested that it was not due to antibody production but was presumably related to histamine release, although its basis was not explored by the sponsor. The rabbit embryofetal development study also revealed no effect of taliglucerase alfa dosing on fetal weights, sex ratios, or embryofetal development. No studies were performed to examine possible placental transfer and excretion in milk. The sponsor argued that such studies were unnecessary because taliglucerase alfa is unlikely (because of its high molecular weight) to cross the placenta by diffusion and because any test article passed in the milk would be digested in the infant's gut.

Table 2: Relative exposure for reproductive toxicity studies

Species	Study	IV Dose (mg/kg)	Mean dosing interval (days)	Exposure ratio[a]
Rat (Sprague Dawley)	Fertility and early embryonic development	11[c]	3.4	4
		55[c]	3.4	20
	Embryofetal development	11[d]	2.75	5
		55[d]	2.75	25
Rabbit (New Zealand White)	Embryofetal development	5.6	3	6
		27.8	3	29

a: Relative to human dose of 1.8 mg/kg/fortnight and using conversion factors (mg/kg to mg/m^2) of 6 (rat- 0.2 kg), 15 (rabbit- 3.0 kg), and 37 (human- 70 kg). To adjust for differences in dosing interval between studies, doses were multiplied by 14 (human dosing interval) and divided by the average dosing interval for that study.

Relative exposure

The sponsor did not measure plasma taliglucerase alfa concentrations in association with the reproductive toxicity studies. Comparison with human exposure, based on body surface area, suggested that high exposure ratios had no effect on fertility or embryofetal development in rats and rabbits (Table 2).

Pregnancy classification

The sponsor has proposed Pregnancy Category B2[3], which is an Australian pregnancy category defined by the absence of adequate reproductive toxicity studies in animals. As the sponsor has provided studies which are adequate in defining the absence of fetal

[3] Definition of category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

damage at high relative exposure levels it is suggested that the Pregnancy Category be changed to B1[4].

Local tolerance

The sponsor did not conduct studies that specifically examined local tolerance of taliglucerase alfa dosing. Injection site changes (scabbing, reddening, and bruising) were noted during repeat dose studies, but these were attributed to the IV infusion technique as they occurred in both control and test article-treated animals.

Antigenicity

Blood samples from the marmoset 29 day and cynomolgus monkey 39 week studies were tested for the presence of anti-taliglucerase alfa antibodies. Six of the eight low dose marmosets (but none of the high dose animals) developed antibodies; as did three of eight low dose and two of eight high dose cynomolgus monkeys. There was no obvious relationship between the development of antibodies and dose, gender, or time. Neutralising antibodies were not detected in any of the antibody-positive animals.

Paediatric use

Taliglucerase alfa is indicated for therapy of both paediatric and adult patients with GD. The sponsor did not, however, conduct studies with juvenile animals and argued that such studies were unnecessary due to the lack of adverse effects of imiglucerase dosing of juvenile patients with GD. Nonclinical studies in juvenile animals are not necessary if safety in paediatric patients has been established by clinical studies.

Comments on the safety specification of the risk management plan

The sponsor has presented an accurate review of the non-clinical studies in version 1.0 of the draft Risk Management Plan, and has suggested that two clinical safety concerns are indicated: (1) local effects at the test article infusion site, and (2) test article-associated swelling (as seen in rats given high doses of taliglucerase alfa). These are considered appropriate from a nonclinical perspective.

Nonclinical summary and conclusions

- The pivotal, nonclinical safety data presented in support of taliglucerase alfa registration were performed by reputable laboratories according to GLP standards.
- Taliglucerase alfa showed dose-dependent uptake into human peripheral blood macrophages, under in vitro culture conditions, that was comparable with imiglucerase (mammalian cell line synthesised form of human β-glucocerebrosidase). The in vivo efficacy of taliglucerase alfa was not, however, demonstrated in a mouse model of GD.
- Secondary pharmacodynamics and safety pharmacology were not examined because of the history of successful use of other forms of human β-glucocerebrosidase for ERT of GD. Repeat dose toxicity studies in monkeys at high IV doses showed no acute effects on CNS or cardiovascular system.

[4] Definition of category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

- Pharmacokinetic studies using marmoset and cynomolgus monkeys, receiving IV doses of taliglucerase alfa, indicated saturation of clearance at high doses. The elimination half-life values for marmosets ranged from approximately 12 to 50 min, dependent on taliglucerase alfa dose, and were comparable with those reported from human studies. Repeat dosing with taliglucerase alfa, in both marmosets and cynomolgus monkeys, had no marked effect on PK parameters, although some results suggested induction of clearance mechanisms. For both monkey species, the PK parameters of taliglucerase alfa showed no sex-dependent differences.
- There were no significant toxicological effects associated with daily IV dosing of marmosets for 29 days or fortnightly IV dosing of cynomolgus monkeys for 39 weeks, at up to 69 and 5 times, respectively, the clinical exposure to taliglucerase alfa. Rats given high doses of taliglucerase alfa in reproductive toxicity studies showed transient swelling of limbs and/or face that was probably related to histamine release.
- Possible genotoxic or carcinogenic action by taliglucerase alfa was not examined. Given taliglucerase alfa's mode of action, its target cells (terminally differentiated), and the assumed lack of genotoxicity of the products of its enzymic action, it would seem unlikely that taliglucerase alfa would have direct carcinogenic activity.
- High exposure ratios of taliglucerase alfa had no effect on male and female rat fertility and reproductive performance, and no effect on embryofetal development in both rats and rabbits.
- A significant fraction of both marmoset and cynomolgus monkeys developed anti-taliglucerase alfa antibodies after several doses of test article. These antibodies were not neutralising and appeared to have no impact on the validity of the toxicity studies.

Conclusions and recommendation

- Taliglucerase alfa showed mannose receptor dependent uptake by macrophages.
- There was no nonclinical study to demonstrate that taliglucerase alfa dosing is able to reverse glycolipid accumulation in tissues.
- Toxicity studies demonstrated no significant toxicological effects (general and reproductive toxicity) associated with taliglucerase alfa dosing in animal species at exposures considerably higher than that anticipated clinically.
- There are no nonclinical objections to the approval of taliglucerase alfa for the proposed indication provided efficacy has been demonstrated in clinical studies.
- The sponsor's draft RMP presented an accurate review of the non-clinical studies.
- Revisions to nonclinical statements in the PI are recommended[5].

IV. Clinical findings: Original submission

A summary of the clinical findings from the original submission is presented in this section. Further details of these clinical findings can be found in Attachment 2 (CER 1).

[5] Details of these are beyond the scope of the AusPAR.

Introduction

Clinical rationale

The clinical rationale for taliglucerase alfa is long-term ERT for the treatment of GD. Following IV infusion, taliglucerase alfa targets and penetrates macrophages through the mannose receptor delivering glucocerebrosidase to the lysosome. This allows the hydrolysis of accumulated glucocerebrosides resulting from reduced activity of the lysosomal enzyme glucocerebrosidase.

Taliglucerase alfa is an analogue of a known human enzyme glucocerebrosidase (GenBank entries M11080 and M16328). The predicted amino acid sequence of taliglucerase alfa differs from the glucocerebrosidase sequence by the addition of amino acids at the N-terminal and C-terminal of the protein, which are introduced by the plant expression cassette. Glucocerebrosidase is a peripheral lysosomal membrane protein that requires an activator molecule (saposin C) and negatively charged phospholipids for optimal activity and, probably, intracellular stability. This enzyme is naturally active in lysosomes and catalyses the hydrolysis of the glycolipid glucocerebroside into ceramide and glucose in subjects not affected by GD. There are no alternative metabolic pathways when glucocerebrosidase activity is deficient. For reasons that remain poorly understood, tissue macrophages are the predominant cell type that accumulate excessive glucocerebroside under enzyme deficient conditions. Consequently, GD is characterised by the presence of lipid-laden macrophages in the liver, spleen, bone, and lungs.

The rationale for taliglucerase alfa includes: GD remains a life-threatening and/or debilitating medical condition; there is a recognised clinical need for effective treatments in Australia; and taliglucerase alfa offers a valuable and reliable alternative therapeutic option for the treatment of patients with GD. The clinical overview states that over the past decade ERT for non-neuronopathic GD has been the treatment of choice for significantly affected patients with this condition (Grabowski and Hopkin 2003[6]). Nevertheless, the clinical overview argues that there are still unmet medical needs within the condition and refers specifically to bone disease and pulmonary hypertension not being successfully addressed by the current ERT, with some of the patients remaining unresponsive to current available therapy. In addition, the sponsor also claims that the plant cell culture system used to produce taliglucerase alfa diminishes the risk of propagation of mammalian infectious agents, associated with the production of imiglucerase in Chinese hamster ovary cells.

> **Evaluator's comment:** In general, the sponsor's clinical rationale for the development of an alternative ERT to the currently approved imiglucerase is acceptable.

Orphan drug designation

Taliglucerase alfa (Elelyso) was designated as an orphan drug *for the treatment of Gaucher disease* on 11 March 2011 by a Delegate of the Secretary, Department of Health and Ageing, Australian Government.

> **Evaulator comment:** The designated orphan drug indication is consistent with that proposed for registration in the current submission. The prevalence of GD in Australia has been estimated to be 1 per 57,000 live births, based on retrospective data both from patient referrals and prenatal diagnosis for the period 1 January 1980 through 31 December 1996 collected from the National Referral Laboratory, Department of Chemical Pathology, Women's and Children's Hospital, Adelaide,

[6] Graboswki GA and Hopkin RJ. Enzyme replacement therapy for lysosomal storage disease: principles practice, an prospects. *Ann Rev Genomics Hum Genet* 2003;4:403-36.

Australia, and from the Division of Chemical Pathology, Royal Brisbane Hospital, Brisbane, Australia (Miekle et al., 1999[7]). Based on the current Australian population of 22 million the maximum prevalence of GD of all types would be 386 people. The Life Saving Drug Program administered by the Australian Government, Department of Health and Ageing has less than 100 people diagnosed with GD.

Contents of the clinical dossier

Clinical data provided in the original submission comprised:

Module 5:

- 8 reports of bioanalytical and analytical methods for human studies (studies MBR05-194, MBR06-154, MBR06-102, MBR07-300, MBR07-378, MBR08-245, MBR09-153, MBR09-180).
- 1 Phase I, non-randomised, open-label, single dose-escalation completed study of taliglucerase alfa in 6 healthy volunteers (Study P-01-2005).
- 1 Phase III, pivotal, multi-centre, randomised, double-blind completed trial to assess the safety and efficacy of two-parallel dose groups of taliglucerase alfa in 31 patients with GD (Study PB-06-001)
- 1 multi-centre, double-blind, ongoing extension trial of PB-06-001 providing interim data only to assess the safety and efficacy of two-parallel dose groups of taliglucerase alfa in patients with GD (Study PB-06-003).
- 1 Phase III, multi-centre, open-label, switchover ongoing trial providing interim data only to assess the safety and efficacy of taliglucerase alfa in up to 30 patients with GD treated with imiglucerase enzyme replacement therapy (Study PB-06-002).
- 2 reports of analyses of data from more than one study (*Efficacy historical comparison and therapeutic goals; and Dose separation post hoc analysis for Studies PB-06-001 and PB-06-003*).
- 1 other ongoing study (PB-06-004) to assess the safety of taliglucerase alfa in patients with GD who require ERT due to a shortage of imiglucerase.
- 91 literature references for background information.

Module 2:

- Clinical overview, Summary of clinical pharmacology, Summary of clinical efficacy, Summary of clinical safety, and literature references.

Paediatric data

The original submission contained no data in paediatric patients. Information on on-going studies in paediatric patients was provided.

Good clinical practice

The sponsor states that the global clinical development program of taliglucerase alfa has been undertaken according to ICH and EU guidelines and is in accordance with the ethical principles of Good Clinical Practice.

[7] Miekle PJ et al., Prevalence of Lysosomal Storage Disorders. *JAMA* 1999; 281:249-254.

Pharmacokinetics

Studies providing pharmacokinetic data

The PK of taliglucerase alfa were assessed in healthy volunteers in one Phase I Study (P-01-2005) and in GD patients in the pivotal Phase III clinical efficacy and safety Study PB-06-001. Neither of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's summary and conclusions on pharmacokinetics

The PK of taliglucerase alfa has been studied in 6 young healthy adult subjects of both sexes (n = 3 males, n = 3 females; Study P-01-2005), and in 30 patients of both sexes with GD (Study PB-06-001). It is considered that the most relevant PK data relate to the patients with GD. The PK data in these subjects relate to the 30 units/kg and the 60 units/kg IV infusion doses of taliglucerase alfa proposed for approval. The basic PK parameters for both these doses were determined at Day 1 and Week 38 using standard non-compartmental methods, and plasma taliglucerase alfa concentrations were measured by a validated assay.

In patients with GD, the plasma concentration of taliglucerase alfa increased rapidly after initiation of the infusion and the T_{max} after both doses was reached prior to the conclusion of the 120 minute infusion at both Day 1 and Week 38. Following T_{max}, plasma concentrations rapidly decreased in what appears to be a bi-phasic fashion reaching baseline levels between 200 and 250 minutes after initiation of the infusion (that is, 80 to 130 minutes after the end of the 120 minute infusion). The data indicate that taliglucerase alfa clearance is rapid and is consistent with uptake of the drug into macrophages via mannose receptors.

Exposure to taliglucerase alfa in patients with GD as assessed by the C_{max} and AUC from time zero to infinity ($AUC_{0-\infty}$) was greater after the 60 units/kg dose than after the 30 units/kg dose, but the increase in exposure was more than dose proportional. This suggests that uptake of taliglucerase alfa into target cells is saturable. The Day 1 and Week 38 exposure data were similar within the 30 units/kg group and within the 60 units/kg, suggesting that taliglucerase alfa does not accumulate with a once every 2 week treatment regimen repeated through to Week 38. Accumulation would be unusual given the mean short half-life of the drug (about 25 to 35 minutes) and the long interval between doses (2 weeks).

The mean half-life of taliglucerase alfa after 30 units/kg was 25.9 and 25.1 minutes at Day 1 and Week 38, respectively, with the corresponding values after 60 units/kg being 25.0 and 34.8 minutes. The half-life results indicate that times are similar for both doses at Day 1, but about 10 minutes longer for the higher dose at Day 38. The mean clearance (CL) of taliglucerase alfa after 30 units/kg was 29.4 and 30.7 L/h at Day 1 and Week 38, respectively, with the corresponding values after 60 units/kg being 20.5 and 19.9 L/hr. The CL results suggest that clearance is slower following the higher dose at both Day 1 and Week 38.

The mean T_{max} of taliglucerase alfa after 30 units/kg was 82.5 minutes at both Day 1 and Week 38, with the corresponding values after 60 units/kg being 86.6 and 95.0 minutes. The T_{max} values were longer for the higher dose at both Day 1 and Week 38. The mean volume of distribution during the terminal elimination phase (Vz) of taliglucerase alfa after 30 units/kg was 17.5 and 16.8 L/h at Day 1 and Week 38, respectively, with the corresponding values after 60 units/kg being 11.7 and 14.4 L/hr. The Vz values were lower for the higher dose at both Day 1 and Day 38.

Overall, there was marked inter-subject variability in the PK parameters for both doses in patients with GD, with the ranges being wide and overlapping for the two doses. However, the mean values for the half-life, CL, Vz and T_{max} values differed for the two doses suggesting non-linear PK for 30 and 60 units/kg doses. There was no marked difference in the half life, CL, Vz and T_{max} parameters as assessed on Day 1 and at Week 38 for either the 30 or 60 units/kg doses.

The PK profile of taliglucerase alfa has not been completely characterised. This is not unusual given that the drug is an orphan with a small number of patients available for study. Pharmacokinetics data were available for young healthy adults with the mean ± standard deviation (SD) age 26 ± 6 years, and patients with GD of mean age of about 36 years (range: 19 to 74). There were no PK data in paediatric, adolescent, or elderly subjects. There were no data comparing PK in males and females with GD. In healthy volunteers it was stated that there was no difference in the PK between males (n = 3) and females (n = 3), but the data confirming this statement could not be located in the study report.

There were no PK data on metabolism or excretion of taliglucerase alfa. The relevant clinical guideline (CHMP/EWP/89249/2004 *Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins*) indicates that while the main elimination pathway should be identified this could be predicted for therapeutic proteins from the molecular size. Therefore, specific studies exploring the main elimination pathway may not be necessary. There are no PK data exploring potential interactions between taliglucerase alfa and other drugs. However, as with other enzyme replacement therapies, drug-drug PK interactions are not expected.

There are no PK data in subjects with hepatic impairment. The sponsor's clinical overview argues that *"despite the fact that all patients with GD have liver involvement most of the patients do not have functional liver impairment so that patients without hepatic dysfunction and GD were not studied due to population relevance"*. The argument is not unreasonable as clearance of taliglucerase alfa is unlikely to be through hepatic metabolism.

There are no PK data in subjects with renal impairment. However, the relevant clinical guideline (CHMP/EWP/89249/2004) indicates that for protein molecules with a molecular weight larger than 50,000 Da elimination through methods other than renal filtration is of greater relative importance. Taliglucerase alfa meets this criterion as it has a molecular weight of approximately 60,000 Da. The clinical overview argues that *"renal impairment is extremely rare in patients with GD, and that when it does occur it is usually in the form of renal hyperfiltration which has no detrimental effect on patients (Becker-Cohen et al., 2005*[8]*)*". In a study of 161 patients with GD, Becker-Cohen et al (2005) found no patients with decreased renal function despite the multi-organ nature of the disease. Glomerular hyperfiltration was observed in a proportion of patients, particularly those with markers of more severe disease, but this did not seem to be associated with a subsequent decline in renal function.

Pharmacodynamics

The submission included no specific studies investigating the pharmacodynamics of taliglucerase alfa in humans. However, the mechanism of action of enzyme replacement therapy for the treatment of GD is well established.

[8] Becker-Cohen R, Elstein D, Abrahamov A, et al. A comprehensive assessment of renal function in patients with Gaucher disease. *Am J Kidney Dis* 2005;46:837–844.

Dosage selection for the pivotal studies

The dose range of taliglucerase alfa of 30 or 60 units/kg was chosen for the pivotal Study PB-06-001 based on previous efficacy and safety study results with commercially available imiglucerase, with supporting nonclinical studies showing comparable potency and safety to that of imiglucerase.

Efficacy

Studies providing efficacy data

Pivotal study

Pivotal efficacy Study PB-06-001 was a Phase III, multi-national (9 countries), multi-centre (11 centres), randomised, double-blind, parallel-group, dose-ranging study was to assess the safety and efficacy of taliglucerase alfa in 30 untreated patients with GD. Patients received an IV infusion of taliglucerase alfa (30 units/kg or 60 units/kg) every two weeks, and the duration of the study was 9 months. At the end of the 9 month treatment period (21 visits, 20 infusions, 38 weeks) eligible patients were offered enrolment in a double blind extension study. The primary efficacy endpoint was the percent change from baseline of spleen volume after 9 months of treatment with taliglucerase alfa. The major secondary efficacy endpoints were the change from baseline at Month 9 of haemoglobin level, liver volume (percent), and platelet count.

Other efficacy studies

- *Study PB-06-002*: An interim analysis of this study was provided. The objective of this ongoing Phase III, multi-centre, open-label, switchover trial is to assess the safety and efficacy of taliglucerase alfa in 30 patients, 2 years or older, with GD who have been receiving imiglucerase (Cerezyme) ERT for at least 2 years at a stable maintenance regimen (dose unchanged) for at least the last six months.
- *Study PB-06-003*: An interim analysis of this study was provided. The objective of this ongoing Phase III, multi-national, multi-centre study is to extend the assessment of safety and efficacy of taliglucerase alfa in up to 60 patients with GD who have completed 9 months of treatment in Studies PB-06-001 or PB-06-002. The total duration of treatment is to be at least 15 months (64 weeks) and no more than 30 months (128 weeks) or until marketing approval has been granted by the appropriate regulatory authority, whichever is earlier.
- *Dose separation post-hoc analyses for taliglucerase alfa*: The objectives of these post-hoc analyses using data from Studies PB-06-001 and PB-06-003 were to compare efficacy endpoints between the 30 and 60 unit/kg doses of taliglucerase alfa after 9 and 12 months of treatment. The primary efficacy endpoint was change from baseline in spleen volume. The secondary efficacy endpoints were changes from baseline in liver volume, platelet count, haemoglobin level, and chitotriosidase activity.
- *Historical comparison:* The objective of this historical data analysis was to review the publicly available data regarding the efficacy of imiglucerase and alglucerase for the treatment of GD by focusing on publications for which the clinical study population and clinical endpoints were as close as possible to those of the pivotal Study PB-06-001. Relevant papers (including reviews) for the historical analysis were identified by a computerised search of the PubMed database, as well as in the websites of European Medicines Agency (EMA) and www.clinicaltrials.gov. This search retrieved 357 papers out of which 305 were written in English and were retained for evaluation. Of these 305 papers, 50 were review articles and the other 255 were original articles.

Evaluator's summary and conclusions on efficacy

The efficacy of taliglucerase alfa for the treatment of GD is based primarily on the data (intent-to-treat (ITT) population) from one pivotal Phase III study in 31 adult patients not previously treated with ERT (Study PB-06-001). Inclusion criteria included splenomegaly greater than 8 times the expected volume and thrombocytopaenia defined as platelet count < 120,000/mm^3, but baseline hepatomegaly and anaemia were not required for inclusion in this study. The pivotal study included two double-blinded doses of taliglucerase alfa, but no placebo or active control. Consequently, it is subject to the well known biases of uncontrolled studies. The sponsor justified the absence of a placebo control on ethical grounds, and this is considered to be acceptable. However, there appeared to be no reason why the study could not have included an active control imiglucerase comparator. The inclusion of a third treatment group would have provided valuable comparative efficacy data for taliglucerase alfa and imiglucerase and assisted in interpretation of the data.

The lack of a control group is mitigated to some extent by the progressive natural history of GD. While the clinical course and life expectancy of patients with non-neuronopathic GD are variable, most often the disease is progressive and symptomatic patients may die prematurely due to sequelae of severe skeletal disease, bleeding complications, infection, liver failure, and severe pulmonary disease (Pastores et al., 2004[9]).Consequently, it is not unreasonable to infer that the observed improvements in the pivotal study are likely to be causally related to treatment with taliglucerase alfa rather than chance occurrences. Furthermore, the efficacy data from the historical analysis in patients with GD treated with ERT (alglucerase, imiglucerase) are consistent with the taliglucerase alfa data from the pivotal study at 9 months (31 patients) and 12 months (26 patients). In addition, the 12 month efficacy data on 26 patients from the pivotal study are consistent with consensus therapeutic goals in patients with GD.

In the pivotal Study PB-06-001, both doses of taliglucerase alfa (30 and 60 units/kg), infused IV over 2 h every 2 weeks for a period of 9 months, statistically significantly reduced spleen volume (primary efficacy outcome) from screening in the ITT population (multiple imputation method for missing data). In the 30 units/kg group (n = 15) the reduction in spleen volume from screening at 9 months was 26.91% ($p < 0.0001$), and in the 60 units/kg group (n = 16) the corresponding reduction was 38.01% ($p < 0.0001$). The study was powered on a reduction in spleen volume of 20%, suggesting that the reductions at Month 9 were clinically significant for both dose groups.

In the pivotal Study PB-06-001, reductions in liver volume (major secondary endpoint) from screening at Month 9 were statistically significant for both the 30 units/kg dose (10.48% [n = 14], $p = 0.0041$) and the 60 units/kg dose (11.11% [n = 16], $p < 0.0001$), but the reductions were of doubtful clinical significance. However, baseline hepatomegaly was not an inclusion criterion for the pivotal study. In a post hoc analysis of patients with hepatomegaly in the pivotal study, reductions in liver volume from baseline at Month 9 were 14% in both the 30 units/kg group (n = 10) and the 60 units/kg group (n = 6). The study was powered on a reduction in liver volume of 11%, which suggests that the reductions in liver volume at Month 9 in patients with baseline hepatomegaly in both dose groups were clinically meaningful.

In the pivotal Study PB-06-001, mean baseline haemoglobin levels (major secondary efficacy endpoint) were within normal limits for both dose groups and increased in both groups over 9 months. The change in haemoglobin level from baseline to Month 9 was statistically significant for both the 30 and 60 units/kg dose groups (1.6 g/dL [n = 14], $p = 0.0010$ and 2.2 g/dL [n = 15], $p < 0.0001$), respectively). However, baseline anaemia

[9] Pastores, G., Weinreb, N. et al. Therapeutic goals in the treatment of Gaucher disease. *Semin Hematol* 2004;41:(4 Suppl 5): 4-14.

was not an inclusion criterion for the pivotal study. In a post hoc subgroup analysis in all patients with baseline anaemia (n = 10) in the pivotal study, the percentage increase in baseline haemoglobin level at Month 9 was 36.0%. The study was powered on an increase in haemoglobin level of 16%, which suggests that the increase in patients with baseline anaemia was clinically meaningful.

In the pivotal Study PB-06-001, the platelet count (major secondary efficacy endpoint) increased from baseline at Month 9 by 41,494/mm^3 ($p < 0.0031$) in the 60 units/kg (n = 16) and by 11,427/mm^3 ($p = 0.0460$) in 30 units/kg (n = 15). The result for the 30 units/kg group was not statistically significant as the increase from baseline failed to meet the pre-specified alpha significance level of 0.025. In an ad hoc analysis, the increase in platelet count from baseline at Month 9 was 72.1% in the 60 units/kg group and 13.7% in the 30 units/kg group. The study was powered on an increase in platelet count of 46%, which suggests the increases in platelet count at Month 9 were clinically meaningful for the 60 units/kg dose but not for the 30 units/kg dose.

In a post hoc dose separation analysis of the efficacy data from the pivotal Study PB-06-001, the 60 unit/kg dose was statistically significantly superior to the 30 units/kg dose at Month 9 and Month 12 as regards the primary efficacy endpoint of reduction in spleen volume from baseline. Similarly, the higher dose was statistically significantly superior to the lower dose at Month 9 and Month 12 as regards the secondary efficacy endpoint of increase in platelet count from baseline. However, there were no statistically significant differences between the two doses from baseline at Month 9 or Month 12 as regards changes in liver volume (reduction) and haemoglobin level (increase).

Supportive efficacy data for taliglucerase alfa was provided from an interim analysis in 15 (60%) of 25 patients enrolled in an ongoing Phase III switchover Study PB-06-002. In this study, patients with stable GD who have been treated with imiglucerase for at least 2 years, and have been on a stable dose for at least six months prior to enrolment, are switched over to taliglucerase alfa administered at a starting dose equivalent to their stable imiglucerase before the switch. The total duration of treatment with taliglucerase alfa is 9 months and the maximum dose is 60 units/kg. No primary efficacy endpoint was defined in this study. The efficacy outcome of main interest was whether patients deteriorated clinically during treatment with taliglucerase alfa as assessed by protocol specified changes in platelet count, haemoglobin level, spleen volume and liver volume. The control is the patient's historical status while on imiglucerase therapy. The data showed that in 15 adult patients with GD, there was no clinically significant deterioration after 9 months of treatment with taliglucerase alfa after switching from imiglucerase. The mean reductions from baseline (stable) to Month 9 in spleen and liver volumes were 5.1% and 1.4%, respectively, while haemoglobin levels and platelet counts also remained stable.

Supportive efficacy data for taliglucerase alfa was also provided from an interim analysis in 26 patients from the pivotal Phase III Study PB-06-001 enrolled in the ongoing Phase III extension Study PB-06-003. No patients from Study PB-06-003 were included in the interim efficacy analysis. The extension study plans to enrol up to 60 patients with GD who have completed 9 months treatment with taliglucerase alfa in Studies PB-06-001 or PB-06-002. The total duration of treatment in the extension study is planned to be at least 15 months (64 weeks) and no more than 30 months (128 weeks) or until marketing approval has been granted by the appropriate regulatory authority, whichever is earlier. The interim analysis was not defined in the study protocol, but was provided by the sponsor as supportive data for marketing applications at the request of the US FDA. The taliglucerase alfa doses were the same as allocated in Study PB-06-001 (30 or 60 units/kg), or the same dose received at the completion of Study PB-06-003. The spleen and liver volumes were measured at Day 1, which corresponds to the final visit (Month 9) of the predecessor trial, and at Month 3 of treatment, representing a total of 12 months treatment with taliglucerase alfa for patients from Study PB-06-001. The results from this study showed

that patients who improved following 9 months treatment in the pivotal Study PB-06-001 maintained this improvement for a further 3 months in the extension Study PB-06-003. The extension study also suggested that patients in the 60 units/kg dose group did better than patients in the 30 units/kg dose group.

The submission included a historical analysis which compared efficacy data for imiglucerase or alglucerase from published articles with efficacy data from the pivotal Study PB-06-001. This analysis showed that changes from baseline at 12 months in the historical data for imiglucerase or alglucerase at doses of 15 to 60 units/kg were similar to changes from baseline at 9 months in the pivotal study (n = 31) for both the 30 and 60 units/kg doses. This similarity was shown for the efficacy outcomes of percentage reductions in spleen and liver volume, and percentage increases in platelet count and haemoglobin level. This comparison for these outcomes was supported by that between the historical efficacy data at 12 months and the 12 month efficacy data (that is, additional 3 months of treatment) from 26 patients from the pivotal study who were included in extension Study PB-06-003. In addition, the sponsor also undertook a comparison between the 12 month efficacy data on the 26 patients from the pivotal study who were included in extension study PB-03-006 and consensus therapeutic goals at 12 months (Pastores et al., 2004). In general, this comparison showed that treatment with taliglucerase alfa (particularly at the 60 units/kg dose) satisfied the consensus therapeutic goals.

In summary, it is considered that the efficacy results for taliglucerase alfa for the treatment of non-neuronopathic GD in adults are promising. However, the submission included pivotal efficacy data following 9 months treatment with taliglucerase alfa on only 31 patients (Study PB-01-001). Supportive efficacy data on 26 of these patients were available following a further 3 months of treatment from the interim analysis of extension Study PB-06-003 giving a total of 12 months treatment for these patients. However, the extension study aims to provide efficacy data in up to 60 patients from Studies PB-06-001 and PB-06-002 following at least 15 months treatment (that is, a total of 64 weeks) and up to 30 months treatment (that is, a total of 128 weeks), depending on whether marketing approval by the appropriate regulatory authorities is granted prior to the planned treatment durations being reached. Consequently, the interim analysis of the extension study only includes limited and preliminary data from the planned study. Further supportive efficacy data from the interim analysis of the switchover Study PB-02-001 were available on 15 patients who had been treated with taliglucerase alfa for 9 months following switchover from imiglucerase. However, the switchover study aims to provide efficacy data on 30 patients treated with taliglucerase alfa for 9 months after being switched from imiglucerase. Consequently, the interim analysis of the switchover study only includes data on about half of the total number of patients planned for the final analysis.

The small number of patients with efficacy data in the submission is a function not only of the limited number of patients available for study due to the rarity of GD, but also of the results of two interim rather than final analyses being presented for evaluation. Taken together, the two interim analyses include data on about half of the total number of patients planned for the final analyses of the extension and switchover studies. In the absence of a controlled efficacy study with imiglucerase, and because total patient numbers for efficacy evaluation are so small, it is considered that the final data from the extension and switchover studies should be evaluated in order to confirm the promising results observed with taliglucerase alfa.

Safety

Studies providing evaluable safety data

The studies providing safety data in support of taliglucerase alfa for the treatment of GD, as of 30 June 2010, is summarised below in Table 3. The data includes 89 subjects (6 healthy volunteers from one PK study and 83 GD patients from four clinical trials). The safety data from the 6 healthy subjects in the PK study included adverse events (AEs), general infusion related toxicities, physical examination including changes in vital signs and body weight, and laboratory tests. In general, the safety data for the 6 healthy subjects are consistent with that for patients with GD, and examination of the small amount of safety data in 6 healthy subjects does not give rise to additional safety concerns beyond those observed for patients with GD. Consequently, the safety data from the 6 healthy subjects were not discussed and the focus of the clinical evaluator was on the 83 predominantly Caucasian patients (n = 79) with GD treated with taliglucerase alfa, of whom 77 were aged 18 to 65 years and 6 were aged > 65 years.

Table 3: Studies providing safety information for taliglucerase alfa.

Study ID (Phase)	Design Control Type	Study Objective	Study and Control Drug Dose, Route and Regimen	Subjects by Arm Completed/ Entered	Duration of Treatment	Study Population Inclusion Criteria
Completed Studies						
P-01-2005 (Phase 1)	Non-randomised, open-label, single-dose escalation	Safety and PK	Day 1: vehicle Day 8: 15 U/kg taliglucerase alfa Day 15: 30 U/kg taliglucerase alfa Day 22: 60 U/kg taliglucerase alfa IV	6/6	3 single dose; 1 week apart	Healthy subjects
PB-06-001 (Phase 3)	Randomised, double-blind, parallel group trial 2 parallel dose groups	Safety and efficacy and PK	Group 1: 30 U/kg Group 2: 60 U/kg IV Every 2 weeks	29/32 LPLV: September 2009	9 months	Untreated patients with Gaucher disease Age 18 or older Leukocyte glucocerebrosidase activity level ≤3 nmol/mg*hr Splenomegaly eight times the expected volume Thrombocytopenia No ERT in past 12 months
Ongoing Studies						
PB-06-002 (Phase 3) *[safety cut-off date: 15 August 2010]*	Open-label, Switchover trial	Safety and efficacy	Same dose as imiglucerase dose	16/25	9 months	Patients with stable Gaucher disease currently treated with Cerezyme under a stable maintenance regimen
PB-06-003 (Phase 3)	Double-blind* extension study	Safety and efficacy	Same dose as received during PB-06-001 or PB-06-002	26 + 5 =31	15 months	Eligible patients from PB-06-001 and PB-06-002
PB-06-004 EAP	Open-label, expanded access trial	Safety	Same dose as imiglucerase before reduction or discontinuation due to drug shortage	26	38 weeks	Age 18 years or older Diagnosis of GD treated historically with imiglucerase

Source: Module 2, Summary of Clinical Safety [2.7.4], Table 2.7.4-1, page 10.
Abbreviations: U= unit; NA= not applicable; GD: Gaucher disease; LPLV: last patient, last visit; ERT: enzyme replacement therapy; EAP: expanded access program; CUP: compassionate use programs; MA: marketing authorization.
* This study will be modified as an open-label extension when PB-06-001 will be unblinded.

Patient exposure

The exposure data in GD patients from the four clinical trials who received treatment with taliglucerase alfa IV are summarised below in Table 4.

Table 4: Total taliglucerase alfa exposure in GD patients from the completed pivotal clinical Study PB-06-001, ongoing supportive clinical Studies PB-06-002, PB-06-003, and expanded access program PB-06-004.

Months of treatment													
Study	#*	3	6	9	12	15	18	21	24	27	30	33	36
PB-06-001	32	31	29	29									
PB-06-002	25	25	24	16									
PB-06-003	31					30	27	23	15	3	2	1	
PB-06-004	26	16	6										
Total	83	72	59	45	30	27	23	15	9	3	2	1	

*Number of subjects enrolled and treated as of June 30, 2010 for all studies except PB-06-002, which is August 30, 2010.

Post-marketing experience

No post-marketing data are available on taliglucerase as the drug had not been approved for marketing in any country.

Safety issues with the potential for major regulatory impact

- *Liver toxicity*: There was no evidence of liver toxicity associated with taliglucerase alfa in the submitted safety data.
- *Haematological toxicity*: There was no evidence of haematological toxicity associated with taliglucerase alfa in the submitted safety data.
- *Serious skin reactions*: There was no evidence of serious skin reactions associated with taliglucerase alfa in the submitted safety data.
- *Cardiovascular safety*: There was no evidence of cardiovascular toxicity associated with taliglucerase alfa in the submitted safety data.
- *Unwanted immunological events*: Overall, in the total safety population (n = 83), 4 (4.8%) patients experienced a hypersensitivity reaction and 1 (1.2%) developed a fixed drug eruption during the taliglucerase alfa infusion. In addition, 1 (1.2%) patient developed oesophageal pain and delayed erythema under the eyes and blepharitis, symptoms which the sponsor considered not to be typical of a Type I sensitivity reaction, but which responded to pre-treatment with diphenhydramine 50 mg IV Overall, 3 (6.4%) of 47 patients tested positive for anti-taliglucerase alfa IgG.
- *Pregnancy*: Although pregnancy was an inclusion criterion in all studies, one female patient in the pivotal study became pregnant at Week 18 of the study and was withdrawn from the study. The patient delivered a normal baby girl. The spouse of a male patient in this study became pregnant while he was being treated and also went on to deliver a normal baby girl.

Evaluator's summary and conclusions on safety

The submission included safety data at the cut-off date of 30 June 2010 on 83 adult patients with GD who have been exposed to taliglucerase alfa, including safety data on 59 patients exposed for 6 months and 30 patients exposed for 12 months. The "rule of threes" suggests that 30 patients exposed to taliglucerase alfa for 12 months will identify treatment related AEs occurring with an incidence of 10% (with 95% confidence) (Jovanovic and Levy, 1997[10]). Consequently, the 12 month safety population is too small to allow identification of AEs occurring with an incidence of < 10% with taliglucerase alfa over this time interval. The "rule of threes" suggests that the overall safety data in 83 patients exposed to taliglucerase alfa will identify AEs occurring with an incidence of about 3.5% (with 95% confidence). Consequently, the total population exposed to taliglucerase alfa at any dose and for any duration is too small to allow identification of AEs occurring with an incidence of < 3.5%.

The TGA adopted guidelines relating to the extent of population exposure to assess clinical safety for medicines intended for long term treatment of non-life-threatening conditions (CPMP/ICH/375/95. ICH Topic E 1. *Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety*) anticipates that the total number of patients treated with an investigational drug will be 1500, with 300 to 600 exposed for 6 months and a minimum of 100 exposed for 1 year. The number of patients exposed to taliglucerase alfa in the current submission is well below the ICH specified target figures. However, the guideline also states that *"[I]n some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small."* Consequently, the guidelines appear to accommodate applications to register orphan drugs where the intended treatment population is small. Furthermore, the ICH E1 guidelines are not strictly applicable to the current submission as non-neuronopathic GD can be considered to be a life-threatening condition.

In the overall safety population, 83 patients with GD treated with taliglucerase alfa experienced a total of 526 AEs (518 mild or moderate, 12 severe or very severe, 5 serious AEs (SAEs), 392 treatment related, 134 not treatment related). Of the 83 patients, there were 72 (86.7%) with at least 1 AE irrespective of relationship to treatment. The most common AEs reported in taliglucerase alfa treated patients (occurring in ≥ 3 % of patients) were: headache (20.5%, n = 17), arthralgia (16.9%, n = 14), fatigue (12.0%, n = 10), nasopharyngitis (12.0%, n = 10), upper respiratory tract infection (10.8%, n = 9), back pain (9.6%, n = 8), influenzae (8.4%, n = 7), nausea (7.2%, n = 6), infusion related reactions (7.2%, n = 6), pharyngitis (7.2%, n = 6), pharyngolaryngeal pain (7.2%, n = 6), pain (6.0%, n = 5), pyrexia (6.0%, n = 5), gastroenteritis (6.0%, n = 5), urinary tract infection (6.0%, n = 5), cough (6.0%, n = 5), erythema (6.0%, n = 5), pruritus (6.0%, n = 5), abdominal pain (4.8%, n = 4), constipation (4.8%, n = 4), diarrhoea (4.8%, n = 4), asthenia (4.8%, n = 4), lymphadenopathy (3.6%, n = 3), and spleen disorder (3.6%, n = 3). Of the 83 patients, 31 (37.3%) experienced at least one treatment related AE. The most common treatment related AEs in patients treated with taliglucerase alfa (occurring in ≥ 5% of patients) were infusion related reactions (6%, n = 5) and headache (6%, n = 5).

Hypersensitivity reactions during the taliglucerase alfa infusion occurred in 4.8% (n = 4) of the 83 patients in the safety population, and 1 patient developed a fixed drug eruption during the infusion. None of the patients with hypersensitivity reactions were reported to have developed anti-taliglucerase alfa immunoglobulin G (IgG) antibodies. The 2 patients with hypersensitivity reactions in Study PB-06-001 were discontinued from treatment. The 2 other patients with hypersensitivity reactions (1 from Study PB-06-003 and 1 from Study PB-06-004) were reported have continued to receive treatment with taliglucerase alfa but with appropriate pre-infusion anti-allergy medication, while the 1 patient with the

[10] Jovanovic BD and Levy PS. A look at the rule of three. *The American Statistician* 1997;51(2):138-139.

fixed-drug eruption was reported to have continued treatment with taliglucerase alfa without modification.

Anti-taliglucerase alfa IgG antibodies were detected in 6.3% (2/32) of patients tested at the end of pivotal Study PB-06-001, and neutralising antibodies were negative in both IgG antibody positive patients. In Study PB-06-002, 6.7% (1/15) of patients were anti-taliglucerase alfa IgG antibody positive, and neutralising antibodies were negative in this patient. None of the 3 patients identified in the submission who were IgG antibody positive were reported to have experienced a hypersensitivity reaction. In the data to date, the presence of anti-taliglucerase alfa IgG antibodies has not been found to predict the development of hypersensitivity reactions.

There were no deaths reported in the 83 patients, while SAEs (immune thrombocytopaenia; epistaxis; renal stone; prolapsed rectum, bladder and cervix) were reported in 4 (4.8%) patients. Discontinuations occurred in 2 patients in Study PB-06-001 due to hypersensitivity reactions, and no patients in Studies PB-06-002 and PB-06-003. There was no evidence in the submission of a causal association between significant biochemical or haematological toxicities and taliglucerase alfa. Similarly, there was no evidence in the submission of causal association between taliglucerase alfa and hepatic toxicity, renal toxicity or cardiovascular toxicity.

The data from the pivotal study suggests that there is no clinically significant difference in the safety profiles of the 30 units/kg and the 60 units/kg doses of taliglucerase alfa. The most commonly experienced AE in both dose groups was headache, which occurred in 6 patients (1 in the 30 units/kg group; and 5 in the 60 units/kg group), and 5 patients each had pharyngitis and upper respiratory tract infection (taliglucerase alfa 30 U/kg, 3 in the 30 units/kg group; 2 in the 60 units/kg group), all the AEs resolved without sequelae by the end of the study.

There are no specific safety data relating to drug-drug interactions and special groups such as the elderly (aged ≥ 65 years), and patients with hepatic, renal, or cardiovascular disease. While patients with newly diagnosed GD are unlikely to be elderly, it is possible that younger patients in whom successful treatment is initiated will continue treatment to 65 years or beyond. Furthermore, despite there being no specific safety data relating to drug-drug interactions and special groups it is considered that the absence of such data should not preclude approval.

First round benefit-risk assessment: Original submission

First round assessment of benefits

The single pivotal study showed in adult patients with non-neuronopathic GD treated with taliglucerase alfa statistically significant improvements from baseline at 9 months in spleen volume, liver volume, haemoglobin level, and platelet count. The primary efficacy outcome was the percentage change in spleen volume from baseline at month 9, and the major secondary efficacy endpoints were the changes from baseline at month 9 in percentage liver volume, haemoglobin level and platelet count. In addition, reductions in chitotriosidase activity from baseline at month 9 were also statistically significant following treatment with taliglucerase alfa, while exploratory efficacy endpoints relating to bone mineral density and quantitative chemical shift imaging (QCSI) showed numerical trends towards improvement. Although the pivotal study indicated that both the 30 units/kg and the 60 units/kg doses of taliglucerase alfa are efficacious, the post-hoc dose separation analysis suggests that the higher dose is more effective than the lower dose following 9 and 12 months of treatment.

In the pivotal Study PB-06-001, treatment of non-neuronopathic GD in adult patients with taliglucerase alfa for 9 months was associated with statistically and clinically significant reductions from screening in the primary efficacy endpoint of spleen volume of 26.91% ($p < 0.0001$) in the 30 units/kg group (n = 15) and 38.01% ($p < 0.0001$) in the 60 units/kg group (n = 16).

In the pivotal study, mean baseline haemoglobin levels were within normal limits for patients in both treatment groups. The baseline levels statistically significantly increased following 9 months treatment by 1.6 g/dL ($p = 0.0010$) in the 30 units/kg group (n = 14) and 2.2 g/dL ($p < 0.0001$) in the 60 units/kg group (n = 15). In an ad hoc analysis, the increases in haemoglobin levels from baseline to Month 9 were 14.6% in the 30 units/kg group and 22.2% in the 60 units/kg group. Although the percentage increase from baseline in patients treated with the 60 units/kg dose was greater than the pre-specified clinically significant percentage increase of 16%, both baseline and post-treatment haemoglobin levels in the treatment group were within normal limits. Consequently, the statistically significant increases in haemoglobin levels from baseline at Month 9 for both doses are of doubtful clinical significance. However, in a post hoc subgroup analysis of all patients who were anaemic at baseline (n = 10), mean haemoglobin levels increased from baseline of 9.5 g/dL (range: 5.5 to 10.7) to Month 9 of 12.7 g/dL (range: 8.6 to 15.4), while the haemoglobin level increased from baseline to Month 9 by 36.0%.

In the pivotal study, reductions in liver volume from screening at Month 9 were statistically significant for both the 30 units/kg dose (10.48% (n = 14), $p = 0.0041$) and the 60 units/kg dose (11.11% (n = 16), $p < 0.0001$), but the observed reductions were of doubtful clinical significance. However, in a post hoc subgroup analysis of patients with hepatomegaly at screening the reductions in liver volume from baseline at Month 9 were 14% in both the 30 units/kg group (n = 10) and the 60 units/kg group (n = 6).

In the pivotal study, the platelet count increased from baseline at Month 9 by 41,494/mm^3 ($p < 0.0031$) in the 60 units/kg (n = 16) and by 11,427/mm^3 ($p = 0.0460$) in 30 units/kg (n = 15). The result for the 30 units/kg group was not statistically significant as the increase from baseline failed to meet the meet the pre-specified alpha significance level of 0.025. In an ad hoc analysis, the increase in platelet count from baseline at Month 9 was 72.1% (clinically significant) in the 60 units/kg group, and 13.7% (not clinically significant) in the 30 units/kg group.

The efficacy results observed in the pivotal study were supported by the interim results of the switchover from imiglucerase Study PB-06-002, and the extension Study PB-06-003. In addition, the data from the historical analysis suggests that taliglucerase alfa and alglucerase or imiglucerase have similar efficacies as regards reductions in spleen and liver volumes, and increases in haemoglobin levels and platelet counts. Furthermore, a post-hoc analysis of the efficacy outcomes at 12 months in 26 patients from the pivotal study showed that taliglucerase alfa can achieve consensus therapeutic goals.

First round assessment of risks

The submission included safety data at the cut-off date of 30 June 2010 on 83 adult patients with non-neuronopathic GD who have been exposed to taliglucerase alfa, including safety data on 59 patients exposed for 6 months and 30 patients exposed for 12 months. Of the 83 patients, there were 72 (86.7%) patients with at least 1 AE irrespective of relationship to treatment.

Details of AEs, including most common AEs (occurring in ≥ 3% of patients) and SAEs, and of deaths and discontinuations are shown above under *Evaluator's summary and conclusions on safety*. In summary:

- There were no deaths reported in the 83 patients, while SAEs were reported in 4 (4.8%) patients;

- Discontinuations occurred in 2 patients in Study PB-06-001 due to hypersensitivity reactions;
- There was no evidence in the submission of a causal association between significant biochemical or haematological toxicities and taliglucerase alfa;
- There was no evidence in the submission of a causal association between taliglucerase alfa and hepatic toxicity, renal toxicity or cardiovascular toxicity;
- Infusion reactions occurring during or after the taliglucerase alfa infusion were reported in 45.8% (n=38) of the 83 treated patients;
- Hypersensitivity reactions during the taliglucerase alfa infusion occurred in 4.8% (n=4) of the 83 patients in the safety population, and 1 patient developed a fixed drug eruption during the infusion;
- Anti-taliglucerase alfa IgG antibodies were detected in 6.3% (2/32) of patients tested at the end of pivotal Study PB-06-001, and neutralising antibodies were negative in both of IgG antibody positive patients. In the data to date, the presence of anti-taliglucerase alfa IgG antibodies has not been found to predict the development of hypersensitivity reactions.

First round assessment of benefit-risk balance

The submitted data suggest that the benefit-risk balance of taliglucerase alfa is favourable given the proposed usage, but it is considered that this should be confirmed by evaluation of the final efficacy and safety data from pivotal Study PB-01-001 and supportive Study PB-02-001.

First round recommendation regarding authorisation: Original submission

It is recommended that the application to register taliglucerase alfa should be rejected due to the absence of final efficacy and safety data from pivotal Study PB-01-001 and supportive Study PB-02-001. It is considered that the efficacy and safety of the drug for the treatment of GD can only be satisfactorily established by evaluation of the final data from these two studies.

The submission included interim pivotal efficacy data following 9 months treatment with taliglucerase alfa on only 31 patients, and there was no active control group to assist interpretation of the data [Study PB-01-001]. Supportive interim efficacy data on 26 of the 31 patients who successfully completed 9 months treatment in the pivotal study were available following a further 3 months of treatment from the extension Study PB-06-003. Further supportive interim efficacy data from switchover Study PB-02-001 were available on 15 patients who had been treated with taliglucerase alfa for 9 months following switchover from imiglucerase. The small number of patients with efficacy data in the submission is a function not only of the limited number of patients available due to the rarity of non-neuronopathic GD, but also of interim rather than final data from the two supportive studies being presented for evaluation. The interim analyses appear to include data on about half the number of patients planned for the final analyses. In the absence of a controlled efficacy study with imiglucerase, and because total patient numbers for efficacy evaluation are so small, it is considered that the final data from the extension and switchover studies should be evaluated in order to confirm the promising results observed with taliglucerase alfa.

The submitted interim safety data showed that taliglucerase alfa was generally well tolerated at the doses proposed for approval. The interim data from the pivotal study suggested that there was no clinically significant difference in the safety profiles of the 30 and 60 units/kg doses. However, the safety data are limited by the small number of

patients with non-neuronopathic GD who have been exposed to the drug. The total number of patients exposed to the drug for 12 months is insufficient to satisfactorily identify AEs occurring with an incidence of less than 10% at 12 months. In addition, the total number of patients exposed to taliglucerase alfa is insufficient to satisfactorily identify AEs occurring at an incidence of less than 3.5%. It is considered that the promising safety data identified in the interim analyses of the submitted studies should be confirmed by analyses of the final safety data from these studies before approval is granted.

In the event of the application to register taliglucerase alfa being approved on the basis of the submitted data, it is recommended that it should be a condition of registration that the sponsor submit the final study reports for the pivotal and supportive studies to the TGA, as evaluable data within the context of a category 1 [registration] submission, as soon as these reports become available.

Clinical questions: Original submission

Pharmacokinetics

What were the reasons for the anomalous PK results in one subject (outlier) in the pilot study in normal healthy subjects (Study P-01-2005)?

Other relevant clinical matters

- When will the analyses of the final efficacy and safety data from the pivotal and supportive studies be available?
- What was the nature of the clinical deficiencies in the US new drug application (NDA) submission identified in the FDA's Complete Response Letter (CRL) to Protalix (the sponsor of taliglucerase in the US)?
- What actions have been undertaken by the sponsor to address the clinical deficiencies in the US NDA identified by the FDA in its CRL to Protalix?

Second round evaluation of clinical data submitted in response to questions: Original submission

The sponsor's response to the question on PK was satisfactory. The PK of taliglucerase are highly variable in both healthy volunteers and patients with GD as demonstrated by the high coefficient of variation (CV%) values for both the C_{max} and the AUC to the last measurable time point (AUC_{last}).

The sponsor's responses to additional clinical questions (above) and the clinical evaluation of these responses are shown under *Second round evaluation of clinical data submitted in response to questions* in Attachment 2 (CER 1) of this AusPAR.

The sponsor's response to TGA questions included updated clinical efficacy and safety reports from two ongoing supportive Studies PB-06-002; PB-06-003, and updated immunogenicity data from Studies PB-06-001, PB-06-002 and PB-06-003, based on new IgG assay cut-points, an updated SCS, and additional information relating to the updated immunogenicity data. The evaluation of these additional data is shown under *Second round evaluation of clinical data submitted in response to questions* in Attachment 2 (CER 1) of this AusPAR. Summaries of these additional data are incorporated in the *Second round benefit-risk assessment: Original submission*, below.

Second round benefit-risk assessment: Original submission

Second round assessment of benefits

The clinical evaluator considered that the totality of the efficacy data provided in the initial submission and in the sponsor's response to TGA questions have satisfactorily established the benefits of taliglucerase alfa for the treatment of GD.

The clinical study program (Studies #001, #002, #003, #004, #005[11]) includes efficacy data following treatment with taliglucerase alfa from about 57 patients at 9 months, 31 patients at 12 months, and 26 patients at 24 months. These patient numbers are small, but are considered adequate for this particular orphan drug (taliglucerase alfa). The efficacy data show that taliglucerase alfa can achieve and maintain meaningful clinical benefits in patients naïve to ERT treatment, and maintain clinical benefits in patients treated with imiglucerase (approved for the treatment of GD) after switching to taliglucerase alfa.

The initial data from completed pivotal Study #001 in 31 ERT naïve patients showed that treatment with taliglucerase alfa at doses of 30 units/kg (n = 15) and 60 units/kg (n = 16) achieved meaningful clinical benefits following 9 months treatment. Furthermore, the updated efficacy data from ongoing extension Study #003 demonstrated that the benefits in ERT naïve patients achieved after 9 months treatment with taliglucerase alfa were maintained for at least 24 months in 26 patients continuing from Study #001 (30 units/kg, n = 12; 60 units/kg, n = 14).

In addition, the updated efficacy data from supportive Study #002, showed that the clinical benefits achieved in patients following imiglucerase treatment for at least 2 years could be maintained for 9 months after switching to taliglucerase alfa (n = 25). Furthermore, the updated efficacy data from ongoing extension Study #003 showed that the benefits observed after 9 months treatment with taliglucerase alfa after switching from imiglucerase could be maintained for at least another 3 months (that is, a total of 12 months) in 7 patients.

In the initial dossier, the single pivotal Study (#001) showed that adult patients (n = 31) with GD treated with taliglucerase alfa had statistically significant improvements from baseline at 9 months in spleen volume, liver volume, haemoglobin level, and platelet count. The efficacy results observed in the pivotal study were supported by the efficacy data from the ongoing switch-over Study #002, and the ongoing extension Study #003. In addition, the data from the historical analysis suggested that taliglucerase alfa and alglucerase or imiglucerase had similar efficacies as regards reductions in spleen and liver volumes, and increases in haemoglobin levels and platelet counts. Furthermore, a post-hoc analysis of the efficacy outcomes at 12 months in 26 patients from the pivotal Study #001 showed that taliglucerase alfa achieved consensus therapeutic goals. The updated efficacy data for ongoing supportive Studies #002 and #003 included in the sponsor's response to TGA questions are considered to provide satisfactory support to the efficacy findings observed in the pivotal Study #001.

The updated report for ongoing supportive Study #002 included efficacy data on patients treated with taliglucerase alfa for 9 months after switching from imiglucerase and showed that there was no clinical deterioration over this period of time in the efficacy parameters of spleen and liver volume, haemoglobin level, platelet count and chitotriosidase activity. The updated report included information on 28 treated patients (2 of whom were aged less than 18 years), and provided 9 month efficacy data on 25 of these patients. At the time of the database freeze (1 May 2011), the mean ± SD taliglucerase dose for the 28 treated patients was 29.2 ± 15.8 units/kg, and the median dose was 25.5 units/kg (range: 11 to

[11] In the second round evaluation, the prefix 'PB-06' used to identify the sponsor's studies was replaced by a hash (#) sign.

60 units/kg). Study #002 plans to enrol 30 patients and there are now 9 month efficacy data on 83.3% (n = 25) of the planned number.

No primary efficacy variable was selected for analysis in Study #002. The efficacy outcome of interest was whether patients stabilised on imiglucerase deteriorate clinically during treatment after switching to taliglucerase alfa. Clinical deterioration was primarily assessed 9 months after switching by changes in spleen volume, liver volume, haemoglobin level, and platelet count. The efficacy outcomes of taliglucerase alfa following switching from imiglucerase were:

- The mean ± SD spleen volume (n = 20) decreased from 822.4 ± 603.7 mL at baseline to 749.3 ± 559.7 mL at Month 9. This represented a reduction in mean ± SD spleen volume of 7.6 ± 13.3%. The mean ± SD spleen volume was 5.5 ± 4.8 times normal at baseline and 5.1 ± 5.1 times normal at Month 9. No clinical deterioration as assessed by change in spleen volume at 9 months was observed in 19 (95%) patients, while clinical deterioration was reported in 1 (5%) patient.
- The mean ± SD liver volume (n = 23) decreased from 1857.4 ± 440.0 mL at baseline to 1785.8 ± 423.7 mL at Month 9. This represented a mean ± SD reduction in liver volume of 3.5 ± 8.1%. No clinical deterioration as assessed by change in liver volume at 9 months was observed in 22 (95.7%) patients, while clinical deterioration was reported in 1 (4.3%) patient. The mean ± SD liver volume as multiples of normal liver volume was 1.0 ± 0.2 at baseline and 0.9 ± 0.2 at Month 9.
- The mean haemoglobin level remained stable over the 9 months of treatment and the mean level at Month 9 (n = 26) was consistent with the mean level at baseline (n = 28). No patients (n = 26) were reported to have experienced clinical deterioration at Month 9 based on haemoglobin changes.
- The mean platelet count remained relatively stable over the 9 months of treatment, and the mean ± SD count at Month 9 (n = 26) was 1.0 ± 21.3% lower than at baseline. No clinical deterioration based on platelet counts at 9 months was observed in 24 patients (92.3%), while clinical deterioration was reported in 2 (7.7%) patients.

The updated report for the extension Study #003 included a total of 44 patients aged 19 to 74 years, consisting of 26 patients who continued from Study #001 and 18 patients who continued from Study #002. In the updated report, there were efficacy data on 31 patients (Study #001, n = 26; Study #002, n = 10) at Month 3 (that is, after 12 months treatment), and on 26 patients (all from #001) at Month 15 (that is, after 24 months treatment). In Study #003, treatment with taliglucerase treatment is planned to continue for at least 15 months, but for no more than 30 months, or until marketing approval has been granted by the appropriate regulatory authority (presumably the FDA or EMA), whichever is earlier.

No primary efficacy outcome was specified in Study #003. The efficacy outcome of interest was whether patients deteriorate clinically during treatment with taliglucerase alfa as assessed by changes in spleen volume, liver volume, haemoglobin level, and platelet count.

- In patients from Study #001 who continued blinded treatment in the extension study, the mean ± SD reduction in spleen volume from baseline at Month 15 was 40.5 ± 9.6% in the 30 units/kg group (n = 12), and 54.9 ± 12.8% in the 60 units/kg group (n = 14); $p < 0.001$. There were 2 patients with Month 27 data (36 months treatment) in whom mean reductions from baseline in spleen volume were 44.7% (30 units/kg) and 56.1% (60 units/kg). In patients with relevant data (n = 7) from Study #002 who continued in the extension study, the mean ± SD reduction in spleen volume from baseline was 10.7 ± 12.4% at Month 3.
- The updated study report also included an analysis of change in spleen volume from screening until last follow-up visit based on magnetic resonance imaging (MRI) results. In patients from Study #001 who continued in the extension study, the mean ±

SD reduction in spleen volume was 41.3 ± 9.5% in the 30 units/kg group (n = 12) after a mean ± SD duration of 26.5 ± 4.5 months of follow-up, and 55.8 ± 12.3% in the 60 units/kg group (n = 14) after a mean ± SD duration of follow-up of 25.6 ± 4.0 months. In patients from Study #002 who continued treatment in the extension study and had relevant data (n = 15), the mean ± SD reduction in spleen volume was 8.0 ± 12.6% after a mean ± SD duration of follow-up of 16.1 ± 4.2 months.

- In patients from Study #001 who continued treatment in the extension study, the mean ± SD reduction in liver volume from baseline at Month 15 was 20.6 ± 6.9% in the 30 units/kg group (n = 12) and 17.5 ± 13.3% in the 60 units/kg group (n = 14); p = 0.473. There were 2 patients with Month 27 data (36 months treatment) in whom mean reductions in liver volume from baseline were 22.3% (30 units/kg) and 14.4% (60 units/kg). In patients from Study #002 who continued in the extension study and had relevant data (n = 8), the mean ± SD reduction in spleen volume from baseline was 4.2 ± 5.8% at Month 3.
- The updated report also included an analysis of change in liver volume from baseline screening until last follow-up visit based on MRI results. In patients from Study #001 who continued in the extension study, the mean ± SD reduction in liver volume from baseline was 21.5 ± 6.3% in the 30 units/kg (n = 12) group after a mean ± SD duration of 26.5 ± 4.5 months of follow-up, and 17.9 ± 13.2% in the 60 units/kg group (n = 14) after a mean ± SD duration of follow-up of 25.9 ± 4.0 months. In patients from Study #002 who continued in the extension study and had relevant data (n = 16), the mean ± SD reduction in spleen volume was 2.0 ± 7.5% after a mean ± SD duration of follow-up of 15.9 ± 4.1 months.
- Patients from Study #001 who continued treatment in the extension study showed mean increases in haemoglobin levels from baseline at Months 3, 9 and 15. At Month 15, the mean ± SD increase in haemoglobin level from baseline was 1.3 ± 1.7 g/dL in the 30 units/kg group (n = 11), and 2.4 ± 2.3 g/dL in the 60 units/kg group (n = 14); p = 0.207. In patients from Study #002 who continued treatment in the extension study and who had relevant data, there were no meaningful changes in haemoglobin levels from baseline at Month 3 (n = 12) or Month 9 (n = 10).
- Patients from Study #001 who continued treatment in the extension protocol showed mean increases in platelet counts from baseline at Months 3, 9, and 15. At Month 15, mean ± SD increases in platelet counts from baseline were 28,433 ± 31,996 /mm^3 in the 30 units/kg group (n = 12), and 72,029 ± 68,157/mm^3 in the 60 units/kg group (n = 14); p = 0.054. In patients from Study #002 who continued treatment in the extension study and who had relevant data, there were no meaningful changes in platelet counts at Month 3 (n = 12) or Month 9 (n = 9).

The effect of anti-taliglucerase antibodies on efficacy was investigated in Study #001. In the 30 units/kg group there were no statistically significant differences between antibody positive and antibody negative patients for the primary and secondary efficacy outcome measures. However, in the 60 units/kg group, antibody negative patients had statistically significantly greater reductions in mean liver volume from baseline to last follow up than antibody positive patients (approximately 32% versus 13%, p = 0.005). Furthermore, the mean reduction in liver volume in the antibody positive group was < 20% and, consequently, is unlikely to be clinically significant. The results for each of the 3 other efficacy endpoints in the 60 units/kg group favoured antibody negative patients compared with antibody positive patients, but the differences were not statistically significant. Interpretation of the results in the 60 units/kg are complicated by small patient numbers, and an imbalance in patient numbers between the antibody positive group (n = 11) and the antibody negative group (n = 4). In addition, the results for the 60 units/kg group are inconsistent with the results for the 30 units/kg group. Overall, the limited available data

suggest that efficacy is unlikely to significantly differ between antibody positive and negative patients. However, this matter warrants further investigation.

Second round assessment of risks

It is considered that the safety data provided in the initial submission, and in the sponsor's response to TGA questions have satisfactorily the safety of taliglucerase alfa for the treatment of GD. The safety data are based on 1 completed Phase III pivotal study (Study #001), and 4 ongoing Phase III supportive studies (Studies #002, #003, #004, #005). In addition, safety data were available on patients from multinational ongoing Compassionate Use Programs, and a small Phase I study in healthy volunteers.

The safety dataset from the Phase III clinical studies includes 121 patients treated with taliglucerase alfa for GD as of 1 May 2011. Of these 121 patients, 96 have been treated for 6 months, 59 for 12 months, 33 for 18 months, and 24 for 12 months. These patient numbers are small, but are considered adequate for the safety assessment of this particular orphan drug (taliglucerase alfa).

Of the 121 patients, 67 (55.4%) were male and 54 (44.6%) were female, and nearly all were Caucasian (96.7%, n = 117), with the remainder being Native American (n = 1) or Other (n = 3). Of the 121 patients, 13 (10.7%) were aged < 18 years, 101 (83.5%) were aged 18 to 65 years, and 7 (5.8%).

Of the 121 patients, 104 (86.0%) experienced at least 1 all causality AE and the majority of these events were classified as mild or moderate in intensity. There were 52 (43.0%) patients reported by the investigators as experiencing at least one AE considered to be related to treatment. There were no deaths reported in the 121 patients, and at least one SAE was reported in 10 (8.3%) patients.

Commonly reported adverse events

The most commonly reported AEs (≥ 5%) in the 121 patients were nasopharyngitis (21.5%), arthralgia (18.2%), headache (18.2%), upper respiratory tract infection (15.7%), pain in extremity (11.6%), cough (10.7%), fatigue (9.9%), back pain (9.9%), vomiting (8.3%), pain (7.4%), pharyngolaryngeal pain (7.4%), pruritus (7.4%), diarrhoea (6.6%), pyrexia (6.6%), influenzae (6.6%), pharyngitis (6.6%), sinusitis (6.6%), nausea (5.8%), dizziness (5.8%), epistaxis (5.8%), gastroenteritis (5.8%), bone pain (5.0%), and hypertension (5.0%).

Serious adverse events

Serious AEs (11 events) were reported in 10 (8.3%) patients. No pattern of SAEs was observed. The only SAE considered by the investigator to be treatment related was gastroenteritis in the paediatric Study #005.

Treatment discontinuations

Treatment discontinuation had occurred in 24 (19.8%) patients as of 21 September 2011. In Study #001, 2 patients discontinued due to an AE (hypersensitivity reaction): 1 treated with 30 units/kg and 1 treated with 60 units/kg. In addition, 4 patients (1 from Study #002, and 3 from Study #004) withdrew voluntarily or for "other reasons", but details of the discontinuations include mention of infusion associated events in 3 cases and generalised body stiffness in 1 case. In 1 additional patient, the investigator recommended discontinuation after 38 infusions in order to assess a possible allergic reaction. Among the other patients, reasons included travel or scheduling problems (7 patients), pregnancy (1 patient), and "other" (9 patients).

Hypersensitivity adverse events

Adverse events of particular interest relate to disorders mediated by the immune system (that is, hypersensitivity reactions and infusion related reactions). Hypersensitivity Type I (acute) events were identified in 18 (14.9%) patients (73 all causality events), and in 15 (12.4%) of the 18 patients the events were judged by investigators to be treatment related (56 treatment related AEs). The most commonly reported hypersensitivity Type I AE was pruritus (9 patients; 7.4%), followed by "hypersensitivity" (5 patients; 4.1%) and pruritus generalised (2 patients; 1.7%). Each of the following hypersensitivity Type I AEs were reported in 1 patient (eye swelling, lip swelling, face oedema, periorbital oedema). In Study #001, 4/16 patients in the 60 units/kg group reported 15 AEs related to hypersensitivity compared with 2/16 patients in the 30 units/kg group reporting 5 hypersensitivity Type I AEs.

Of the 15 (12.4%) patients reported by investigators as having treatment related hypersensitivity Type I events, 9 patients required no intervention or only temporary intervention with interruption of the infusion and/or medication to manage the event (6 pruritus, 1 generalised pruritus, 1 face oedema, 1 lip swelling), 4 patients required discontinuation of the infusions (3 hypersensitivity, 1 eye swelling), and 2 patients continued infusions with pre-treatment medications (2 hypersensitivity). Of the 4 patients discontinuing, 3 discontinued because of hypersensitivity events (in 2 patients these events occurred with the first infusion), and 1 patient experienced multiple repeated events of eye swelling not responding to pre-treatment and chose to discontinue taliglucerase alfa and return to imiglucerase.

Hypersensitivity Type II-IV (chronic) events were reported in 5 (4.1%) patients. Of these 5 patients, 4 (12.5%) patients came from Study #001 (2 in each of the 30 units/kg and 60 units/kg groups) and 1 (3.6%) patient came from Study #002. The hypersensitivity Type II-IV (chronic) events were reported as mild or moderate in intensity, except for 1 patient in the 60 units/kg dose group (Study #001) who experienced a very severe autoimmune thrombocytopaenia (reported as a non-treatment related SAE). Non-treatment related contact dermatitis was reported in 2 patients in Study #001 (1 in each of the 30 units/kg and 60 units/kg dose groups). The 1 patient in Study #002 was reported to have experienced non-treatment related arthritis (knee inflammation) associated with gonarthrosis.

Infusion reactions

Infusion reactions occurring during the infusion or within 2 h after the completion of the infusion occurred commonly with 45 (37.2%) patients experiencing 168 AEs of which 134 were considered treatment related. The infusion reactions occurring during the infusion or within 2 h of completion of the infusion in ≥ 2% of patients were headache (5.0%), hypersensitivity (4.1%), nausea (3.3%), vomiting (3.3%), pruritus (3.3%), flushing (3.3%), chest discomfort (2.5%), infusion related reaction (2.5%), and throat irritation (2.5%).

Bone events

Bone events were of particular interest. A total of 10 (8.3%) patients experienced 15 bone events, the most common of which were bone pain (6 patients), followed by musculoskeletal pain, and bone infarction (1 patient).

Prolonged activated partial thromboplastin time (aPPT)

Prolonged aPPT is a feature of GD. In the clinical studies, aPPT reported as an AE occurred in 1 patient with an onset between 2 to 24 h post-infusion. The AE was considered to be mild (Grade 1) and did not require treatment. The taliglucerase alfa dose was not changed and the patient recovered from the event. Additionally, in the ERT naïve Study #001 6 patients in the 30 units/kg group and 4 patients in the 60 units/kg group experienced

prolonged aPTTs that were not reported as AEs. In the switchover Study #002, 9 subjects experienced prolonged aPTTs that were not reported as AEs.

Anti-taliglucerase antibodies

The most significant difference between the inital and updated safety data relate to the markedly greater proportion of patients reported with anti-taliglucerase alfa antibodies in the updated safety data. The difference appears to be due to the use of more sensitivity assays for detecting anti-taliglucerase alfa IgG antibodies in the updated safety data.

The incidence of anti-taliglucerase alfa IgG antibodies was investigated in Studies #001, #002, and #003. Using the IgG assay cut-point of 40.33%, the number of patients who were positive at any time point (including those positive at baseline only or positive at baseline and without significant increase in titre) for studies #001, #002 and #003 were 59.4% (19/32), 19.2% (5/26) and 35.6% (16/45), respectively. Of the 26 patients entering extension Study #003 from Study #001 and receiving a total of 24 months treatment, 13 (50%) patients were found to have positive test results for IgG antibody at least at one visit. Of the 18 patients entering extension Study #003 from Study #002 and receiving 12 months treatment, 3 (16.6%) patients were IgG positive at least at one visit.

The proportion of patients with antibodies was notably higher in Study #001 in ERT naïve patients (59.4%) compared with Study #002 in ERT experienced patients (19.2%). It is likely that ERT experienced patients treated in Study #002 were relatively resistant to developing anti-taliglucerase antibodies compared with ERT naïve patients treated in Study #001. In Study #002, patients were switched from imiglucerase to taliglucerase alfa, but patients with infusion reactions suspected to be allergic in nature to imiglucerase or alglucerase or receiving premedication to prevent infusion reactions were excluded from the study.

Irrespective of antibody status, the overall incidence of hypersensitivity Type I (acute) events in the ERT naïve population (28%, 9/32) was similar to that in the ERT experienced population (27%, 7/26). However, based on data using the IgG assay cut-point of 52.97%, the overall incidence of hypersensitivity type I (acute) events in the antibody positive population was 44% (8/18) compared with 20% (8/40) in the antibody negative population. This suggests that patients who develop anti-taliglucerase antibodies are likely to be at a greater risk for hypersensitivity Type I (acute) reactions compared with patients who remain antibody negative.

In 21 antibody positive patients (52.97% cut-point) experiencing hypersensitivity Type I (acute) AEs (all causality) and infusion related AEs (all causality), 13 continued treatment with no intervention, 3 discontinued treatment follow “hypersensitivity” events, 2 continued treatment with use of antihistamines for rash or pruritus, 2 subjects experiencing infusion related reactions continued treatment with over the counter medication for headaches, and 1 subject who experienced “hypersensitivity” continued treatment with pre-treatment regimens.

In the available safety data, neutralising antibodies have been found in 3 (5.2%) patients using the in vivo assay, but all 3 patients were found to be negative for neutralising antibodies using the cell based assay.

Other safety issues

It is known that intermittent elevations of liver enzymes can occur in patients with GD without co-existing morbidities. Review of the available data has shown that the elevations in alanine aminotransferase (ALT) or aspartate transaminase (AST) observed in the current dataset are mild and explainable, either due to concomitant medication or illness. All patients with liver function test abnormalities showed either clinical improvement or clinical stability while on taliglucerase treatment. Increased ALT was reported as an AE in 3/121 (2.5%) patients.

There were 4 (3.3%) patients who developed abnormal echocardiograms (ECHO) findings during treatment with taliglucerase alfa, none of which were associated with deterioration in cardiac function. The significance of these abnormal ECHO finding are unknown. There were no notable changes in vital signs, electrocardiogram (ECG) findings or pulmonary function tests during treatment with taliglucerase.

Safety issues of general regulatory concern

There were no safety signals in the available data suggesting that taliglucerase alfa is hepatotoxic or has significant adverse effects on the renal, cardiovascular, or haematological systems.

Risks in special patient groups

Taliglucerase alfa has been administered to 13 (10.7%) patients younger than 18 years of age (2 to < 18 years) in the clinical study program. No unusual AEs have been observed specifically in paediatric subjects. However, the sample size in paediatric patients is too small to conclude that there are no significant differences in the safety profile of taliglucerase alfa in paediatric and adult patients. Paediatric patients are dosed on a unit/kg basis in the same way as adults using the standard IV formulation, and there are no plans to develop a specific paediatric formulation.

No conclusions can be drawn about safety in patients aged > 65 years: the 121 patients in the clinical safety population included only 7 (5.8%) in this age group. There are no apparent differences in the AE profiles between male and female patients. No conclusions can be drawn about safety in different racial groups as almost all patients in the clinical study program have been Caucasian.

Safety data from the Compassionate Use Program

As of 1 May 2011, there were 212 patients enrolled in Compassionate Use Programs, and safety data were available on 18 of these patients. In these 18 patients there have been 49 AEs reported, and 16 of the patients have experienced hypersensitivity reactions. There has been 1 reported death (pneumonia, lung disorder, tuberculosis) considered to be unrelated to treatment, and other SAEs have been reported in 3 patients including hypersensitivity in 1, anaphylactoid reaction in 1, and anaphylactic shock, dyspnoea, and cyanosis in 1. Treatment has been discontinued in 12 patients, and in all of these patients the reported AEs could be characterised as hypersensitivity reactions.

Unresolved safety issues

There is an unresolved safety issue associated with the potential for taliglucerase alfa to induce antibodies to plant sugars (the sponsor reports that almost all commercial batches contain xylose and some contain fructose). The sponsor acknowledges that *"issues of pre-existing antibody and immunogenicity of plant glycans were not sufficiently discussed in the application"* and has undertaken to evaluate this matter. The sponsor expects to complete the evaluation of anti-taliglucerase antibodies generated in patients in an attempt to determine whether these have specificity for the plant-derived glycans on taliglucerase alfa or are primarily against the protein core of the molecule by the end of July 2012. In any event, even if specific antibodies to plant sugars are found in patients treated with taliglucerase alfa it is unlikely that these will result in significant new safety issues. The incidences of hypersensitivity and infusion reactions have now been reasonably well characterised in Studies #001, #002, and #003 in antibody positive and negative patients. Consequently, if anti-plant sugar antibodies are found in antibody positive or negative patients it is unlikely that this will change the known safety profiles of the two patient groups.

There are no safety data on the use of taliglucerase alfa in patients with pre-existing liver, renal or cardiovascular disease. There are no safety data relating to potential drug-drug

interactions involving taliglucerase alfa. There are limited safety data in patients aged < 18 years, and no safety data on patients aged > 65 years.

Second round assessment of benefit-risk balance

It is considered that benefit-risk balance of taliglucerase alfa for the treatment of GD is acceptable. The submitted data demonstrate that clinically meaningful benefits in ERT naïve patients are achieved after 9 months treatment with taliglucerase alfa and that these benefits can be maintained with treatment for at least a further 15 months. In addition, the submitted data demonstrate that patients stabilised on imiglucerase and switched to taliglucerase can maintain clinical benefits obtained with imiglucerase for at least 12 months with taliglucerase treatment.

The main risks associated with taliglucerase alfa relate to the high incidence of infusion related reactions with 37.2% of patients experiencing a reaction during or within 2 h after completion of the infusion. Hypersensitivity Type I (acute) reactions (all causality) occurred in 14.9% of patients, and in 12.4% of patients the reactions were considered by the investigators to be treatment related. The available data suggests that hypersensitivity Type I (acute) reactions occur more frequently in antibody positive patients (44%) than in antibody negative patients (20%). The submitted data indicate that infusion and hypersensitivity Type I (acute) reactions occurring in both antibody positive and antibody negative patients can be satisfactorily managed in the majority of cases by standard treatment methods rather than treatment discontinuation. No deaths have been reported due to hypersensitivity reactions, although safety data from the Compassionate Use Programs indicates that there has been 1 report of anaphylactic shock.

Second round recommendation regarding authorisation: Original submission

It is recommended that taliglucerase alfa be approved:

> *for long-term enzyme replacement therapy for the treatment of systemic symptoms in patients with a confirmed diagnosis of Gaucher disease.*

It is recommended that the following should be conditions of registration:

- submission of the final clinical study reports from Studies #002, #003, #004, and #005 on completion of these studies; and
- submission of the results relating to the sponsor's attempt to evaluate anti-taliglucerase antibodies generated in patients to determine whether these have specificity for the plant-derived glycans on taliglucerase alfa or are primarily against the protein core of the molecule.

The clinical evaluator's recommended revisions to product literature are beyond the scope of the AusPAR.

V. Clinical findings: Resubmission

A summary of the clinical findings presented in the resubmission is presented in this section. Further details of these clinical findings can be found in Attachment 3 (CER 2).

Introduction

The original application to register taliglucerase alfa was withdrawn by the sponsor to allow time to address matters raised in the quality evaluation reports. The resubmission dossier included new clinical data, summarised below.

Contents of the clinical dossier

Clinical data provided in the resubmission comprised:

Module 5:

- 3 bioanalytical and analytical validation biopharmaceutical studies.
- 1 clinical efficacy and safety study in paediatric patients with GD.
- Literature references.

Module 2:

- Clinical overview Module 2.7.1.3, Addendum, immunogenicity overview; Summary of clinical safety (SCS, including 5 appendices).

Paediatric data

The resubmission included data on 11 patients from the paediatric clinical efficacy and safety Study PB-06-005, and the SCS included data on 16 children (11 from Study PB-06-005 plus 5 from Study PB-06-001).

Information on on-going studies in paediatric patients was also provided.

Good clinical practice

The sponsor stated that clinical Study PB-06-005 in paediatric patients was "conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline".

Pharmacokinetics

Studies providing pharmacokinetic data

The resubmission included no clinical PK studies. However, it included 3 biopharmaceutical reports (reports of bioanalytical analytical methods for human studies).

Evaluator's summary and comments on the three validation reports

- *Study PCL-11-020*: To support a determination of whether anti-taliglucerase alfa antibodies bind to the protein backbone or to the glycan moieties of taliglucerase alfa the sponsor developed an ELISA-based assay to compare the binding of these antibodies to taliglucerase alfa with their binding to imiglucerase.
- *#PCL-12-010(1)*: The objective of this study was to provide supporting data for experiments conducted during the development of the assay described in validation report 70-66-027R. The glycan analysis results described in this study confirmed that horse-radish protein (HRP) is appropriate for use as the competitor in the assay in order to demonstrate antibody specificity to the plant glycan structures on taliglucerase alfa.
- *Report 70-66-0272R*: The objective of this study was to validate the performance of an ELISA for the detection of antibodies to plant-specific glycans that are present on taliglucerase alfa in human serum.

None of the three reports included data on antibodies specific to plant glycans on taliglucerase alfa in patients with GD treated with the product. Study report PCL-11-021

suggests that the majority of anti-taliglucerase alfa antibody activity is likely to be specific for the protein backbone of taliglucerase alfa, with the minority of the reactivity being specific for epitopes that are either unique to taliglucerase alfa (for example, plant glycan structures) or are more highly expressed or exposed on taliglucerase alfa compared with imiglucerase. Study report PCL-12-010(1) showed that anti-taliglucerase alfa antibodies are highly cross-reactive with imiglucerase, which has extensive structural and sequence homology to taliglucerase alfa but lacks the plant glycan structures. Study report 70-66-027 suggests that a notable number of healthy human serum samples test "positive" for antibodies specific to plant glycans on taliglucerase alfa (8.4% [12/143] excluding outliers; and 15.4% [24/156] including outliers]). This suggests that healthy subjects can develop antibodies to naturally occurring plant glycans (presumably in food) identical or similar in structure to those on taliglucerase alfa.

Pharmacodynamics

The resubmission included no specific studies investigating the pharmacodynamics of taliglucerase alfa in humans.

Dosage selection for the pivotal study

The dose of taliglucerase alfa (30 or 60 units/kg) for paediatric patients aged 2 to < 18 years (Study PB-06-005), was selected based on the safety data from the pivotal, Phase III Study PB-06-001 in adult patients with GD who received either 30 or 60 units/kg.

Efficacy

Studies providing efficacy data

Study PB-06-005 in a paediatric population was provided in the resubmission. Study PB-06-005 was a Phase IIIb, multi-national, multi-centre, double-blind, clinical study designed to assess the efficacy and safety of taliglucerase alfa in previously untreated patients with GD aged 2 to < 18 years. Patients were randomised to taliglucerase alfa (30 or 60 units/kg) administered by IV infusion every 2 weeks for 12 months, with an option to continue beyond 12 months. The study was undertaken in 3 centres from 3 countries (Israel, South Africa, and Paraguay).

The efficacy objectives were to assess the efficacy of taliglucerase alfa in patients between 2 to <18 years of age with GD, as measured by the primary, secondary and exploratory efficacy variables. The primary efficacy variable was median percent change in haemoglobin levels from baseline, and the interquartile range of median percent change in haemoglobin levels from baseline.

Evaluator's conclusions on clinical efficacy in Study PB-06-005

The resubmission included one small efficacy and safety study in 11 paediatric patients, ranging in age from 3 to 14 years, with a definitive diagnosis of GD and who were ERT naïve. The patients were randomised to taliglucerase alfa 30 units/kg (n = 6) or 60 units/kg (n = 5) administered by IV infusion every 2 weeks for 12 months. Interpretation of the efficacy results of this study is limited due to the absence of an active treatment control group. The changes from baseline through to Month 12 in the efficacy parameters were summarised descriptively with no statistical analyses of the results being undertaken. The sample size was determined pragmatically due to the limited number of paediatric patients with this rare disease available for study.

The primary efficacy endpoint was the median change from baseline (Visit 1) and the interquartile range of the median percent change in haemoglobin. In both treatment groups, a median increase in haemoglobin level from baseline to Month 12 was observed (12.2%, interquartile range 20.6%, 30 units/kg group; 14.2%, interquartile range 10.4%, 60 units/kg). In both treatment groups, each of the secondary efficacy endpoint outcomes showed improvement from baseline to Month 12, with results for the 60 units/kg group being numerically superior compared with the results for the 30 units/kg group.

Overall, it is considered that this small, uncontrolled, open-label study suggests that taliglucerase alfa 30 units/kg and 60 units/kg administered by IV infusion every second week for 12 months is efficacious for the treatment of GD in ERT naïve children and adolescents. Improvements from baseline to Month 12 included increases in haemoglobin levels and platelet counts, reduction in spleen and liver volumes, and reductions in chitotriosidase activity and the biomarker chemokine (C-C motif) ligand 18 (CCL18) concentration. The results are consistent with those observed in adult patients evaluated in the original submission.

Safety

Studies providing evaluable safety data

- Study PB-06-005: 11 children and adolescents completed 52 weeks of treatment with taliglucerase alfa and were included in the safety evaluation.
- Summary of clinical safety: The safety data provided in the SCS was based on 132 patients (116 adults, 16 children) who had accrued 2,761.0 patient-months of exposure to taliglucerase alfa as of 1 May 2012.

  Evaluator's comment: There were data on an additional 11 patients in the SCS (resubmission) compared with the SCS in the original submission. The main difference between the two SCS documents was the greater number of patients in the resubmission exposed for ≥ 6, ≥ 12, ≥ 24, and ≥ 36 months. The total patient-months of exposure was 59% higher in the SCS (resubmission) compared with the SCS in the original submission.

Patient exposure

- Study PB-06-005: the mean (SD) taliglucerase alfa doses were 34.7 (5.4) units/kg (range: 30, 45) in the 30 units/kg group (n = 6) and 63.7 (3.5) units/kg (range: 61, 69) in the 60 units/kg (n = 5) group.
- Summary of clinical safety:
  - Adults: The 116 adult patients exposed to taliglucerase alfa as of 1 May 2012 have accrued 2,556.3 months of person-time exposure.
  - Children: The 16 children exposed to taliglucerase alfa as of 1 May 2012 have accrued 204.6 months of person-time exposure.
  - Total subject exposure to taliglucerase alfa by dose in all completed and ongoing studies by dose in all patients (n = 132) is summarised below in Table 5.

Table 5: SCS: Exposure in total population (n = 132) by dose, completed and ongoing studies, as of 1 May 2012

Dose (units/kg)	N	Person Time (months)
< 25	34	585.2
25-35	42	866.1
>35 - <55	17	398.2
>=55	39	911.5

Note: Duration of exposure is computed from date of first dose until last dose before cut-off date.

The mean dose in each of the adult and paediatric studies is summarised below in Table 6. The mean dose across all studies was similar, and the mean doses in the 30 units/kg and 60 units/kg groups in the paediatric Study PB-06-005 was similar to the mean doses in the corresponding dosage groups in the adult Study PB-06-001.

Table 6: SCS: Mean dose in completed and ongoing studies, as of 1 May 2012

Average of All Dose Infusions (U/kg)	PB-06-001		PB-06-002	PB-06-004	PB-06-005		Overall
	30 U/kg	60 U/kg			30 U/kg	60 U/kg	
N	16	16	31	58	6	5	132
Mean	32.7	60.4	31.2	34.4	33.1	61.1	37.5
SD	3.7	2.1	16.6	16.4	4.1	2.6	16.9
Median	31.6	60.4	25.8	30.4	31.3	60.3	31.8
Range	30 to 44	57 to 65	11 to 60	13 to 63	30 to 41	58 to 65	11 to 65

Note: Duration of exposure is computed from date of first dose until last dose before cutoff date.

Post-marketing experience

Since 1 May 2012, taliglucerase alfa has been marketed in the USA for adults with GD. In the post-marketing dataset from 01 May 2012 to 01 February 2013, there have been 2 serious AEs in 2 patients (major depression in 1 patient, and hypertension in 1 patient [non-serious AE of nasopharyngitis also reported in this patient]), and 29 non-serious AEs in 8 patients. Non-serious AEs reported more than once were: weight increased (3 reports) diarrhoea (2 reports); weight decreased (2 reports); and headache (2 reports). In the 10 patients with spontaneous AEs reports, the events were considered related to treatment in 9 patients. None of the spontaneously reported events were fatal. The post-marketing data is too limited to allow any meaningful conclusions to be drawn.

Evaluator's summary and conclusions on safety

The evaluator considered that the safety data from Study PB-06-005 in children were consistent with the previously evaluated safety data in adults. In addition, it was considered that the safety data in the original and updated SCS documents are consistent. Overall, it was considered that the safety of taliglucerase alfa for the treatment of non-neuronopathic GD has been adequately demonstrated in the original and updated submissions. However, the safety assessment is limited due to the small number of patients exposed to the medicine in the ongoing and completed clinical trials, and the absence of a randomised study comparing the medicine with an active control such as imiglucerase or velaglucerase alfa. The safety data are limited to patients with non-neuronopathic GD as there were no data in patients with neuronopathic GD.

The safety assessment is based on data from 132 patients exposed to taliglucerase alfa in the ongoing and completed GD clinical trial program (116 adults; 16 children). Based on the "rule of three", 132 patients exposed to taliglucerase alfa provide a population of sufficient size to support detection of adverse drug reactions (ADRs) occurring with an

upper 95% confidence interval of ≥ 2.2% (Jovanovic and Levy[12], 1997; Jacobsen et al., 2001[13]). However, the safety population (n = 132) is of insufficient size to ensure detection of ADRs occurring with a frequency of ≤ 2%. Furthermore, exposures of ≥ 6 and ≥ 12 months have been reported in only 111 patients (98 adults, 13 children) and 95 patients (83 adults, 12 children), respectively. However, the number of patients available for studies assessing the clinical efficacy and safety of taliglucerase alfa for the treatment of GD is limited due to the rarity of the disease. Overall, the limited safety database is considered to be adequate for an orphan drug.

The primary safety concern arising from the original submission was the absence of data relating to the potential immunogenicity of the plant-specific glycans found on taliglucerase alfa. The resubmission provided no data directly assaying the immunogenicity of these plant-specific glycans in patients with GD treated with taliglucerase alfa. However, new in vitro data in the re-submission provides indirect evidence suggesting that the immunogenicity of taliglucerase alfa is likely to arise primarily from the protein backbone of the molecule rather than from the plant-specific glycans. Furthermore, it is considered that the clinical studies have adequately characterised the immune response to taliglucerase alfa, irrespective of whether the response arises from antibodies induced by the protein backbone and/or the plant-specific glycans.

In the clinical studies, assessment of IgG ADA was carried out in a total of 71 patients (43 ERT naïve, 28 ERT experienced). Of the 43 ERT naïve patients, 19 (44.2%) were found to have treatment-induced IgG ADA (17/32 [53.1%] adults, 2/11 [18.1%] children). Of the 28 ERT experienced patients, 5 (17.9%) were found to have IgG ADA (3 adults, 2 children). Based on these figures, 24/71 (33.8%) patients were positive for treatment-induced IgG ADA, and the incidence of treatment-induced IgG ADA was notably higher in ERT naïve patients (44.2%) than in ERT experienced patients (17.9%).

There appears to be an association between treatment-induced IgG ADA and Type I hypersensitivity AEs in the total, ERT naïve, and ERT experienced populations. In the total population (n = 71), 10 (44.7%) of the 24 patients with treatment-induced IgG ADA experienced Type I hypersensitivity reactions compared with 10 (21.3%) of the 47 patients without treatment-induced IgG ADA. In the 20 patients experiencing Type I hypersensitivity reactions, irrespective of treatment-induced IgG ADA status, 10 continued treatment with no intervention, 3 discontinued treatment following Type I hypersensitivity AEs (1 declined premedication), 5 continued treatment with symptomatic use of medications such as antihistamines for rash or pruritus, and 2 continued treatment with a pretreatment regimen aimed at preventing or minimising allergic reactions associated with the infusion. The results suggest that Type I hypersensitivity AEs were manageable in the majority of the 20 patients, irrespective of treatment-induced IgG ADA status.

There were 4/58 (6.9%) adult patients who were IgG ADA positive pre-dose. Of these 4 patients, 2 fulfilled the criteria for treatment-induced IgG ADA. There were 2/13 (15.4%) paediatric patients who were IgG ADA positive pre-dose. Of these 2 patients, neither fulfilled the criteria for treatment-induced IgG ADA. It is possible that the 6 patients with pre-dose IgG ADA had pre-existing cross-reactive antibodies to plant glycans shared with taliglucerase alfa.

None of 24 adult patients testing positive for IgG ADA tested positive for neutralising antibodies measured in both independent assays (3 [12.5%] tested positive in the in vitro enzymatic assay but not in the cell based assay). No children tested positive for

[12] Jovanovic BD and Levy PS. A look at the rule of three. *The American Statistician* 1997;51(2):138-139.
[13] Jacobsen RM et al. Adverse events and vaccination – the lack of power and predictability of infrequent events in pre-licensure studies. *Vaccine* 2001;19:2428-2433.

neutralising antibodies. Two (2) patients tested positive for IgE ADA (1 adult, 1 child), and both patients were positive at the baseline visit. The adult patient discontinued after the first infusion due to an infusion-related reaction, while the paediatric patient completed the study. It is not possible to determine the incidence of patients with IgE ADA pre-dose or post-dose as not all patients were tested for this antibody. Only patients who experienced allergic reactions were tested for IgE ADA.

In the adult population (n = 116), there were 20 (17.2%) patients with all-causality Type I hypersensitivity AEs, and all events were reported as being mild/moderate in intensity. The events reported in the 20 adult patients were pruritus in 11 patients (9.5%), hypersensitivity in 5 (4.3%) patients, eye swelling in 2 (1.7%) patients, and eye oedema, scleral oedema, lip swelling, and face oedema in 1 (0.9%) patient each. There were 18 adult patients considered to have investigator-designated treatment-related Type I hypersensitivity AEs. Of these 18 patients, 10 required no intervention or only temporary intervention to manage the events, while 8 required premedication or treatment discontinuation. One (1) Type I hypersensitivity AE (angioedema) was reported in 1 paediatric patient, and this event was considered by the investigator to be unrelated to treatment.

Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (9/116 [7.8%]). Of the 14 events, 13 were reported as mild or moderate in severity and 1 was reported as severe (autoimmune thrombocytopaenia, non-treatment related SAE). Events reported in more than 1 patient were arthritis (3 patients, 2.3%), and contact dermatitis (2 patients, 1.5%). All other events occurred in 1 (0.8%) patient each (autoimmune thrombocytopenia, drug eruption, dyshidrosis, macula-papular rash). The only event reported as treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

Bone events are of special interest in patients with GD. In adults (n = 116), 55 (47.4%) patients experienced bone events, and SAE bone events were reported in 2 (1.7%) patients. In 8 (6.9%) patients, bone events were judged by the investigator to be treatment-related. The majority of treatment-related bone events were categorised as musculoskeletal discomfort (15 events, all in 1 patient). Of the treatment-related bone events, 4 events occurred during the infusion or within 2 h after the completion of the infusion (arthralgia, back pain, muscle spasm, and musculoskeletal discomfort). In children (n = 16), 5 (31.3%) patients experienced bone events, and none of the events were considered to be SAEs. There was 1 (6.3%) paediatric patient with a bone event judged by the investigator to be treatment-related (pain in extremity). None of the bone events in children occurred during the infusion or within 2 h of the completion of the infusion.

In adult patients, 93.1% (108/116) experienced a total of 1,252 AEs and the most commonly reported AEs (> 10% of patients) were nasopharyngitis (23.3%), arthralgia (23.3%), headache (22.4%), viral upper respiratory tract infection (19.8%), pain in extremity (16.4%), cough (15.5%), fatigue (12.9%), abdominal pain (11.2%), pyrexia (11.2%), back pain (11.2%), diarrhoea (10.3%), nausea (10.3%), and oropharyngeal pain (10.3%).

In paediatric patients, 75.0% (12/16) experienced a total of 73 AEs, and the most commonly reported AEs (> 10% of patients) were vomiting (31.3%), abdominal pain (18.8%), nasopharyngitis (18.8%), headache (18.8%), pain in extremity (18.8%), tonsillitis (12.5%), diarrhoea (12.5%), arthralgia (12.5%), epistaxis (12.5%), and tooth extraction (12.5%).

In adults, the proportion of patients with AEs in the ERT naïve group was higher than in the ERT experienced group (96.9% [31/32] versus 91.7% [77/84]). There were 425 AEs in the 32 ERT naïve patients (that is, 13.3 events/patient), and 827 AEs in the 84 ERT

experienced patients (that is, 9.8 events/patient). In children, the proportion of patients with AEs in the ERT naïve group was higher than in the ERT experienced group (90.9% [10/11] versus 40.0% [2/5]). There were 68 AEs in 11 ERT naïve paediatric patients (6.2 events/patient), and 5 AEs in the 5 ERT experienced paediatric patients (1 event/patient). The difference between the ERT naïve and ERT experienced groups in children as regards AEs should be interpreted cautiously due to the small number of patients in each group.

Overall, SAEs were reported in 13 (11.2%) adult patients (20 events), and 2 (12.5%) paediatric patients (2 events). In adults, none of the SAEs were considered to be treatment related while in paediatric patients 1 SAE was considered to be treatment-related (gastrointestinal inflammation). There were no deaths reported in the ongoing and completed studies in the GD clinical program. There was 1 death reported in the Compassionate Use Program considered to be unrelated to treatment (tuberculosis/pneumonia).

The closer the AEs occurred to the taliglucerase alfa infusion the greater the risk of them being considered by the investigator to be treatment-related. Investigator-designated treatment-related AEs occurring during or within 2 h of completion of the infusion were reported in 27.6% of adult patients (n = 32) and 12.5% (n = 2) of paediatric patients. The most commonly reported investigator-designated treatment related AEs in adult patients (≥ 2% of patients) during or within 2 h of the completion of the infusion were hypersensitivity (4.3%), nausea (3.4%), infusion-related reactions (3.4%), headache (3.4%), pruritus (3.4%), rhinorrhoea (2.6%), sneezing (2.6%) and flushing (2.6%). AEs in paediatric patients designated as treatment-related by the investigator were gastrointestinal inflammation and vomiting in 1 patient, and chest discomfort in 1 patient.

Only 3 adult patients withdrew from treatment due to AEs (2x hypersensitivity; 1 x eye swelling). There were no treatment discontinuations in children due to AEs.

There were no clinically significant changes in laboratory tests, vital signs, ECG, ECHO or pulmonary function tests during the course of the study. Commonly reported AEs occurred more frequently in female patients than in male patients, but the observed differences are considered not to require dosing adjustments. The AE profile is similar in children and adults.

First round benefit-risk assessment: Resubmission

First round assessment of benefits

The benefits of treatment with taliglucerase alfa (30 units/kg; 60 units/kg) in ERT naïve and ERT experienced adult and paediatric patients with non-neuropathic GD include reduction in spleen volume, reduction in liver volume, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been shown to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced). The duration of treatment with taliglucerase alfa in the pivotal Phase III studies was 12 months in children and adolescents aged 2 to < 18 years in Study PB-06-005, and 9 months in adults aged ≥ 18 years in Study PB-06-001. In addition, Study PB-06-002 showed that in adults and children/adolescents whose disease had been stabilised with imiglucerase, the treatment benefit could be maintained for at least a further 9 months after switching to taliglucerase alfa. Support for treatment benefit achieved with imiglucerase being maintained following switching to taliglucerase alfa was also provided from Study PB-06-004 (expanded access treatment protocol). Furthermore, Study PB-06-003 showed that patients from Studies PB-06-001 and PB-06-002 who had benefited from 9 months treatment with taliglucerase alfa could continue to benefit from further treatment with taliglucerase alfa for at least 15 months.

First round assessment of risks

Overall, the risks of treatment with taliglucerase alfa for the proposed indication are considered to be acceptable. There are limited data on the safety of the taliglucerase alfa in children and adolescents due to the small number of patients with GD aged ≤ 18 years treated with the medicine in the clinical trial program. However, the available data in children and adolescents suggests that the risks of treatment in this age group are similar to those in adults.

The risks of taliglucerase alfa for the treatment for GD appear to require no specific intervention, or are manageable by symptomatic treatment for both infusion-related and non-infusion related risks, or by prophylactic premedication for infusion-related risks. The risk of treatment discontinuation due to AEs related to taliglucerase alfa is low. Treatment discontinuation due to AEs in the ongoing and completed clinical trial program for GD was reported in only 3 (2.6%) adult patients (two with hypersensitivity; 1 with eye swelling). No treatment discontinuations resulting from AEs were reported in children.

In adults, 93.1% (108/116) of patients experienced at least one AE (all causality). In children, 75.0% (12/16) of patients experienced at least one AE (all causality). Details of AEs, including most common AEs (occurring in > 10% of patients) and SAEs, and of deaths and discontinuations are shown above under *Evaluator's summary and conclusions on safety*. In summary:

- In both adults and children, the risk of experiencing AEs is greater in ERT naïve patients compared with ERT experienced patients.
- The risks of experiencing AEs appear to be minimal for the following groups of disorders "blood and lymphatic system", "cardiac", "hepatobiliary", "renal and urinary" and "skin and subcutaneous tissue".
- In adults, none of the SAEs were considered to be treatment related and no single preferred term was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation).
- There were no deaths reported in the ongoing and completed studies in the GD clinical program, but there was 1 death reported in the Compassionate Use Program considered to be unrelated to treatment (tuberculosis/pneumonia).
- Investigator-designated treatment-related AEs occurring during or within 2 h of completion of the taliglucerase alfa infusion were reported in 27.6% of adult patients (32/116) and 12.5% (2/16) of paediatric patients.
- There was a risk of Type I hypersensitivity AEs (acute allergic reactions) in patients treated with taliglucerase alfa.
- There appears to be an increased risk of Type I hypersensitivity reactions in patients testing positive for treatment-induced IgG anti-taliglucerase antibodies compared with patients testing negative (10/24 [44.7%] versus 10/47 [21.3%], respectively).
- Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (9/116 [7.8%]).
- Bone events were reported in 55 (47.4%) adult patients, and SAE bone events were reported in 2 (1.7%) adult patients. In children, 5 (31.3%) patients experienced bone events, and none of the events were considered to be SAEs.
- The risks of taliglucerase alfa inducing abnormalities in clinical laboratory tests, vital signs, ECGs, ECHOs, or pulmonary function tests appear to be minimal.

Overall, there is limited information on the risks of taliglucerase alfa in patients with GD aged from > 2 years to < 18 years (n = 16), and there is no information on the risks of

treatment in patients aged ≤ 2 years. There is limited information on the risks of treatment in patients with GD aged ≥ 65 years (n = 8). There is no meaningful information on the risks of taliglucerase alfa treatment in non-Caucasian patients (n = 5). The risk of experiencing commonly reported AEs appears to be greater in female than in male patients, but there is no evidence that the taliglucerase alfa treatment regimen should differ for females and males.

There are no data on the risks of taliglucerase alfa in patients with neuronopathic GD, patients with pre-existing hepatic disease, patients with pre-existing renal disease or patients with pre-existing cardiovascular disease. There are no data on the potential risks of drug-drug interaction involving taliglucerase alfa and other co-administered medicines.

First round assessment of benefit-risk balance

The benefit-risk balance of taliglucerase alfa, given the proposed usage, is favourable. The data provided in the original and re-submission satisfactorily demonstrate the benefits of taliglucerase alfa in both adult and paediatric patients. The benefits of treatment with taliglucerase alfa in ERT naïve and ERT experienced patients with non-neuropathic GD include clinically meaningful reductions in spleen and liver volumes, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa reduced GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced). Taliglucerase alfa is intended for chronic administration every 2 weeks. Consequently, the risk-benefit balance of the product over prolonged and potentially life-long administration will only emerge from post-marketing pharmacovigilance data.

The original submission and the resubmission satisfactorily demonstrate that the risks of treatment with taliglucerase alfa in both adults and children with non-neuropathic GD are acceptable. Although AEs occurred very commonly in both adults and children treated with taliglucerase alfa (93.1%, 108/116 and 75.0%, 12/16, respectively), these events generally required either no intervention or were manageable with symptomatic treatment. Treatment discontinuation due to AEs in the ongoing and completed clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 with hypersensitivity; 1 with eye swelling). No treatment discontinuations resulting from AEs were reported in children.

Details of the safety findings are given above under *Evaluator's summary and conclusions on safety.*

The major uncertainty relating to the benefit-risk balance relates to the potential effect of treatment-induced IgG ADA on the therapeutic response to taliglucerase alfa. The sponsor states that this matter is "currently unclear". In the original submission, there were limited data from Study PB-06-001 relating to the effect of IgG ADA status on efficacy and PK in adults. In this study, change from baseline to last follow-up visit were assessed for four efficacy endpoints in IgG ADA positive and negative patients in two dosage groups (30 and 60 units/kg). The four efficacy endpoints were percentage change in spleen volume, percentage change in liver volume, change in haemoglobin concentration, and change in platelet count.

In the 30 units/kg group, there were no statistically significant differences between IgG ADA positive patients (n = 6) and IgG ADA negative patients (n = 8) for the 4 efficacy endpoints. In the 60 units/kg group, improvements in each of the four efficacy endpoints were numerically greater in IgG ADA negative patients (n = 4) than in IgG ADA positive patients (n = 11), with the difference for percentage change in liver volume being statistically significant (approximately 32% versus 13%, respectively, p = 0.005). However, the efficacy comparison between IgG ADA positive and negative patients in the 60 units/kg group should be interpreted cautiously due to the small sample size. In

addition, the results in the 60 units/kg group were inconsistent with the results in the 30 units/kg group. Overall, it is considered that the data from Study PB-06-001 are too limited to conclude that efficacy is impaired in patients positive for IgG ADA.

Pooled PK data from patients in the 30 and 60 units/kg groups in PB-06-001 in the original submission showed that exposure to taliglucerase alfa at Day 38 (dose normalised C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) was notably greater in IgG ADA positive patients (n = 17) than in IgG ADA negative patients (n = 9). In addition, there was no consistent correlation between taliglucerase alfa exposure and the four efficacy outcomes in patients with and without IgG ADA. The re-submission included the time courses of IgG ADA and titre evaluated against each of the four key efficacy endpoints in individual patients from Studies PB-06-001, PB-06-002 and PB-06-003. There were no clear associations between IgG ADA status and the efficacy endpoints in the individual time course plots.

There is an important risk-benefit issue relating to whether treatment with taliglucerase alfa should be confined to adult patients with GD (that is, patients aged ≥ 18 years). The clinical data in children and adolescents (2 to < 18 years) are limited, but suggest that the benefits and risks of taliglucerase alfa are similar in children/adolescents and in adults. Overall, it is considered that treatment with taliglucerase alfa should not be restricted to adult patients aged ≥ 18 years.

First round recommendation regarding authorisation: Resubmission

It is recommended that ELELYSO (taliglucerase alfa) be approved for:

> *long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease characterised by one or more of the following, splenomegaly, hepatomegaly, anaemia, thrombocytopenia, or bone disease.*

Clinical questions: Resubmission

Biopharmaceutical study

1. In validation Report #70-66-027R, it was stated that "while testing serum samples of 52 individual healthy subjects, 15.38% (all data included: 24 samples of 156 samples tested, or 8.39% if outliers are excluded, 12 samples of 143) had a % inhibition value above the inhibitory cut-point and could be considered as 'Positive' for antibodies to plant glycans on taliglucerase alfa". Why was the ELISA validated in this report not used to test serum samples of patients with GD for antibodies to plant glycans on taliglucerase alfa?

Efficacy

1. What is the relationship between the taliglucerase alfa formulation used in the paediatric Study PB-06-005 and the formulation proposed for Australian marketing?
2. IgG ADA assessment has been carried out in 71 patients (43 ERT naïve; 28 ERT experienced) from Studies PB-06-001, PB-06-002, PB-06-003 and PB-06-005. Do these 71 patients include all patients from the relevant clinical studies who could have been tested? If not, what proportion of the total number of patients who could have been tested do these 71 patients represent? If they do not represent the total number of patients who could have been tested what were the reasons for selecting only a proportion of these patients for antibody analysis?
3. IgG ADA assessment has been carried out in 71 patients (43 ERT naïve; 28 ERT experienced), and of these patients 24 (33.8%) developed treatment-induced Ig ADA

while 47 (66.2%) were negative for treatment induced Ig ADA. Please provide data comparing efficacy in the 24 patients positive for treatment-induced Ig ADA with efficacy in the 47 patients negative for treatment-induced Ig ADA. The efficacy endpoints should include change from baseline in haemoglobin parameters, spleen volume, liver volume, platelet count and biomarker activity (chitotriosidase and CCL18). Please discuss any differences in efficacy observed between the two groups.

4. In the 71 patients assessed for Ig ADA there were 20 (28.2%) patients who experienced a Type I hypersensitivity reaction (10 antibody positive and 10 antibody negative patients). Please provide data comparing efficacy in the 10 antibody positive patients and the 10 antibody negative patients. The efficacy endpoints should include change from baseline in haemoglobin parameters, spleen volume, liver volume, platelet count and biomarker activity (chitotriosidase and CCL18). Please discuss any differences in efficacy observed between the two groups.
5. The SCS indicates that of 24 adult subjects with IgG ADA, 3 tested positive for neutralising activity in the in vitro assay but not in the in vivo assay. The efficacy response was reported as not appearing to decrease in the two ERT naïve patients with neutralising antibodies. However, the switch-over patient (that is, ERT experienced) who had neutralising antibody activity maintained organ volumes compared to baseline, but showed decreases in haemoglobin and platelet count at the last follow up visit. Please provide data comparing efficacy in the 3/24 IgG ADA positive patients with neutralising antibodies with the 21/24 IgG ADA positive patients without neutralising antibodies. The efficacy endpoints should include change from baseline in haemoglobin parameters, spleen volume, liver volume, platelet count and biomarker activity (chitotriosidase and CCL18). Please discuss any differences in efficacy observed between the two groups.
6. In the Addendum, immunogenicity overview, two appendices were provided showing the time course in individual patients for each of the four key efficacy endpoints of change from baseline in spleen volume, liver volume, haemoglobin and platelet count based on IgG ADA status for Studies PB-06-001, PB-06-002, and PB-06-003. Please provide tabulated summary data comparing the four efficacy outcomes in patients with and without IgG ADA at end of study for PB-06-002 and PB-06-003, and for PB-06-001 (if it differs from that provided in the original submission). Please comment on the observed differences in efficacy outcomes between IgG ADA positive and negative patients. It is noted that sponsor's current position is that "the relevance of ADA to therapeutic response is currently unclear".

Safety

1. In the SCS, the number of adult patients with at least one severe or very severe AE is reported as 17 in table 12 (consistent with table 21). However, in the first paragraph in section 2.7.4.2.1.1.2 it is stated that 23 adults experienced AEs that were severe of very severe. It is assumed that the 23 patients include separate counts for patients who experienced more than one event. Is this assumption correct?
2. In the SCS, in adults the number of AEs categorised as severe or very severe is given as 26 in table 13, but as 24 in tables 20 and 21. Please account for this apparent discrepancy.
3. In the SCS, treatment outcomes were provided for 20 patients tested for treatment-induced anti-taliglucerase alfa antibodies in whom an immune mediated Type I hypersensitivity event occurred: 10 subjects continued treatment with no intervention; 3 subjects discontinued treatment following events of Type I hypersensitivity, one of whom declined premedication; 5 subjects continued treatment with use of medications such as antihistamines for rash or pruritus; and 2

subjects who experienced Type I hypersensitivity continued treatment with a pre-treatment regimen. It is assumed that the 20 patients include the 10 patients who tested positive for treatment-induced anti-taliglucerase antibodies, and the 10 patients who tested negative for treatment-induced anti-taliglucerase antibodies. If this assumption is correct, please indicate whether the patients identified for each of the outcomes were antibody negative and/or antibody positive.

4. In the SCS, it is stated that there are 13 adult patients with 20 SAEs, while in tables 12 and 13 it is stated that there are 14 patients with 18 SAEs. Please account for the discrepancies.

5. In the SCS, it is stated that analysis of anti-taliglucerase alfa IgG antibody has been carried out with samples from 71 clinical study subjects, of which 24 (34%) had treatment induced antibody. It appears from tables 48 and 49 in the SCS that the 71 patients included 58 adults and 13 children, and that 22/58 adults and 2/13 children were treatment-induced IgG ADA positive. However, other data in the SCS suggests that of 43 ERT naïve patients, 19 (44.2%) were found to have treatment-induced IgG ADA (17/32 [53.1%] adults, 2/11 [18.1%] children), and of 28 ERT experienced patients, 5 (17.9%) were found to have IgG ADA (3/26 [11.5%] adults, 2/2 [100%] children). Therefore, these data suggest that of the 24 patients who were treatment-induced IgG ADA positive, there were 20/58 adults and 4/13 children. It is then stated in the SCS that the incidence of treatment-induced ADA responses were 19 of 32 treatment-naïve adults, 2 of 11 treatment-naïve paediatric subjects, and 5 of 28 subjects previously treated with other ERTs (26/71 subjects with treatment–induced IgG ADA).

   To further complicate the issue, it is stated in the Addendum, immunogenicity overview that "based on current assay cut-points, the incidence of post-treatment induced ADA responses observed was 17 of 32 treatment-naïve adult subjects who were monitored for up to 39 months (Studies PB-06-001/PB-06-003), 5 of 28 subjects (26 adult, 2 paediatric) previously treated with other ERTs who were monitored for up to 24 months (Studies PB 06- 002/PB-06-003), and 2 of 11 treatment-naïve paediatric subjects who were monitored for up to 12 months (Study PB-06-005)".

   Please explain the apparent discrepancies in the number of patients positive for treatment-induced IgG ADA in the submitted data. Please provide definitive data on the number of ERT naïve (total, adult, paediatric) and ERT experienced (total, adult, paediatric) patients who were treatment-induced IgG ADA positive in the clinical trial program.

6. Please comment on the notably higher proportion of ERT naïve patients who were treatment-induced IgG ADA positive compared with ERT experienced patients.

7. In the SCS, it is stated that of 24 adult patients with IgG ADA who were tested for neutralising antibody, 3 were determined to be positive for neutralising antibody assay and negative in the cellular uptake neutralising assay. However, table 48 of the SCS indicates that there were 25 patients assessed as Ig ADA positive (including 22 who were categorised as treatment-induced IgG ADA positive). Therefore, it appears that 1 of the 25 adult patients positive for Ig ADA was not tested for neutralising antibodies. Please clarify this matter.

8. In the SCS, table 49 indicates that 4 of the 13 paediatric patients tested were IgG ADA positive, and that 2 of these 4 patients were categorised as treatment-induced IgG ADA positive. Please confirm that the 4 IgG ADA positive patients all tested negative for neutralising antibodies.

9. The SCS indicates that subjects who experienced allergic reactions were tested by ELISA for IgE ADA in addition to the IgG ADA testing. Two patients were reported as

testing positive for IgE ADA and both were positive pre- and post-dose. How many patients were tested for IgE ADA and what was the outcome of testing? Please comment on the significance of pre-dose IgE ADA in these two patients. Was consideration given to assessing IgE ADA in all patients irrespective of allergic reactions?

10. In the SCS, table 48 indicates that 4/58 (6.9%) adult patients and 2/13 (15.4%) paediatric patients were IgG ADA positive pre-dose. Please comment on the significance of pre-dose IgG ADA in these patients.

Second round evaluation of clinical data submitted in response to questions: Resubmission

Overview of the clinical aspects of the response to TGA questions

The sponsor provided comprehensive responses to the clinical questions raised following the first round evaluation of the submission.

The sponsor's responses and the clinical evaluation of the response are shown under *Second round evaluation of clinical data submitted in response to questions* in Attachment 3 (CER 2) of this AusPAR.

In addition, the final study report for Study PB-06-002 was provided in the sponsor's response. Other information in the response were: (i) a protocol (B3031002) for A Multicenter, Multicountry, Postmarketing Active Surveillance Taliglucerase Alfa Registry in Patients with GD; (ii) an in vitro bioanalytical study detailing the development of an ELISA for the detection of anti-taliglucerase alfa plant-specific glycan antibodies in human serum (PCL-12-010); and (iii) an in vitro bioanalytical study describing ELISA based assay to compare the binding of anti- taliglucerase alfa antibodies to taliglucerase alfa with their binding to imiglucerase (PCL-11-020). The clinical information also included literature references relevant to the sponsor's response to the clinical questions. The evaluation of these additional data is shown under *Second round evaluation of clinical data submitted in response to questions* in Attachment 3 (CER 2) of this AusPAR. Summaries of these additional data are incorporated in the *Second round benefit-risk assessment: Resubmission*, below.

Second round benefit-risk assessment: Resubmission

Second round assessment of benefits

After consideration of the sponsor's response to the clinical questions, and to the clinical aspects of the sponsor's response to quality questions it is considered that the benefits of treatment with taliglucerase remain favourable.

The benefits of treatment with taliglucerase alfa (30 units/kg; 60 units/kg) in ERT naïve and ERT experienced adult and paediatric patients with non-neuropathic GD include reduction in spleen volume, reduction in liver volume, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been shown to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced). The duration of treatment with taliglucerase alfa in the pivotal Phase III studies was 12 months in children and adolescents aged 2 to < 18 years in Study PB-06-005, and 9 months in adults aged ≥ 18 years in Study PB-06-001. In addition, Study PB-06-002 showed that in adults and children/adolescents whose disease had been stabilised with imiglucerase, the treatment benefit could be maintained for at least a further 9 months after switching to taliglucerase alfa. Support for treatment benefit

achieved with imiglucerase being maintained following switching to taliglucerase alfa was also provided by Study PB-06-004 (expanded access treatment protocol). Furthermore, Study PB-06-003 showed that patients from Studies PB-06-001 and PB-06-002 who had benefited from 9 months treatment with taliglucerase alfa could continue to benefit from further treatment with taliglucerase alfa for at least 15 months.

Clinical data provided in the sponsor's response to clinical questions showed that in the cohort of 71 patients with IgG ADA assessments from the clinical trial program the presence of treatment-induced IgG ADA did not impair the efficacy of taliglucerase alfa. In fact, the absolute change from baseline in the pooled analysis (PB-06-001, PB-06-005) at the last measure (1 May 2012) was consistently greater in the treatment-induced ADA positive group (n = 24; 33.8%) compared with the ADA negative group (n = 47; 66.2%) across all six efficacy endpoints. The reason for this observation is unclear. Limited data from three IgG ADA positive patients with neutralising antibodies suggests that the presence of neutralising antibodies might have a negative impact on efficacy. However, it is unclear whether the negative impact on efficacy of neutralising antibodies is clinically meaningful.

Clinical data provided in the sponsor's response to questions in the first round evaluation included an assessment of the effect of anti-taliglucerase alfa plant-specific glycan antibodies on efficacy using previous data from the 71 patients with an IgG ADA assessment. This new analysis identified 29 out 71 patients (40.8%) who were IgG ADA positive at any time-point (baseline and/or post-baseline) and 42 out of 71 patients (59.2%) who were IgG ADA negative. The efficacy assessments included comparison of patients positive for anti-taliglucerase alfa plant-specific glycan antibodies (8/71, 11.3%), patients who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies but were IgG ADA positive (21/71, 29.6%), and patients who were IgG ADA negative or were IgG positive but anti-taliglucerase alfa plant-specific glycan antibody negative (63/71, 88.7%). Overall, no significant efficacy differences between patients who were positive or negative for anti-taliglucerase alfa plant-specific glycan antibodies were observed for the efficacy endpoints of spleen volume, liver volume, haemoglobin level, platelet count, chitotriosidase activity and CCL18 level. However, the interpretation of the data is limited by the small number of patients (n = 8) who were anti-taliglucerase alfa plant-specific glycan antibody positive.

Second round assessment of risks

After consideration of the sponsor's response to the clinical questions, and to the clinical aspects of the sponsor's response to the quality questions it is considered that the risks of treatment with taliglucerase alfa for GD remain favourable.

There are limited data on the safety of taliglucerase alfa in children and adolescents due to the small number of patients with GD aged ≤ 18 years treated with the medicine in the clinical trial program. However, the available data in children and adolescents suggests that the risks of treatment in this age group are similar to those in adults.

The data summarised below are from the integrated SCS provided in the current submission unless otherwise stated. The additional safety data relating to the Final Study Report for PB-06-002 provided in the response to TGA questions were almost identical to the previously evaluated interim safety data for this study. The final safety data from Study PB-06-002 have no substantial effect on the general safety conclusions drawn from the evaluation of the integrated SCS.

The sponsor's response to questions in this evaluation [resubmission] included a significant amount of additional data concerning the immunogenicity of taliglucerase alfa and the effect of IgG anti-taliglucerase alfa antibody status (that is, IgG ADA status) on safety. In the clinical trial program, assessment of IgG ADA status was carried out in a total

of 71 patients (43 ERT naïve, 28 ERT experienced). Of the 43 ERT-naïve patients, 19 (44.2%) were found to have treatment-induced IgG ADAs (17/32 [53.1%] adults, 2/11 [18.1%] children). Of the 28 ERT experienced patients, 5 (17.9%) were found to have treatment-induced IgG ADAs (3/26 [11.5%] adults, 2/2 [100%] children). The proportion of ERT naïve patients who developed treatment-induced IgG antibodies was notably higher than in ERT experienced patients. The sponsor postulates that patients treated with taliglucerase alfa who had been previously exposed to ERT might have been more immune tolerant and less likely to develop antibodies with further glucocerebrosidase treatment than ERT-naïve patients treated with taliglucerase alfa.

The response to TGA questions provides data from an analysis of anti-taliglucerase alfa plant-specific glycan antibodies in the 71 patients who were tested for treatment-induced IgG ADAs. This analysis identified 29 patients who were confirmed IgG ADA at any time point (baseline and/or post-baseline) of whom 8 were positive for anti-taliglucerase alfa plant-specific glycan antibodies and 21 were negative for these antibodies (Cohort A). Combining the 21 IgG ADA positive patients who were negative for anti-taliglucerase alfa plant-specific glycan antibodies with the 42 IgG ADA negative patients resulted in 63 patients being considered to be negative for anti-taliglucerase alfa plant-specific glycan antibodies (Cohort B). Therefore, of the 71 patients with IgG ADA data, 8 (11.3%) were positive for anti-taliglucerase alfa plant-specific glycan antibodies and 63 (88.7%) were negative for these antibodies.

The sponsor's response included a comparison of safety in the 8 patients with anti-taliglucerase alfa plant-specific glycan antibodies with the 21 patients in Cohort A, and with the 63 patients in Cohort B. Treatment-related AEs occurred more frequently in subjects who were considered to be anti-taliglucerase alfa plant-specific glycan antibody positive (9 events in 8 patients, estimated frequency of 1.4 events/patient) compared with subjects who were considered to be negative for these antibodies (44 events in 63 patients, estimated frequency of 0.7 events/patient). However, these figures should be interpreted cautiously due to the marked imbalance between the two patient groups. Of the 8 patients with anti-taliglucerase alfa plant-specific glycan antibodies, 5 experienced 9 treatment-related AEs while 3 reported no treatment-related AEs. Each of the 9 treatment-related AEs was reported only once. Seven (7) of the 8 patients continued treatment with taliglucerase alfa despite the detection of anti-taliglucerase alfa plant-specific glycan antibodies, while 1 patient discontinued treatment due to a possible allergic reaction (itching, rash, skin irritation). Four (4) of the 8 patients had anti-taliglucerase alfa plant-specific glycan antibodies prior to taliglucerase alfa treatment while the other 4 patients had treatment-induced anti-taliglucerase alfa plant-specific glycan antibodies. Overall, no obvious safety signals of particular concern associated with anti-taliglucerase alfa plant-specific glycan antibodies were identified in the submitted data.

Adverse events related to taliglucerase alfa for the treatment of GD appear to require no specific intervention, or are manageable by symptomatic treatment for infusion-related and non-infusion related AEs, or by prophylactic premedication for infusion-related AEs. The risk of treatment discontinuation due to AEs related to taliglucerase alfa is low. Treatment discontinuation due to AEs in the taliglucerase alfa clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 reports of hypersensitivity; 1 of eye swelling). No treatment discontinuations due to AEs were reported in children.

In adults, 93.1% (108/116) of patients experienced at least one AE (all causality). The most commonly reported AEs (>10% of patients) in adults were nasopharyngitis (23.3%), arthralgia (23.3%), headache (22.4%), viral upper respiratory tract infection (19.8%), pain in extremity (16.4%), cough (15.5%), fatigue (12.9%), abdominal pain (11.2%), pyrexia (11.2%), back pain (11.2%), diarrhoea (10.3%), nausea (10.3%), and oropharyngeal pain (10.3%).

In children, 75.0% (12/16) of patients experienced at least one AE (all causality). The most commonly reported AEs (> 10% of patients) in children were vomiting (31.3%), abdominal pain (18.8%), nasopharyngitis (18.8%), headache (18.8%), pain in extremity (18.8%), tonsillitis (12.5%), diarrhoea (12.5%), arthralgia (12.5%), epistaxis (12.5%), and tooth extraction (12.5%).

In both adults and children, the risk of experiencing AEs was greater in ERT naïve patients compared with ERT experienced patients.

The risks of experiencing AEs appear to be minimal for the following groups of disorders "blood and lymphatic system", "cardiac", "hepatobiliary", "renal and urinary" and "skin and subcutaneous tissue".

Serious AEs were reported in 11.2% (n = 13) of adult patients and 12.5% (n = 2) of paediatric patients. In adults, none of the SAEs were considered to be treatment-related and no single preferred term was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation). No deaths have been reported in the taliglucerase alfa clinical trial program for GD, but there was 1 death reported in the Compassionate Use Program considered to be unrelated to treatment (tuberculosis/pneumonia).

Investigator-designated treatment-related AEs reported during or within 2 h of completion of taliglucerase alfa infusions occurred commonly, and were observed in 27.6% of adult patients (32/116) and 12.5% (2/16) of paediatric patients. The most commonly reported investigator-designated treatment related AEs reported during or within 2 h of completion of the infusion in adult patients (≥ 2% of patients) were hypersensitivity (4.3%), nausea (3.4%), infusion-related reactions (3.4%), headache (3.4%), pruritus (3.4%), rhinorrhoea (2.6%), sneezing (2.6%) and flushing (2.6%). In the 2 paediatric patients, the events were gastrointestinal inflammation and vomiting in 1 patient and chest discomfort in 1 patient.

There was a risk of Type I hypersensitivity AEs (acute allergic reactions) in patients treated with taliglucerase alfa. These events occurred predominantly in adult patients, but this might reflect the greater number of adult patients exposed to taliglucerase alfa compared with paediatric patients. In adults, 20 patients (17.2%) experienced one or more Type I hypersensitivity AEs (68 events in total), and all events were reported as being mild/moderate in intensity. The events reported in the 20 adult patients were pruritus in 11 (9.5%), hypersensitivity in 5 (4.3%), eye swelling in 2 (1.7%), and 1 (0.9%) patient each for eye oedema, scleral oedema, lip swelling, and face oedema. One (1) Type I hypersensitivity AE was reported in 1 paediatric patient (angioedema).

Treatment-related (investigator designated) Type I hypersensitivity AEs were reported in 18 adult patients, and no children. Of the events reported in the 18 adult patients, 10 patients required no intervention or only temporary intervention to manage the events, while 8 patients required significant intervention characterised by premedication or treatment discontinuation. The required interventions in the 8 patients were: 2 patients with hypersensitivity and 1 patient with pruritus/eye oedema continued infusions with premedication; 4 patients discontinued treatment because of hypersensitivity or hypersensitivity-related events, and in 3 of these patients discontinuation occurred with the first infusion; and 1 patient experienced multiple mild AEs of eye swelling in spite of premedication and decided to discontinue taliglucerase alfa and return to imiglucerase. Perusal of the case narratives for the 5 patients experiencing events described as "hypersensitivity" indicates that these included typical acute allergic reactions such as flushing, tightness in the chest wheezing, urticaria, itching, chills, periorbital oedema, lacrimation and rhinorrhoea.

There appears to be an increased risk of Type I hypersensitivity reactions in patients testing positive for treatment-induced IgG ADA compared with patients testing negative

(9/24 [37.5%] versus 9/47 [19.1%], respectively). Re-analysed data provided in the response to TGA questions indicate that of the 18 patients who were tested for treatment-induced IgG ADA and experienced Type I hypersensitivity AEs: 50% (9/18) continued treatment with taliglucerase alfa with no intervention (28% [5/18] treatment-induced ADA positive, 22% [4/18] treatment-induced negative); 17% (3/18) discontinued treatment with taliglucerase alfa (6% [1/91] treatment-induced ADA positive, 11% [2/18] treatment-induced negative); 22% (4/18) continued treatment with taliglucerase alfa with use of medications to control symptoms of AEs (11% [2/18] treatment-induced ADA positive, 11% [2/18] treatment-induced ADA negative); and 11% (2/18) continued treatment with taliglucerase alfa with a premedication treatment regimen (6% [1/18] treatment-induced ADA positive, 6% [1/18] treatment-induced ADA negative). The data show that IgG ADA status in the 18 re-analysed patients reported to have experienced Type I hypersensitivity reactions had no effect on the clinical intervention taken to manage the reactions. Consequently, although Type I hypersensitivity reactions occur more commonly in IgG ADA positive patients than in IgG ADA negative patients, clinical management of the events is similar regardless of IgG ADA status.

Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adult patients (9/116 [7.8%]). Of the 14 reported events, 13 were categorised as mild or moderate in severity and 1 as severe (autoimmune thrombocytopaenia, non-treatment related SAE). Events reported in more than 1 patient were arthritis (3 patients, 2.3%) and contact dermatitis (2 patients, 1.5%). All other events occurred in 1 (0.8%) patient each (autoimmune thrombocytopenia, drug eruption, dyshidrosis, macula-papular rash). The only Type II-IV hypersensitivity AE reported as treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

Bone events were reported in 55 (47.4%) adult patients, and SAE bone events were reported in 2 (1.7%) adult patients. In 8 (6.9%) adult patients, bone events were judged by the investigator to be related to treatment, and the majority of these events were described as musculoskeletal discomfort (15 events; all in 1 patient). Of the treatment-related bone events in adults, 4 occurred during the infusion or within 2 h after the completion of the infusion (arthralgia, back pain, muscle spasm, and musculoskeletal discomfort [14 events in 1 patient]). In children, 5 (31.3%) patients experienced bone events, and none of the events were considered to be SAEs. There was 1 (6.3%) paediatric patient with a bone event judged by the investigator to be treatment-related (pain in extremity). None of the bone events reported in children occurred during the infusion or within 2 h of the completion of the infusion.

The risks of taliglucerase alfa inducing abnormalities in clinical laboratory tests, vital signs, ECGs, ECHOs, or pulmonary function tests appear to be minimal.

Overall, there is limited information on the risks of taliglucerase alfa in patients with GD aged from > 2 years to < 18 years (n = 16), and there is no information on the risks of treatment in patients aged ≤ 2 years. There is limited information on the risks of treatment in patients with GD aged ≥ 65 years (n = 8). There is no meaningful information on the risks of taliglucerase alfa treatment in non-Caucasian patients (n = 5). The risk of experiencing commonly reported AEs appears to be greater in female than in male patients, but there is no evidence that the taliglucerase alfa treatment regimen should differ for females and males.

There are no data on the risks of taliglucerase alfa in patients with neuronopathic GD, patients with pre-existing hepatic disease, patients with pre-existing renal disease or patients with pre-existing cardiovascular disease. There are no data on the potential risks of drug-drug interaction involving taliglucerase alfa and other co-administered medicines.

Second round assessment of benefit-risk balance

After consideration of the clinical aspects of the sponsor's response to TGA questions it is considered that the benefit-risk balance of taliglucerase alfa, given the proposed usage, remains favourable. The data provided in the original and current submissions are considered to have satisfactorily demonstrated the efficacy and safety of taliglucerase alfa for the treatment of non-neuropathic GD in both adult and paediatric patients.

The benefits of treatment with taliglucerase alfa in ERT naïve and ERT experienced patients with non-neuropathic GD include clinically meaningful reductions in spleen and liver volumes, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been observed to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced).

The risks of treatment with taliglucerase alfa in both adults and children with non-neuropathic GD are considered to be acceptable. Although AEs occurred very commonly in both adults and children treated with taliglucerase alfa (93.1%, 108/116 and 75.0%, 12/16, respectively), these events generally required either no intervention or were manageable with symptomatic treatment. Treatment discontinuation due to AEs in the clinical trial program for GD was reported in only 3 (2.6%) adult patients (2 reports of hypersensitivity; 1 of eye swelling). No treatment discontinuations resulting from AEs were reported in children.

Serious AEs were reported in 11.2% (n = 13) of adult patients and 12.5% (n = 2) of paediatric patients. In adults, none of the SAEs were considered to be treatment-related and no single preferred term event was reported in more than 1 patient. In children, 1 SAE was considered to be treatment-related (gastrointestinal inflammation). No deaths have been reported in the GD clinical trial program, but there was 1 death reported in the Compassionate Use Program considered to be unrelated to treatment (tuberculosis/pneumonia).

In 71 patients who were tested for IgG anti-taliglucerase alfa antibodies (ADAs), 24 (33.8% developed treatment-induced IgG ADAs while 47 (66.2%) were negative for these antibodies. However, the presence of IgG ADAs appeared not impair the efficacy of taliglucerase alfa. In addition, the benefits of treatment with taliglucerase were similar in patients considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies and patients considered to be negative for these antibodies. However, there was a marked imbalance in patient numbers between those considered positive and those considered negative anti-taliglucerase alfa plant-specific glycan antibodies (8/71, 11.3% and 63/71, 87.7%, respectively).

The most clinically important risks of treatment with taliglucerase alfa are considered to relate to Type I hypersensitivity reactions (acute allergic reactions). In adults, 18 (15.5%) patients were reported as experiencing investigator-designated treatment-related Type I hypersensitivity reactions. These reactions were manageable by no intervention or temporary intervention in slightly more than half of the cases (10/18), while slightly less than half of the cases (8/18) were managed by premedication or treatment discontinuation.

There appears to be an increased risk of Type I hypersensitivity reactions in patients testing positive for treatment-induced IgG anti-taliglucerase antibodies (ADAs) compared with patients testing negative (9/24 [37.5%] versus 9/47 [19.1%], respectively). However, there did not appear to be a difference in the severity of Type I hypersensitivity reactions between IgG ADA positive and negative patients, and management of these reactions was similar in both patient groups. Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (7.8%, 9/116), and the only event

considered to be treatment-related was drug-eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

The frequency (events/patient) of treatment-related and all causality AEs was greater in patients considered to be anti-taliglucerase alfa plant-specific glycan antibody positive than in patients considered to be negative for these antibodies. However, as noted previously there was a marked imbalance in patient numbers between those considered to be positive and those considered to be negative for these antibodies. Furthermore, of the 8 patients considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies, 7 continued treatment with taliglucerase alfa while 1 discontinued treatment due to what appears to be a hypersensitivity reaction to taliglucerase alfa. Overall, the limited data suggest that the presence of anti-taliglucerase alfa plant-specific glycan antibodies does not present a significant treatment risk.

There is an important risk-benefit issue relating to whether treatment with taliglucerase alfa should be confined to adult patients with GD (that is, patients aged ≥ 18 years). The clinical data in children and adolescents (2 to < 18 years) are limited, but suggest that the benefits and risks of taliglucerase alfa are similar in children/adolescents and in adults. Overall, it is considered that treatment with taliglucerase alfa should not be restricted to adult patients aged ≥ 18 years.

Second round recommendation regarding authorisation: Resubmission

After consideration of the sponsor's response to the clinical questions and to the clinical aspects of the sponsor's response to the quality questions it is recommended that Elelyso (taliglucerase alfa) be approved for:

> *"Elelyso is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease characterised by one or more of the following, splenomegaly, hepatomegaly, anaemia, thrombocytopenia, or bone disease".*

The clinical evaluator's recommended revisions to product literature are beyond the scope of the AusPAR.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), EU-RMP Version 3.3, dated 18 June 2012, with an Australian Specific Annex (ASA) Version: 1.0, dated 14 March 2013, which was reviewed by the TGA's Office of Product Review (OPR).

Summary of ongoing safety concerns

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7: Summary of ongoing safety concerns

Ongoing safety concerns	
Important identified risks	Hypersensitivity Other infusion related reactions

Ongoing safety concerns	
Important potential risks	Immunogenicity Off-label paediatric use Prolonged activated partial thromboplastin time Elevated liver enzymes
Important missing information	Pregnancy and lactation Paediatric Elderly patients (≥ 65 years) History of allergy to carrots Presence of neuronopathic Gaucher disease Anaphylactoid or infusion-related reaction to previous ERT Potential drug-drug interactions History of pre-existing hepatic impairment History of pre-existing renal impairment History of pre-existing cardiovascular disease Long term treatment

OPR reviewer comment:

Notwithstanding the evaluation of the clinical aspects of the safety specification (SS), it is considered that this list of ongoing safety concerns is acceptable.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.

The sponsor proposes to further monitor and characterise all the specified ongoing safety concerns by conducting a prospective, multi-centre, multi-country, non-interventional active surveillance drug registry of patients with GD undergoing taliglucerase alfa treatment. The registry will be operational for at least ten years.

Risk minimisation activities

Routine risk minimisation activities are proposed.

The EU-RMP states that based on the data, the sponsor proposes that no risk minimisation plan is necessary at this time. The ASA states in relation to additional risk minimisation activities specific to Australia: *"There are no specific risk minimisation activities for Australia at this time."*

OPR reviewer comment:

The specified ongoing safety concerns would not appear to warrant additional risk minimisation activities, except for perhaps the important identified risk: 'Infusion-related reactions and hypersensitivity' in the context of home administration.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the evaluators through the TGA consolidated request for further information and/or the CER. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states that the TGA request for information did not include any safety considerations from the clinical evaluator and the CER had not yet been issued for this application. However, the sponsor has noted the recommendations by the RMP evaluator and will consider any safety concerns raised by the TGA and will provide information that is relevant and necessary to address the issue in the RMP, as necessary. The sponsor has also advised that a revised EU-RMP will be available in December 2013.	In relation to the clinical aspects of the safety specification, the clinical evaluator advised the following: *"The SS in the draft RMP (Version 3.3, dated 18 June 2012) is not entirely satisfactory and should be revised, having regard to the following:* *The RMP (3.3, dated 18 June 2012) does not reflect all the data submitted to the TGA in the resubmission of 7 April 2013. The RMP should be updated to include the safety information from the Summary of Clinical Safety provided in the resubmission. However, while the safety data in the RMP should be updated, no new safety signals or concerns were identified in the SCS provided in the resubmission."* In light of these comments, the sponsor should advise whether the safety data in the EU-RMP has been updated accordingly. If not, the sponsor should provide an assurance that the EU-RMP will be so updated at the next opportunity.
The sponsor should provide the final	The sponsor has now provided a copy of the	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
protocol for the taliglucerase alfa exposure registry, as agreed with by the US FDA, to the TGA when it becomes available and include it as an attachment to the ASA when this document is next updated.	final taliglucerase alfa registry protocol (B3031002, amendment 3, dated 11 October 2013 as approved by the US FDA) and an assurance that a copy will be included as an attachment in the revised ASA for taliglucerase alfa, once finalised. The sponsor also commits to updating the ASA in line with the availability of the revised EU-RMP, estimated to be available in December 2013.	
Another post-marketing requirement to the US FDA was to complete the ongoing trial PB-06-002, entitled *"A Multicenter, Open-label, Switchover Trial to Assess the Safety and Efficacy of Taliglucerase alfa in Patients with Gaucher Disease Treated with Imiglucerase (Cerezyme) Enzyme Replacement Therapy."* This trial will obtain safety and efficacy data in adult and paediatric patients with Type 1 GD, including data on allergic and immune-mediated reactions, and unexpected risks from antibody development. The sponsor should provide compelling justification as to why this ongoing study has not been included in the pharmacovigilance plan. Alternatively the sponsor may include this ongoing study in the	The sponsor advised that Study PB-06-002 is now complete and the Clinical Study Report is provided for assessment of safety data only. Additional studies are also underway in which safety data with relevance to the RMP will be collected. A final protocol for Study B3031002 and synopses for Studies PB-06-006 and PB-06-007 have been provided. The post-marketing registry protocol (B3031002) is now finalised and will be included in the RMP pharmacovigilance plan and ASA. The ongoing clinical Studies PB-06-006 and PB-06-007 are extension studies in paediatric and adults, respectively. These studies have also been included in the pharmacovigilance plan.	This is acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
pharmacovigilance plan and amend the ASA accordingly.		
The sponsor should provide a tabular 'Summary of the Risk Management Plan in Australia' in a revised ASA, including reference to specific routine risk minimisation in the Australian PI.	The sponsor provided a tabular summary including columns addressing each individual safety concern, the proposed pharmacovigilance activities for each concern and the proposed risk minimisation activities. The proposed risk minimisation activities include relevant text from the Australian PI. The sponsor has provided an assurance that the ASA will be updated to include this tabular summary.	This is acceptable.
The studies referenced in the pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	The sponsor has now provided details of the ongoing interventional and non-interventional clinical studies and anticipated submission dates in Australia in a table. The sponsor commits to updating the ASA in line with the availability of the revised RMP, with these details as an attachment in the ASA.	This is acceptable.
As previously agreed the specified ongoing safety concerns would not appear to warrant additional risk	The sponsor has noted these comments.	NA

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
minimisation activities, except for perhaps the important identified risk: 'Infusion-related reactions and Hypersensitivity' in the context of home administration).		

Summary of recommendations

The OPR recommended to the Delegate that the conditions of registration should include the following:

- The European RMP (Version: 3.3, dated 18 June 2012) with an Australian Specific Annex (Version: 1.0, dated 14 March 2013), to be revised as specified in the sponsor's correspondence dated 30 November 2013, must be implemented.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Taliglucerase alfa rpc (Elelyso) powder for injection in a single use vial is proposed for registration as follows:

> *Elelyso is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopaenia, bone disease.*

After the powder is reconstitution with water for injection, the solution contains 40 units (approximately 1.2 mg) of taliglucerase alfa rpc per mL, the reconstituted volume allowing accurate withdrawal of a total of 5.0 mL, equivalent to 200 units, from each vial.

An application for Elelyso was submitted to the TGA in 2011 (PM-2011-00478-3-3). The nonclinical and clinical evaluators recommended approval based on the respective data sets submitted for Module 4 and for Module 5. A number of quality related deficiencies in the Module 3 data set were identified by the biochemistry (quality) evaluator, deficiencies which could not be resolved within the allotted evaluation period. Pfizer, the sponsor, decided to withdraw the application in April 2012.

At a subsequent meeting held between Pfizer and the TGA on 8 June 2012, agreement was reached on the content of any resubmission dossier. A dossier with a complete Module 3 would be prepared and submitted. The resubmission dossier was to contain only new and updated clinical data; no new nonclinical data were available for the resubmission. Clinical and nonclinical data previously evaluated by the TGA for the original submission would remain applicable to the resubmission. The resubmission of April 2013, numbered PM-2013-00303-1-3, is this new submission.

The major deficiency identified in the original submission by the biochemistry evaluator was that pertaining to the characterisation of the glycosylation profile of the drug taliglucerase alfa rpc and of any immunogenicity effects related to that profile. As a result there is considerable attention devoted to what is known about the clinical immunogenicity profile of the drug by the clinical evaluator.

Quality

Advice from the September 2013 meeting of the PSC was sought for this submission (PM-2013-00303-1-3) The PSC's concerns about the marked difference between levels of some glycoforms of the drug substance in the formulation used in the clinical trials and that in the formulation proposed for registration were allayed by the fact that the sponsor had been able to supply much more detailed information about the glycosylation profile of the drug. The PSC maintained its concern in relation to the possible immunogenic profile of the drug and recommended that the sponsor should be asked to provide data on antibody status in subjects at baseline and after treatment. Overall, the PSC was of the view that the Module 3 data, particularly with regard to glycosylation and immunogenicity profiles, rendered the submission unacceptable.

Nonetheless and in accordance with standard practice, the Module 3 evaluation continued (see *Quality summary and conclusions* above).

Taliglucerase alfa is a recombinant form of the human lysosomal enzyme, β-glucocerebrosidase. During development, a number of manufacturing process changes were made, some of which had [limited] effects on the composition of the product. The accumulated difference in levels of some glycoforms meant that the batches made by the final commercial process have significantly different levels of some glycans from those used in the early stages of the Phase III clinical trials. The clinical impact of this difference has been assessed in detail in the clinical evaluation report.

The amino acid sequence was confirmed and the secondary, tertiary and quaternary structures supported with evidence. Disulphide bonding and N-glycosylation sites were demonstrated. The oligosaccharides were comprehensively profiled and the commercial product shown to be consistently glycosylated. The drug substance was shown to have full enzyme activity.

The major glycan will direct the product to the lysosome without modification but the xylose and α(1,3) linked fucose are plant-specific sugars reported to be immunogenic in humans and animals. The issue of immunogenicity of the drug has been examined in detail in the clinical evaluation report.

The drug product is supplied in a carton with a single use vial containing 200 units of the enzyme in powder form. The powder is reconstituted with water for injection, diluted with normal saline and infused intravenously over a period of 1-2 h once every two weeks. The proposed specifications of the drug product are satisfactory.

The proposed shelf life of the drug product is two years when stored at 2-8°C. A single thermal cycling study on a single batch was conducted but this gave equivocal results. The Module 3 evaluator has recommended both a further thermal cycling study and the imposition of a temporary registration provision that storage should be maintained at 2-8°C including the maintenance of a cold chain during transport with an excursion to no more than 27°C for no more than 96h.

The Delegate proposed that the provision (above) will remain in place until a new cycling study is submitted to the TGA to change it. In its response to this overview, the Delegate requested the sponsor provide an assurance that all necessary monitoring and recording equipment will be in place to satisfy the provision, particularly during any shipping or transport of the drug. Furthermore, the sponsor is requested to provide information on

whether the temperature records generated will be available for audit and who will be auditing these records.

Quality evaluator's recommendation

Overall, the Module 3 evaluator has no objection to the approval of Elelyso (taliglucerase alfa rpc) 200 units powder for injection for infusion. The sponsor had provided sufficient glycosylation data overall to permit the Module 3 evaluator to make meaningful recommendations. For example, while some clinical trial batches would have been potentially less immunogenic than those for commercial distribution, it became apparent that patients were exposed to products with both glycosylation states during the clinical trials. There was considerable discussion of this issue in the clinical evaluation reports.

Nonclinical

Taliglucerase alfa showed dose dependent uptake into human peripheral blood macrophages in vitro, such uptake being comparable with that of imiglucerase. The in vivo efficacy of taliglucerase alfa was not demonstrated in any non-clinical model such as the mouse model of GD.

Pharmacokinetic studies using marmoset and cynomolgus monkeys receiving IV doses of taliglucerase alfa indicated saturation of clearance at high doses. The elimination half-life values for marmosets ranged from approximately 12 to 50 min, depending on the dose of taliglucerase alfa and were comparable with those reported from human studies. Repeat dosing with taliglucerase alfa in both species had no marked effect on PK parameters, although some results suggested induction of clearance mechanisms.

Toxicity studies demonstrated no significant toxicological effects (general and reproductive toxicity) associated with taliglucerase alfa dosing in animal species at exposures considerable higher than those anticipated clinically. A significant fraction of both marmoset and cynomolgus monkeys developed anti-taliglucerase alfa antibodies after several doses. These antibodies were not neutralising and importantly appeared to have no impact on the toxicity studies.

Given taliglucerase alfa's mode of action, its terminally differentiated target cells and the assumed lack of genotoxicity of the products of its enzymatic action, possible genotoxic or carcinogenic action by taliglucerase alfa was not examined.

Nonclinical evaluator's recommendation

The nonclinical evaluator concluded that there are no nonclinical objections to the approval of taliglucerase alfa for the proposed indication provided efficacy is demonstrated in the clinical studies.

Recommendations for the amendment of the PI have been addressed.

Clinical

Four clinical evaluation reports were prepared for this application: the first two (first and second round CER 1; Attachment 2 of this AusPAR) arising from the first submission and the second two (first and second round CER 2; Attachment 3 of this AusPAR) arising from the current submission. Clinical evaluation report 1 (CER 1) deals with all the usual clinical studies expected in a submission of this type, from early PK studies in healthy human volunteers to pivotal Phase III studies in subjects with GD. Clinical evaluation report 2 (CER 2) assesses a new paediatric study, updated clinical study reports (some of the studies in the original submission had interim reports only) and also assesses the

many analyses undertaken by the sponsor to determine whether there were any possible hitherto unidentified immunogenicity effects on either efficacy or safety.

In the second round of CER 2 (the final clinical evaluation report), the clinical evaluator notes that there is an important risk-benefit issue relating to whether treatment should be confined to adult patients with GD. While the clinical data in children and adolescents is limited, it did suggest that the benefits and risks of taliglucerase are similar in children and adolescents and in adults. Overall, the clinical evaluator was of the opinion that treatment with taliglucerase alfa should not be restricted to adult patients.

Finally the proposed indications include the sub-population of subjects with GD who exhibit bone disease. However, no parameter relating to bone disease was included in the inclusion criteria for the pivotal clinical trial, nor was any parameter related to bone disease examined as a primary efficacy endpoint or even a major secondary endpoint.

Pharmacology

Pharmacokinetics

The PK properties of taliglucerase alfa were assessed in healthy volunteers in one Phase I study, P-01-2005 and in patients with GD in the pivotal Phase III clinical efficacy and safety study, PB-06-001.

- Study P-01-2005

This was an initial, Phase I, first-in-human, single centre, non-randomised, open-label safety and PK study of taliglucerase alfa administered by IV infusion over 1.5 h to 6 human volunteers. The four administered treatments were 1 vehicle treatment and 3 increasing dose treatments of taliglucerase alfa (15, 30 and 60 units[14]/kg body weight). The elimination of taliglucerase alfa was rapid for both the 30 and 60 units/kg doses with the mean half-life being 8 minutes [range 8-9] and 17 minutes [range 13-21], respectively.

- Study PB-06-001

This was the pivotal, Phase III, multi-centre, randomised, double-blind, parallel-group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in 30 untreated patients with GD, the latter receiving an infusion every two weeks over a 9-month period. There were two different dosage groups: Group I: 30 units/kg every 2 weeks, and Group II: 60 units/kg every 2 weeks.

The mean normalised $AUC_{0\text{-}t}$ values for the 60 units/kg dose were 1.4 fold and 1.5 fold higher than for the 30 units/kg dose on day 1 and at week 38, respectively, with overlapping ranges at both time points for the two doses. The mean normalised C_{max} values for the 60 units/kg dose were 1.3 fold and 1.6 fold higher than for the 30 units/kg dose on day 1 and at week 38, respectively, with overlapping ranges at both time points for the two doses. These results suggest that the uptake of taliglucerase alfa into target cells is saturable.

Exposure does not notably increase between Day 1 and Week 38 following IV infusion once every 2 weeks at either dose.

In patients with GD, the mean volumes of distribution in the elimination phase were 17.5 L [range 6.2 to 50.0] and 16.8 L [range 7.0 to 55.3] at Day 1 and at Week 38, respectively, for the 30 units/kg dose. The corresponding values for the 60 units/kg dose were 11.7 [range 5.7 to 55.3] at Day 1 and 14.4 L [range 3.9 to 24.8] at Week 38.

[14] One (1) unit of taliglucerase alfa = the amount of enzyme which catalyses the hydrolysis of 1 micromole of the synthetic substrate paranitrophenyl-beta-D-glucopyranoside (pNP-G1c) per minute at 37^0C.

Overall, there was marked inter-subject variability in the PK parameters for both doses in patients with GD, with the ranges being wide and overlapping. This is not unexpected. The mean values for the major parameters differed between the two doses and this suggests non-linear PK.

The PK profile of taliglucerase alfa has not been completely characterised, which is not unusual. There were no PK data in paediatric, adolescent or elderly subjects. There were no PK data on metabolism or excretion of taliglucerase alfa. Nor were there any PK data in subjects with either hepatic or renal impairment.

In the round 2 of CER 1, the clinical evaluator evaluated the sponsor's response to a question about the anomalous results for a subject (outlier) in the Phase I study in healthy human volunteers (P-01-2005). The question was a minor one and the sponsor's response was satisfactory.

Pharmacodynamics

The submission contained no specific studies investigating the pharmacodynamics of taliglucerase alfa in humans. However, as noted by the clinical evaluator, the mechanism of action of ERT for the treatment of GD is well known.

Other reports

The current submission included no additional clinical PK studies but did include 3 biopharmaceutical reports of bioanalytical methods for human studies.

None of these biopharmaceutical studies included data on antibodies specific to plant glycans on taliglucerase alfa in patients with GD treated with the product. However, there was useful information generated. Firstly the results suggested that the majority of anti-taliglucerase alfa antibody activity is likely to be specific for the protein backbone of taliglucerase alfa, with the minority of the reactivity being specific for epitopes that are either unique to taliglucerase alfa (such as the plant glycan structures) or are more highly expressed or exposed on taliglucerase alfa compared with imiglucerase. Secondly, it was shown that anti-taliglucerase alfa antibodies are highly cross-reactive with imiglucerase. Imiglucerase and taliglucerase share extensive structural and sequence homology but imiglucerase lacks the plant glycan structures. Thirdly, it was shown that a notable proportion of healthy human samples tested "positive" for antibodies specific to the plant glycans on taliglucerase alfa (8.4% or 12/143 when outliers were excluded and 15.4% or 24/156 when outliers were included). The latter suggests that healthy subjects can develop antibodies to naturally occurring plant glycans identical or similar in structure to those on taliglucerase alfa. Presumably the development of such antibodies in healthy human subjects is via exposure to these plant glycans in food.

The clinical evaluator asked the sponsor why the ELISA test validated in the biopharmaceutical studies was not used to test serum samples of patients with GD for antibodies to plant glycans on taliglucerase alfa. The sponsor indicated that it was now in a position to report on the use of the validated ELISA for the detection of antibodies to plant-specific glycans in taliglucerase alfa in human serum. The sponsor provided results of the analyses of serum samples from GD subjects in 4 clinical studies: PB-06-001, PB-06-002, PB-06-003 and PB-06-005.

From the analysis it was concluded that anti plant-specific glycan antibodies occur in a subgroup of GD patients pre- and post-treatment with taliglucerase alfa. However, the immune response to these structures appears limited in magnitude. There was no clear demonstrated correlation between the appearance of anti-plant glycan-specific antibodies and an increased clinically relevant immunogenic risk.

Of the 71 subjects tested for anti-taliglucerase alfa ADA for the submission, 8 were considered to anti-plant glycan-specific antibody positive and 63 were considered to be negative for anti-plant glycan-specific antibodies (the 63 consisting of 21 who had no

detectable antibodies to plant-specific glycans on taliglucerase alfa but IgG ADA positive and of 42 who were negative for IgG ADA including antibodies to plant-specific glycans on taliglucerase alfa).

Further data on the immunogenicity risk profile of taliglucerase alfa is being generated in the completed analysis of the PB-06-003 study, 2 ongoing extension studies, the first PB-06-006 (extension study for paediatric subjects from PB-06-002 and PB-06-005) up to a possible 3 years' exposure and the second PB-06-007 (extension study for treatment-naïve adults who complete PB-06-003) up to a possible 5 years' exposure. A 10 year post marketing registry has been initiated to provide additional data.

Efficacy

Pivotal efficacy Study PB-06-001:

This was evaluated in CER 1 round 1 (see Attachment 2).

The objective of this Phase III, multi-national, multi-centre, randomised, double-blind, parallel-group, dose-ranging study was to assess the safety and efficacy of taliglucerase alfa in 30 untreated patients with GD. Patients received an IV infusion of taliglucerase alfa (30 units/kg or 60 units/kg) every 2 weeks over 9 months. At the end of the 9 month treatment period, eligible patients were offered enrolment in a double-blind extension study. This study had no placebo or active control arms. Clearly a placebo control arm would not have been ethical. However, the Delegate agreed with the clinical evaluator that the study would have been strengthened by the inclusion of an imiglucerase comparator arm. Given the rare nature of the disorder, the small study size is understandable.

The study included males and females, 18 years or older with a diagnosis of GD with leukoctye glucocerebrosidase activity level ≤ 3 nM/mg.h (≤ 30% of the mean of the reference range). Patients were also required to have splenomegaly defined as greater than 8 times the expected volume and thrombocytopaenia with or without anaemia. There is no mention in the full list of inclusion criteria of any bone disease criteria. Eligible patients were randomised centrally in a ratio of 1:1 to one of the two treatment groups.

The primary efficacy endpoint was the percentage change from baseline in spleen volume after 9 months of treatment. The major secondary endpoints were the change from baseline at Month 9 in haemoglobin level, liver volume (%) and platelet count. The other secondary outcome measures were chitotriosidase activity (a biomarker of disease activity) and the proportion of patients with greater than 10% reduction in spleen volume at 9 months. The primary efficacy analysis was based on one-sample t-tests for each dose group and was performed on the intent-to-treat (ITT) group. There was no formal statistical comparison of one dosage group versus the other, that is, of high versus low dose. The power calculations appear satisfactory.

The study screened 44 patients of whom 33 were eligible with 16 randomised to the low dose group and 17 to the high dose group. Of these 33 randomised patients, 32 received treatment, 16 in each group and 29 received treatment and completed all study visits, 14 in the low dose group and 15 in the high dose group. There were 3 patients who received treatment and discontinued prematurely, 2 experiencing AEs (1 in each treatment group) and 1 patient who became pregnant. There was 1 patient who voluntarily withdrew for personal reasons before receiving any study treatment.

There were 31 patients in the ITT population with mean age of 36 years [range 19 to 74 years] and an almost even split between males and females. All except one patient (who was described as South African black) were Caucasian.

Both dose groups demonstrated statistically significant reductions ($p < 0.0001$) in spleen volume from screening to Month 9 of 26.91% in the 30 units/kg dose group (n = 15) and

38.01% in the 60 units/kg dose group (n = 16). There was no statistically significant difference observed between the dose groups. The result is shown in Table 9.

Table 9: Study PB-06-001. Spleen volume percent change from screening to Months 6 and 9; imputed values averaged (ITT population).

		prGCD	
		30 units/kg N = 15	60 units/kg N = 16
SPLEEN VOLUME (mL) -- Imputed Values Averaged			
PERCENT CHANGE FROM SCREENING TO 6-MONTH	N	15	16
	MEAN	-22.21	-29.94
	SD	4.63	12.65
	MEDIAN	-22.35	-32.10
	RANGE	-30.99 to -12.49	-52.72 to 3.43
	p-value	<0.0001*	<0.0001*
PERCENT CHANGE FROM SCREENING TO 9-MONTH	N	15	16
	MEAN	-26.91	-38.01
	SD	7.79	9.38
	MEDIAN	-27.85	-37.63
	RANGE	-42.60 to -15.58	-56.30 to -20.04
	p-value	<0.0001*	<0.0001*

Multiple Imputation (100 times) for Missing.

*p-value is from one-sample t-test (combined) to test the null hypothesis that percent change = 0.

In the ITT population, the mean haemoglobin levels at baseline were at the lower limit of the normal range for both dose groups. The change in haemoglobin level from baseline to Month 9 was statistically significant in both the 30 and 60 units/kg dose groups (1.6 g/dL, n = 14, p = 0.0010 and 2.2 g/dL, n = 15, p < 0.0001, respectively).

There was a statistically significant reduction in liver volume from screening to Months 6 and 9 for both doses, the reductions at Month 9 being 10.48%, p = 0.0041 for the 30 units/kg dose (n = 14) and 11.11%, p < 0.0001 for the 60 units/kg dose (n = 16).

There was an increase in mean platelet count from baseline to Month 9 of 41,494/mm^3 (p = 0.0031) in the 60 units/kg dose group (n = 16) and 11,427/mm^3 in the 30 units/kg group (n = 15). The increase was statistically significant in the high dose group but not in the low dose group as the change failed to meet the pre-specified significance level of 0.025.

There was a statistically significant reduction in chitotriosidase activity from baseline to Month 9 in both dose groups. Mean reduction of at least 10% in spleen volume was observed in 100% (15/15) of patients at both Months 6 and 9 in the 30 units/kg dose group and in 93.8% (15/16) at Month 6 and 100% (16/16) at Month 9 in the 60 units/kg dose group.

The only bone disease measurements were via lumbar spine, femoral neck and total hip dual energy X-ray absorptiometry (DEXA) scans at screening and at Month 9. This was a tertiary endpoint only. Furthermore all that was noted was a trend towards improvement in mean change in T and Z scores for lumbar spine and femoral neck after 9 months' treatment in both dose groups. There was finally an exploratory endpoint, quantitative chemical shift imaging (QCSI), which measured bone marrow fat fraction content.

Other efficacy studies

Ongoing Phase III Study PB-06-002 – interim analysis:

This was evaluated in CER 1 round 1 (Attachment 2).

This was a Phase III, multi-centre, open-label, switchover trial to assess the safety and efficacy of taliglucerase alfa in 30 patients, 2 years or older, with GD who have been receiving imiglucerase (Cerezyme) ERT for at least 2 years with a stable dose for at least

the last 6 months. The first patient was enrolled on 15 Dec 2008 and at the time of writing the CER, the study was ongoing. There was an investigational site in Australia.

The administered taliglucerase alfa was equivalent to the imiglucerase dose at screening. No primary efficacy variable was selected for analysis. The efficacy outcome of main interest was whether patients deteriorated clinically during treatment with taliglucerase alfa. There were 25 treated patients, mean age 47 years [range 18 to 66], 13 male and 12 female. All patients were Caucasian, 14 of Ashkenazi Jewish descent and 11 non-Jewish.

The study was designed to include data on 30 patients. This reported interim analysis includes data on 15 patients. In these 15 patients completing 9 months of treatment at the first database lock point, the mean spleen volume decreased from 760.5 mL at baseline to 722.2 mL at Month 9, a mean reduction of 5.1%. This result together with comparable results for liver volume, haemoglobin, platelet count and chitotriosidase levels demonstrated that there had been no clinical deterioration in the switch from imiglucerase to taliglucerase alfa.

Phase III extension trial, PB-06-003 – interim analysis:

This was evaluated in CER 1 round 1 (Attachment 2).

The objective of this study was to extend the assessment of efficacy and safety of taliglucerase alfa in up to 60 patients with GD who had completed 9 months of treatment in either of the Studies PB-06-001 or PB-06-002. The total duration of treatment was to be at least 15 months and no more than 30 months or until the granting of marketing approval by the appropriate regulatory authority, whichever was the earlier. There are 3 treatment groups: Group 1 with patients on 30 units/kg from PB-06-001, Group 2 with patients on 60 units/kg from PB-06-001, and Group 3 with patients from PB-06-002 receiving the same dose as at the completion of PB-06-002. Where relevant the dose could be increased to a maximum of 60 units/kg. As noted by the clinical evaluator, there are limited efficacy data available from this interim analysis. The available data in the 26 patients with results at the end of Study PB-01-006, that is, at Month 9, showed that mean reductions in spleen and liver volume and increases in haemoglobin and platelet counts could all be maintained for another 3 months, that is, 12 months from baseline. There was evidence to suggest that the higher dose of 60 units/kg is more efficacious than the lower dose of 30 units/kg with the differences at 12 months from baseline being statistically significant for spleen volumes and platelet counts.

Historical comparison

This is evaluated in CER 1 round 1 (Attachment 2).

This was a review of the publicly available data on the efficacy of imiglucerase and alglucerase for the treatment of GD by focussing on publications for which the clinical study population and clinical endpoints were as close as possible to those of the pivotal Study PB-06-001. There were 14 papers selected with information on over 1,000 patients which provided summaries of historical control data for the major parameters of spleen volume, liver volume, haemoglobin and platelet count. The results for the latter from the pivotal Study PB-06-001 (baseline to 9 months) and from the extension Study PB-06-003 (additional 3 months of data) were within the ranges derived from the historical analysis.

All of the above efficacy results (those from the pivotal study, the other efficacy studies and the historical comparison) have been detailed in CER 1. In the second round of CER 1 there is a section devoted to the evaluation of clinical data submitted in responses to questions. These include a question on study availability (the expected completion dates of various studies) and a question regarding the FDA's Complete Response Letter to Protalix (the sponsor of taliglucerase alfa at that time in the USA). The Delegate considered it was clear that the issue of immunogenicity also concerned the FDA evaluators. It was noted that the product was now approved in the USA.

Following the evaluator's assessment of the sponsor's response to the clinical questions there was a review of new clinical data provided by the sponsor. Below is a summary of this new clinical data as it relates to efficacy.

Ongoing Phase III Study PB-06-002 – updated report:

This was evaluated in CER 1 round 2 (see Attachment 2).

This was the multicentre, open-label, switchover study (switchover from imiglucerase to taliglucerase). The updated report included information on 28 treated patients as opposed to the 15 patients reported on in the interim analysis. Once again there was confirmation that there was no clinical deterioration up to 9 months after switchover.

Phase III extension trial, PB-06-003 – updated report:

This was evaluated in CER 1 round 2 (see Attachment 2).

In the updated report, the clinical evaluator states that there were efficacy data on 31 patients (26 who had continued from the pivotal Study PB-06-001 and 10 who had continued from the switchover trial PB-06-002). This should make a total of 36 patients. In its response to the overview, the Delegate asked that the sponsor clarify this discrepancy. The previous interim report had detailed the results of the 26 patients from PB-06-001. Once again there was no evidence of clinical deterioration.

Efficacy and anti-taliglucerase antibody status:

This was evaluated in CER 1 round 2 (see Attachment 2).

In the sponsor's response to the clinical questions asked by the evaluator in the first round report of the original submission, the sponsor provided an updated efficacy report for the pivotal Study PB-06-001 in ERT naïve patients based on antibody status. There was no statistically significant difference between antibody positive and negative patients in the 30 units/kg group for any of the four major efficacy endpoints (that is, those to do with spleen volume, liver volume, haemoglobin and platelet count). However, in the 60 units/kg dose group, antibody negative patients had statistically significantly greater reductions in mean liver volume from baseline to last follow-up than antibody positive patients (-31.58% versus -12.66%, p = 0.005). Although for the other three major parameters in the high dose group, the results favoured the antibody negative patients, the differences were not statistically significant. These results need to be viewed with caution as it was a sub-group analysis, that is, from one dose group, and there was an imbalance in patient numbers in the high dose group between antibody positive (n = 11) and antibody negative patients (n = 4). Another analysis, a descriptive analysis of the change from Day 1 to Week 38 in the pivotal study of dose normalised PK parameters versus antibody status, showed that there was no evidence that antibody positive status reduces exposure to taliglucerase alfa.

New efficacy data

Study in the paediatric population, PB-06-005:

This was evaluated in round 1 of CER 2 (Attachment 3)

This was a small efficacy and safety study in 11 paediatric patients, aged from 3 to 14 years, with a definitive diagnosis of GD and who were ERT naïve. As for the adult studies the patients were randomised to taliglucerase alfa 30 units/kg (n = 6) or 60 units/kg (n = 5) administered by IV infusion once every 2 weeks for 12 months. Efficacy parameters were simply summarised descriptively.

The primary efficacy endpoint was the median change from baseline and the interquartile range of the median percentage change in haemoglobin level. In both treatment groups, a median increase in haemoglobin level from baseline to Month 12 was observed [12.2%

with an interquartile range from 1.7% to 22.3% for the 30 units/kg dose group and 14.2% with an interquartile range from 11.4% to 21.7% for the 60 units/kg dose group]. Also in both treatment groups, each of the secondary efficacy endpoint outcomes [biomarkers and spleen and liver volumes] showed improvement from baseline to Month 12, with results for the high dose group being numerically superior to those in the low dose group. The results are consistent with those observed in adult patients in the pivotal study evaluated in the original submission.

In the clinical questions of CER 2 the evaluator asked 6 questions related to efficacy, the first asking about the relationship between the taliglucerase alfa formulation used in the paediatric Study PB-06-005 and the formulation proposed for Australian marketing and the remaining five all related in one way or another to the question of the immunogenicity of taliglucerase alfa. The sponsor's responses were evaluated in round 2 of CER 2 (Attachment 3), that is, the final clinical evaluation report.

The sponsor replied that the drug product used in the paediatric Study PB-06-005 and that proposed for marketing in Australia and presently marketed globally have been shown to be comparable based on the main criteria of excipients, plant-specific glycoforms and manufacturing process.

There were five questions pertaining to immunogenicity. A total of 74 subjects were enrolled in the relevant clinical trials. The cohort of 71 subjects with IgG ADA assessments represents all but 3 paediatric patients in Study PB-06-002. There was in fact a trend in the pooled analysis for the treatment-induced ADA group (n = 24) to have greater improvements in haemoglobin, platelet count and biomarkers than the cohort of patients without treatment-induced IgG ADA (n = 47). The mechanism for this is unclear. Also treatment induced ADA positive status appeared linked to either neutral or positive efficacy outcomes in subjects with Type I hypersensitivity reactions. With regard to neutralising antibodies the data suggest that the development of the latter might reduce the efficacy of taliglucerase alfa. However, it remains unclear whether the reduction is likely to be clinically significant, not least because of the very small numbers of subjects who were positive for IgG ADA neutralising antibodies.

Clinical data provided in the sponsor's response to the first round evaluation showed that in the cohort of 71 patients with IgG ADA assessments from the clinical trial program the presence of treatment-induced IgG ADA did not impair the efficacy of taliglucerase alfa. In fact, the absolute change from baseline in the pooled analysis (PB-06-001, PB-06-005) at the last measure (1 May 2012) was consistently greater in the treatment-induced ADA positive group (n = 24) compared with the ADA negative group (n = 47) across all six efficacy endpoints. The reason for this observation is unclear. Limited data from three IgG ADA positive patients with neutralising antibodies suggests that the presence of neutralising antibodies might have a negative impact on efficacy. However, it is unclear whether the negative impact on efficacy of neutralising antibodies is clinically meaningful.

Clinical data provided in the sponsor response to the first round evaluation included an assessment of the effect of anti-taliglucerase alfa plant-specific glycan antibodies on efficacy using previous data from the 71 patients with an IgG ADA assessment. This new analysis identified 29 out 71 patients (40.8%) who were IgG ADA positive at any time point (baseline and/or post-baseline) and 42 out of 71 patients (59.2%) who were IgG ADA negative. The efficacy assessments included comparison of patients positive for anti-taliglucerase alfa plant-specific glycan antibodies (8/71, 11.3%), patients who had no detectable anti-taliglucerase alfa plant-specific glycan antibodies but were IgG ADA positive (21/71, 29.6%), and patients who were IgG ADA negative or were IgG positive but anti-taliglucerase alfa plant-specific glycan antibody negative (63/71, 88.7%). Overall, no significant efficacy differences between patients who were positive or negative for anti-taliglucerase alfa plant-specific glycan antibodies were observed for the efficacy endpoints of spleen volume, liver volume, haemoglobin level, platelet count, chitotriosidase activity

and biomarker CCL18 level. However, the interpretation of the data is limited by the small number of patients (n = 8) who were anti-taliglucerase alfa plant-specific glycan antibody positive.

Review of the summary data suggests that there was no marked difference in the 4 key efficacy endpoints (spleen volume, liver volume, haemoglobin and platelet count) over time between ADA positive and negative subjects in Studies PB-06-001/PB-06-003 and in Studies PB-06-002/PB-06-003.

Changes in manufacturing process had effects on the glycosylation of the protein. Most of these effects were not in themselves significant, but the cumulative changes in the same direction rendered the drug substance made by the final commercial process very different in glycosylation from that used in the early stages of the Phase III clinical trials. The content of the major fucosylated and xylylated mannose 3 glycan (FcM3X) increased from just over half to over 90% with corresponding decreases in all other glycans, in particular some non-xylylated glycans. The sponsor was asked to comment on the difference between the commercial product and the early Phase III clinical trial product.

Overall, the analysis of ADA status and titres before and after exposure to proportionally more plant glycan species provides no indication of increased immunogenicity. Neither was there any evidence of significant change in efficacy before and after exposure to proportionally more plant glycan species (see Table 10).

Table 10: Efficacy parameters of mean response (mean % change) for Studies PB-06-001 (before commercial-like formulation of taliglucerase alfa) and PB-06-005 (with commercial-like formulation of taliglucerase alfa).

Efficacy Parameter	Absolute (%) Change from Baseline							
	Study PB-06-001 (9 months)				Study PB-06-005 (9 months/12 months)			
	30 U/kg	n	60 U/kg	n	30 U/kg	n	60 U/kg	n
Haemoglobin (g/dL)	1.6(14.6)	14	2.2(22.2)	15	1.0(9.3)/ 1.4(13.8)	6/6	1.3(13.1)/ 1.6(15.8)	5/5
Spleen Volume (mL)	-582.1(-27.3)	15	-756.15(-38.00)	16	-407(-28.6)	6	-499(-41.1)	5
Liver Volume (mL)	-337.4(-10.5)	14	-288.5(-11.1)	15	-98.7(-6.3)	6	-143(-14.0)	5
Platelet Count (/mm3)	11427(13.7)	15	41494(72.1)	16	45500(30.9)	6	72600(73.7)	5
Chitotriosidase (nmol/mL*h)	-13264(-47.3)	14	-12165(-58.4)	15	-12231(-57.2)/ -13210(-58.5)	6/6	-17660(-58.9)/ -20528(-66.1)	4/4*

Source: Supporting Table 1.1.2, Table 1.2.2, Table 1.3, Table 1.4, Table 1.5, Dose data from CSR PB-06-001 03 Statistical Table 16.2; CSR PB-06-005 – Table 6, Table 8, and Table 9, and SCS Table 2.3 (Dose Listing)
*One subject was chitotriosidase deficient; n = number

Although this table reports on a cross-study comparison, that is, between the adult pivotal study PB-06-001 and the paediatric Study PB-06-005 and the numbers are small, the mean percentage change in each of the 4 major parameters is consistently similar.

Safety

The studies providing safety data in support of taliglucerase alfa for the treatment of GD, as of 30 June 2010, are summarised in AusPAR Table 3 (above). This was the data supplied in the original submission (PM-2011-00478-3-3). The dataset included 89 subjects (6 healthy subjects from one PK study and 83 GD patients from 4 clinical trials).

In the group of 83 GD patients there were a total of 526 AEs experienced with 12 severe or very severe, 5 SAEs and 392 treatment-related. The most common treatment-related AEs in patients treated with taliglucerase alfa (occurring in at least 5% of patients) were infusion-related reactions (6%, n = 5) and headache (6%, n = 5).

Hypersensitivity reactions during the taliglucerase alfa infusion occurred in 4.8% (n = 4) of the 83 patients in the safety population and 1 patient developed a fixed drug eruption during the infusion. None of the patients with hypersensitivity reactions were reported to have developed anti-taliglucerase alfa IgG antibodies. The 2 patients with hypersensitivity reactions in the pivotal Study PB-06-001 were discontinued from treatment. The 2 other

patients with hypersensitivity reactions and the patient with the fixed drug eruption continued treatment with taliglucerase alfa.

Anti-taliglucerase alfa antibodies were detected in 6.3% (2/32) patients tested at the end of the pivotal Study PB-06-001 and neutralising antibodies were negative in both IgG antibody positive patients. In Study PB-06-002, 6.7% (1/15) of patients were anti-taliglucerase alfa IgG antibody positive and this one patient tested negative for neutralising antibodies. None of the 3 patients identified as IgG antibody positive were reported to have experienced a hypersensitivity reaction. As noted by the clinical evaluator, the presence of anti-taliglucerase alfa IgG antibodies was not been found to predict the development of hypersensitivity reactions in the dataset.

There were no deaths reported in the 83 patients while SAEs were reported in 4 (4.8%) patients, the four latter being immune thrombocytopaenia, epistaxis, renal stone and lastly prolapse of rectum, bladder and cervix. There were only two discontinuations, both in the pivotal study and both due to hypersensitivity reactions. There was no evidence of any causal association between significant biochemical or haematological toxicities and taliglucerase alfa. Nor was there any evidence of any causal association between hepatic toxicity, renal toxicity or cardiovascular toxicity and the drug. There was no data to suggest any clinically significant difference in the safety profiles of each dosage group.

At the end of the first round report of the original submission, the clinical evaluator had no questions to ask of the sponsor in relation to safety.

In the response to CER 1, the sponsor provided an updated SCS. This safety dataset was based on one completed Phase III pivotal Study, PB-06-001 and 4 ongoing Phase III supportive Studies PB-06-002, PB-06-003, PB-06-004 and PB-06-005. In this list of 4 studies there is a study not previously mentioned, namely PB-06-004. This was a multicentre, open-label study evaluating an expanded access treatment protocol in 50 patients being treated with taliglucerase alfa at the same dose as they had previously been on when treated with imiglucerase. The duration of treatment was for 9 months with extension possible to 24 months or until marketing approval. The efficacy and safety data from this Study PB-06-004 did not appear to have been submitted for evaluation either in the original submission or in the current submission. In its response to the overview, the Delegate asked the sponsor to provide a brief summary of the major efficacy and safety findings from this study. Finally, in the updated SCS there was also data from patients treated in ongoing multi-national Compassionate Use Programmes.

This updated safety dataset, evaluated in the second round of CER 1, included 121 patients treated with taliglucerase alfa for GD up to 1 May 2011. Of these 121 patients, 96 had been treated for 6 months, 59 for 12 months, 33 for 18 months and 24 for 24 months.

The most commonly reported AEs (≥ 5%) in the 121 patients were nasopharyngitis (21.5%), arthralgia (18.2%), headache (18.2%), upper respiratory tract infection (15.7%), pain in extremity (11.6%), cough (10.7%), fatigue (9.9%), back pain (9.9%), vomiting (8.3%), pain (7.4%), pharyngolaryngeal pain (7.4%),pruritus (7.4%), diarrhoea (6.6%), pyrexia (6.6%), influenza (6.6%), pharyngitis (6.6%), sinusitis (6.6%), nausea (5.8%), dizziness (5.8%), epistaxis (5.8%), gastroenteritis (5.8%), bone pain (5.0% and hypertension (5.0%).

Serious AEs (11 events) were reported in 10 (8.3%) patients. No pattern of SAEs was observed. The only SAE considered by the investigator to be treatment-related was gastroenteritis in the paediatric Study PB-06-005.

Hypersensitivity Type I (acute) events were identified in 18 (14.9%) patients and in 15 of these 18 patients the events were judged to be treatment-related. The most commonly reported hypersensitivity Type I event was pruritus. Hypersensitivity Type II-IV (chronic) were reported in 5 (4.1%) patients. These events were reported as either mild or

moderate in intensity except for one patient in the high dose group who experienced a very severe autoimmune thrombocytopaenia, reported as an SAE judged not to be treatment-related. In the response to this overview, the sponsor was requested to give a brief commentary on this case, outlining why the event was judged not to be treatment-related.

Anti-taliglucerase antibodies

The clinical evaluator commented that the most significant difference between the original and the updated safety data was the markedly greater proportion of patients reported with anti-taliglucerase alfa antibodies in the updated safety data. However, this difference appeared to be related to the increased use of the sensitivity assays for the detection of antibodies.

The proportion of patients with antibodies was notably higher in the pivotal Study PB-06-001 in ERT naïve patients (59.4%) compared with Study PB-06-002 in ERT experienced patients (19.2%). Irrespective of antibody status, the overall incidence of hypersensitivity Type I (acute) events in the ERT naïve population (28%, 9/32) was similar to that in the ERT experienced population (27%, 7/26). However, based on data using a higher IgG assay cut-off point (52.97% as opposed to 40.33%), the overall incidence of hypersensitivity Type I (acute) events in the antibody positive population was 44% (8/18) compared with 20% (8/40) in the antibody negative population. As noted by the clinical evaluator, this suggests that patients who develop anti-taliglucerase antibodies are likely to be at greater risk such acute reactions compared with those who remain antibody negative.

In 21 antibody positive patients (52.97% cut-off point) experiencing hypersensitivity Type I (acute) AEs and infusion-related AEs, 13 continued treatment with no intervention, 3 discontinued treatment following 'hypersensitivity' events, 2 continued treatment with the use of anti-histamines for rash or pruritus, 2 subjects experiencing infusion-related reactions continued treatment with OTC medication for headaches and 1 subject who experienced 'hypersensitivity' continued treatment with pre-treatment regimens.

Unresolved safety issues at the end of the original submission

The principal unresolved issue was that associated with the potential for taliglucerase alfa to induce antibodies to plant sugars. By the end of July 2012, the sponsor expected to complete the evaluation of anti-taliglucerase antibodies generated in patients in an attempt to determine whether these antibodies have specificity for the plant-derived glycans on taliglucerase alfa or are primarily directed against the protein core of the molecule. Even if specific antibodies to plant sugars are found in patients treated with taliglucerase alfa it was thought unlikely that these would result in new safety issues.

New safety data

Paediatric Study PB-06-005

In this study 11 children and adolescents completed 52 weeks of treatment with taliglucerase alfa and were included in the safety evaluation. The safety profile of taliglucerase alfa in paediatric patients with GD was consistent with that in adult patients from the previously reported trials. No new safety findings or signals were identified in PB-06-005.

Of the 11 taliglucerase alfa treated patients, 10 patients experienced 53 AEs, all reported as mild or moderate except for 1 severe AE of worsening pulmonary hypertension and 1 severe AE of gastroenteritis. The pulmonary hypertension was unrelated to treatment.

Five patients had 13 AEs that occurred during the infusion or within 2 h of completion of the infusion. There were no clinically significant changes in laboratory test results associated with taliglucerase alfa in the study.

Of the 11 patients tested for the presence of IgG anti-taliglucerase alfa antibodies, 3 developed a positive reaction, one in the low dose group and 2 in the high dose group. One of the latter two patients also developed IgE antibody to taliglucerase alfa. Both of the patients in the high dose group had hypersensitivity reactions to the taliglucerase infusion considered to be treatment related. None of the patients testing positive for IgG antibodies tested positive for neutralising antibodies. All 3 IgG antibody positive patients completed the study.

Updated Summary of clinical safety

There were data on an additional 11 patients in the updated summary compared with the summary in the original submission. In the updated SCS there were data on 132 patients (116 adults, 16 children) compared with 121 patients (110 adults, 11 children) in the summary in the original submission. Importantly there was an extra year of reporting, the cut-off point being 1 May 2012 and the data set came from 2 completed studies (the pivotal and the paediatric) and 5 ongoing supportive studies.

The risks of taliglucerase alfa treatment appear to require no specific intervention or are manageable by symptomatic treatment for both infusion-related and non-infusion related risks or by prophylactic medication for infusion-related risks. The risk of treatment discontinuation due to AEs related to taliglucerase alfa is low. Treatment discontinuations due to AEs in the completed and ongoing clinical trial programme were reported in only 3 (2.6%) adult patients (hypersensitivity in 2, eye swelling in 1). No treatment discontinuations resulting from AEs were reported in children.

In both adults and children, the risk of experiencing AEs is greater in ERT naïve patients compared with ERT experienced patients.

Serious AEs were reported in 11.2% (n = 13) of adult patients and 12.5% (n = 2) of paediatric patients. In adults none of the SAEs were considered to be treatment-related. In children, 1 SAE (gastrointestinal inflammation) was considered to be treatment-related. There were no deaths reported in the completed and ongoing studies in the GD clinical programme but there was one death reported in the Compassionate Use Programme considered to be unrelated to treatment (tuberculosis infection/pneumonia).

Investigator-designated treatment-related AEs occurring during the infusion or within 2 h of its completion were reported in 27.6% of adult patients (32/116) and 12.5% of paediatric patients (2/16).

The majority of Type I hypersensitivity AEs required no treatment or were manageable with pre-medication and/or symptomatic treatment.

In the clinical studies, assessment of IgG anti-taliglucerase alfa antibody status was carried out in a total of 71 patients (43 ERT naïve, 28 ERT experienced). Of the 43 ERT naïve patients, 19 (44.2%) were found to have treatment-induced IgG anti-taliglucerase antibodies (17/32 adults or 53.1% and 2/11 children or 18.1%). Of the 28 ERT experienced patients, 5 (17.9%) were found to have treatment induced IgG anti-taliglucerase antibodies (3/26 adults or 11.5% and 2/2 children or 100%). There appears to be an increased risk of Type I hypersensitivity reactions in patients testing positive for treatment-induced IgG anti-taliglucerase antibodies compared with patients testing negative (10/24 or 44.7% versus 10/47 or 21.3%).

Delayed hypersensitivity reactions were reported only in adults (9/116 or 7.8%). Of the 14 reported events, only 1 was severe (autoimmune thrombocytopaenia, non-treatment related SAE, about which the Delegate has requested further information from the sponsor (see above).

Bone events were reported in 55 (47.4%) adult patients and SAE bone events were reported in 2 (1.7%) adult patients. In children, 5 (31.3%) patients experienced bone events, none of which were considered SAEs.

The risks of taliglucerase alfa inducing abnormalities in clinical laboratory tests, vital signs, electrocardiograms, echocardiograms or pulmonary function tests appear to be minimal.

Apart from requesting clarification of a couple of minor points of discrepancy in the data, the bulk of the questions asked by the evaluator with regard to safety concerned immunogenicity. The major elements of the sponsor's response are discussed below:

An analysis undertaken by the sponsor and evaluated by the clinical evaluator indicated that there was no effect of antibody status on the clinical action taken in response to an adverse event of Type I Hypersensitivity. This was a re-analysis of the data for 18 patients who were tested for treatment-induced IgG ADA and experienced Type I hypersensitivity AEs.

In response to the question concerning the notably higher proportion of ERT naïve patients who were treatment-induced IgG ADA positive compared with ERT experienced patients, the sponsor suggested that ERT experienced subjects tested for treatment-induced IgG ADA might have been immune tolerant. However, as noted by the clinical evaluator, data referred to by the sponsor indicates that the percentage of both ERT naïve and ERT experienced subjects who became ADA-positive following treatment with Vpriv was lower than for taliglucerase alfa while the percentage of ERT naïve subjects who became ADA-positive following treatment with Cerezyme was similar to that for taliglucerase alfa. Overall, the data suggest that there may be differences in the immunogenicity of the glucocerebrosidase products.

There was also the question of the possible effect on safety of the different glycosylation profiles of the early clinical trial product and the commercial product. The sponsor summarised treatment-emergent AEs (all causality and treatment-related) for the 51 subjects in Studies PB-06-001, PB-06-002 and PB-06-003 who received both taliglucerase alfa drug product from the early processes (before change) and from the commercial-like or commercial process (after change). The number of AEs before and after the product change for each individual subject appeared to be approximately equivalent when the duration of treatment is taken into account. The number of events was more closely aligned with duration of treatment rather than the batch of product used.

Clinical evaluator's recommendation

The clinical evaluator recommended that Elelyso (taliglucerase alfa) be approved as follows:

> *Elelyso is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease characterised by one or more of the following, splenomegaly, hepatomegaly, anaemia, thrombocytopenia, or bone disease.*

Risk management plan

The RMP evaluator noted that a revised EU-RMP was to become available in December 2013. In particular, the EU-RMP was to be updated with regard to the use of taliglucerase alfa in children. It was further noted that paediatric submissions to regulatory authorities are underway.

In the response to this overview, the Delegate asked that the sponsor inform the TGA whether the EU-RMP has been updated and to provide a summary of all changes which

have been implemented in the most recent version, in particular of those changes which reference the use of taliglucerase in the paediatric population. In the same response the sponsor was requested to inform the TGA of the status of all paediatric submissions to regulatory authorities world-wide at this time. In particular, whether any of those paediatric submissions contain any more data on the use of taliglucerase alfa in the paediatric population than was contained within either the original submission (PM-2011-00478-3-3) or the current submission to the TGA. The data comparisons are to list not only any extra studies which may have been carried out in the paediatric population but to list any updated reports, such as updates of interim reports or reports of any ongoing and/or extension studies in the paediatric population.

The Delegate agreed the safety specifications in the proposed RMP should be updated as recommended by the RMP evaluator.

The RMP evaluator further recommended the following condition of registration: "*the European Risk Management Plan (Version: 3.3, dated 18 June 2012) with an Australian Specific Annex (Version: 1.0, dated 14 March 2013), to be revised as specified in the sponsor's correspondence dated 30 November 2013, must be implemented*". The Delegate endorsed this recommendation.

Risk-benefit analysis

Delegate's considerations

The clinical evaluator was of the opinion that the data provided in the original and current submissions is considered to have satisfactorily demonstrated the efficacy and safety of taliglucerase alfa for the treatment of non-neuronopathic GD in both adult and paediatric patients.

The benefits of treatment with taliglucerase alfa in ERT naïve (30 adult patients in pivotal Study PB-06-001) and ERT experienced (33 patients, 28 adult and 5 paediatric, previously treated with imiglucerase, in switchover trial PB-06-002) patients with non-neuronopathic GD included consistently meaningful improvements in the 4 major parameters of spleen volume, liver volume, haemoglobin level and platelet count. Comparable results were reported from the study in 11 paediatric patients (PB-06-005). The final report of the switchover trial was evaluated in the round 2 CER 2 evaluation, the data having been presented as part of the sponsor's response to TGA questions. There was no evidence of clinical deterioration in either the adult or paediatric subjects following their switchover from imiglucerase to taliglucerase alfa.

In 71 patients who were tested for IgG anti-taliglucerase alfa ADAs, 24 (33.8% developed treatment-induced IgG ADAs while 47 (66.2%) were negative for these antibodies. However, the presence of IgG ADAs appeared not impair the efficacy of taliglucerase alfa. In addition, the benefits of treatment with taliglucerase were similar in patients considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies and patients considered to be negative for these antibodies. However, there was a marked imbalance in patient numbers between those considered positive and those considered negative anti-taliglucerase alfa plant-specific glycan antibodies (8/71, 11.3% and 63/71, 87.7%, respectively).

As noted by the clinical evaluator, although AEs occurred very commonly in both adults and children treated with taliglucerase alfa, these events generally required either no intervention or were manageable with symptomatic treatment. Treatment discontinuations due to AEs were reported in only 3 (2.6%) adult patients (hypersensitivity in 2, eye swelling in 1). No treatment discontinuations resulting from AEs were reported in children.

In adults no SAE was considered to be treatment-related. In children, one SAE was considered to be treatment-related (gastrointestinal inflammation). No deaths have been reported in the clinical trial programme but there was one death reported in the Compassionate Use Programme considered to be unrelated to treatment (tuberculosis infection/pneumonia).

The most clinically important risks of treatment with taliglucerase alfa are considered to relate to Type I hypersensitivity reactions (acute allergic reactions). In adults, 18 (15.5%) patients were reported as experiencing investigator-designated treatment-related Type I hypersensitivity reactions. These reactions were manageable by no intervention or temporary intervention in slightly more than half of the cases (10/18), while slightly less than half of the cases (8/18) were managed by premedication or treatment discontinuation.

There appears to be an increased risk of Type I hypersensitivity reactions in patients testing positive for treatment-induced IgG ADAs compared with patients testing negative (9/24 [37.5%] versus 9/47 [19.1%], respectively). However, there did not appear to be a difference in the severity of Type I hypersensitivity reactions between IgG ADA positive and negative patients, and management of these reactions was similar in both patient groups. Type II-IV hypersensitivity AEs (delayed hypersensitivity reactions) were reported only in adults (7.8%, 9/116), and the only event considered to be treatment-related was drug eruption (left cheek), which was reported in 1 patient on 6 separate occasions.

The frequency (events/patient) of treatment-related and all causality AEs was greater in patients considered to be anti-taliglucerase alfa plant-specific glycan antibody positive than in patients considered to be negative for these antibodies. However, as noted previously there was a marked imbalance in patient numbers between those considered to be positive and those considered to be negative for these antibodies. Furthermore, of the 8 patients considered to be positive for anti-taliglucerase alfa plant-specific glycan antibodies, 7 continued treatment with taliglucerase alfa while one discontinued treatment due to what appears to be a hypersensitivity reaction to taliglucerase alfa. Overall, the limited data suggest that the presence of anti-taliglucerase alfa plant-specific glycan antibodies does not present a significant treatment risk.

The proposed dosage regimen is consistent with the clinical trial data and importantly contains the provision that the dose must be individualised for each patient.

The Delegate was satisfied that there is sufficient evidence to support a positive benefit/risk balance for the use of taliglucerase alfa in the treatment of patients with Type 1 GD. Since the relevant studies were conducted in patients with Type 1 GD, the indications would be amended to reflect this.

While the clinical evaluator's recommendation of widening the indication to include the paediatric population was acknowledged, the Delegate was not, at this stage, supportive of such a recommendation. The Delegate was aware from the RMP evaluation that the sponsor is in the process of making paediatric submissions to regulatory authorities world-wide. In the response to this overview, the Delegate asked that the sponsor answer a number of questions pertaining to the nature and content of these submissions, particularly in comparison with the paediatric data submitted to the TGA. Until the Delegate is able to evaluate those responses and also assess the advice of the ACPM in relation to these matters, the Delegate was not prepared to make any firm recommendation as to whether the use of taliglucerase alfa should be approved in children.

Finally, the Delegate noted that the proposed indications include the sub-population of subjects with GD who exhibit bone disease. However, no parameter relating to bone disease was included in the inclusion criteria for the pivotal clinical trial, nor was any

parameter related to bone disease examined as a primary efficacy endpoint or even a major secondary endpoint. Therefore the Delegate was of the opinion that any reference to bone disease should be removed from the proposed indications.

Proposed conditions of registration

The Delegate proposed the following as conditions of registration:

1. The European Risk Management Plan (Version: 3.3, dated 18 June 2012) with an Australian Specific Annex (Version: 1.0, dated 14 March 2013), to be revised as specified in the sponsor's correspondence dated 30 November 2013, must be implemented.
2. A condition relating to batch release testing by the TGA.
3. A condition relating to the maintenance of the so-called 'temporary' provision relating to storage temperature restrictions, especially during transport. All excursions outside the appropriate range are to be reported immediately to the TGA. The condition will stay in place until the sponsor provides a new thermal cycling study as part of a category 3 (variation) application and until the latter application has been approved.
4. A condition relating to the provision of the relevant Certified Product Details.
5. A condition relating to the submission of the final or updated reports of any ongoing or extension clinical studies as evaluable data in a category 1 (registration) submission or submissions. The list should also include all studies, whether completed or not, the data of which has not been submitted to the TGA. Any studies for which reports have not previously been submitted to the TGA should be separately identified. Once the Delegate has a confirmed the identity of all such outstanding reports, the condition will be able to be formalised.
6. A condition relating to the submission of regular reports of the findings of the proposed 10 year registry of patients treated with taliglucerase alfa.

Questions for sponsor

The Delegate requested the sponsor address several matters raised in the overview (above). These questions and the sponsor's responses are reproduced below (*Response from Sponsor)*.

Proposed action

The Delegate had no reason to say, at this time, that the application for Elelyso should not be approved for registration for the treatment of adult patients with Type 1 GD. However, the Delegate was not in a position to say, at this time, that the application for Elelyso should be approved for registration for the treatment of paediatric patients with Type 1 GD.

The Delegate's suggested indication is as follows:

> *Elelyso is indicated for long-term enzyme replacement therapy for adult patients with a confirmed diagnosis of Type 1 Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia or thrombocytopaenia.*

Request for ACPM advice

The Delegate proposed to seek advice on this application from the ACPM, and to request the committee advise on the following specific issues in particular:

1. Whether or not the indication should be widened to include paediatric subjects (please note that the sponsor's pre-ACPM response will contain clarification of whether the TGA has been provided with all data in relation to the paediatric population, particularly in comparison with paediatric submissions now taking place around the world).
2. Whether or not the reference to 'bone disease' should be removed from the proposed indications
3. Whether or not the proposed indications should refer to Gaucher Disease patients in general or more specifically to Type 1 Gaucher Disease, Type 1 referring to the non-neuropathic forms of the disease.

Response from Sponsor

In this response, discussion in support of the clinical evaluator's recommendation to expand the label to include paediatric patients with Type 1 GD is provided. Importantly, to the Delegate's concerns regarding expanding the label indication the sponsor has provided information pertaining to the nature and content of paediatric registration submissions submitted to regulatory authorities world-wide.

Label indication for Elelyso (taliglucerase alfa rpc)

Discussion in support of expanding the label to include paediatric patients with Type 1 GD is provided below.

The sponsor's original proposed indication stated "*Elelyso is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia, bone disease*".

The Delegate's proposed indication for approval is "*Elelyso is indicated for long-term enzyme replacement therapy for* ***adult*** *patients with a confirmed diagnosis of* ***Type 1*** *Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia, ~~bone disease~~*".

The sponsor agrees with the Delegate's addition of 'Type 1' GD and the removal of 'bone disease' from the indication. In addition to the Delegate's modifications, the sponsor requests inclusion of paediatric patients with Type 1 GD. The sponsor respectfully requests the ACPM to consider the following indication for Elelyso (taliglucerase alfa rpc).

> *Elelyso is indicated for long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of Type 1 Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia.*

The sponsor considers that it has presented suitable clinical evidence for evaluation by the TGA to support inclusion of paediatric patients in the indication. Paediatric clinical studies have been submitted with the initial application (PM-2011-00478-3-3) in May 2011, and further paediatric study results provided in the resubmission application (PM-2013-00303-1-3) in 2013[15].

[15] For both submissions a positive clinical evaluation was received recommending approval of taliglucerase alfa for Guacher disease. The initial application was withdrawn due to quality deficiencies, which have been rectified with the re-submission application.

In support of the inclusion of paediatric patients within the indication, the sponsor refers to the assessment provided by the clinical evaluator within the second round of CER 2. Overall, the clinical evaluator suggested that *"There is an important risk-benefit issue relating to whether treatment with taliglucerase alfa should be confined to adult patients with GD (that is, patients aged ≥ 18 years). The clinical data in children and adolescents (2 to <18 years) are limited, but suggest that the benefits and risks of taliglucerase alfa are similar in children/adolescents and in adults. Overall, it is considered that treatment with taliglucerase alfa should not be restricted to adult patients aged ≥ 18 years."*, therefore, suggesting a benefit/risk profile that is similar between adults and paediatric subjects. The clinical evaluator further supported the benefit/risk of taliglucerase alfa for the inclusion of paediatric subjects by elaborating that *"...the benefit-risk balance of taliglucerase alfa, given the proposed usage, remains favourable. The data provided in the original and current submissions are considered to have satisfactorily demonstrated the efficacy and safety of taliglucerase alfa for the treatment of non-neuronopathic GD in both adult and paediatric patients."* (CER 2, Attachment 3).

Further, the clinical evaluator described that there are meaningful benefits for the use of taliglucerase alfa in both adults and paediatric patients *"The benefits of treatment with taliglucerase alfa in ERT naïve and ERT experienced patients with non-neuronopathic GD include clinically meaningful reductions in spleen and liver volumes, improvement in haemoglobin level, and improvement in platelet count. In addition, taliglucerase alfa has been observed to reduce GD biomarker activity in both adult and paediatric patients (chitotriosidase activity reduced; CCL18 concentration reduced)".*

The clinical studies to support the safe and efficacious use of taliglucerase alfa in paediatric patients as submitted and evaluated by the TGA are:

- Study PB-06-005: Phase III, double-blind, randomised, 12 month study evaluating the efficacy and safety of 2 dose groups (30 and 60 units/kg) of taliglucerase alfa rpc in paediatric patients aged 2 to <18 years with GD; and
- Study PB-06-002: an open-label, switch-over 9 month study evaluating the safety and efficacy of taliglucerase alfa in paediatric patients aged from 2 years with GD previously treated with imiglucerase.

A favourable assessment of the efficacy for these paediatric Studies PB-06-005 and PB-06-002 has been provided by the clinical evaluator:

PB-06-005: *"Overall, it is considered that this small, uncontrolled, open-label study suggests that taliglucerase alfa 30 units/kg and 60 units/kg administered by IV infusion every second week for 12 months is efficacious for the treatment of GD in ERT naïve children and adolescents. Improvements from baseline to Month 12 included increases in haemoglobin levels and platelet counts, reduction in spleen and liver volumes, and reductions in chitotriosidase activity and CCL18 concentration. The results are consistent with those observed in adult patients evaluated in the original submission".*

PB-06-002: *"In this study, of the 31 enrolled patients 30 patients (26 adult, 5 children) completed 9 months of treatment with taliglucerase alfa following switching from imiglucerase.... The efficacy analysis showed no clinically significant deterioration in efficacy in patients who switched from imiglucerase to taliglucerase alfa. The mean % change from Baseline in spleen size, liver size, haemoglobin level, and platelet count were all less than the pre-specified changes defining clinical deterioration. The results support the efficacy of taliglucerase alfa for the treatment of GD."*

Overall, the clinical evaluator also described that there is acceptable risk for the use of taliglucerase alfa in both adults and paediatric patients *"The risks of treatment with taliglucerase alfa in both adults and children with non-neuronopathic GD are considered acceptable..."*.

Further, there are Australian treatment guidelines as sourced from, *Guidelines for the treatment of Gaucher disease through the Life Saving Drugs Program* (July 2013). These guidelines reflect how ERTs are used in clinical practice for treatment of children with GD. The guidelines recommend children (< 16 years of age) with symptomatic GD be treated for any relevant physical signs and that young children with severe visceral manifestations of GD be considered for therapy, provided that other criteria are met including the absence of features consistent with a neurophathic form of GD. The clinical evidence presented within the registration filing (PB-06-002 and PB-06-005) have been conducted in children with visceral and haematological manifestation of the disease in line with the local treatment guidelines.

In summary, based on the clinical data provided in both the original application (PM-2011-00478-3-3) and the resubmission application (PM-2013-00303-1-3), it has been concluded that the overall benefit/risk profile supports the expansion of the label to include paediatric patients with Type 1 GD.

Delegate's questions

In addition to the above, the sponsor provided information to address the nine points raised in the Delegate's overview:

Delegate's question 1

The sponsor is to provide an assurance that all necessary temperature monitoring and recording equipment will be in place to satisfy the 'temporary' provision mentioned above, particularly during any shipping or transport of the drug. Will the temperature records generated be available for audit and who will be auditing these records?

Sponsor response 1

An assurance is provided that all necessary temperature monitoring and recording equipment will be in place to satisfy the 'temporary' provision during any shipping or transport of the product. Once the product is received from the manufacturing site, the sponsor will review the temperature data recordings and quality documentation. Records can be made available to the TGA for review as part of the batch release program.

Delegate's *question* 2

The sponsor is requested to clarify the discrepancy (31 patients versus 36 patients) mentioned in the updated report of the Phase III extension trial, PB-06-003.

Sponsor's response 2

The sponsor has carefully investigated the Delegate's concern regarding the "discrepancy" 31 patients versus 36 patients in the updated report of the Phase III extension Study PB-06-003 and believes the stated discrepancy may be an error. With reference to round 2 CER 1, for the initial Category 1 submission (PM-2011-00478-3-3), the subject number total for the updated report for Study PB-06-003 is correctly reported as 44 patients, stating *'At the time of the database lock (1 May 2011) for the updated PB-06-003 report, 44 patients were enrolled in the extension Study PB-06-003, 26 patients from the naïve trial (PB-06-001) and 18 from the switch Study PB-06-002.'*

Delegate's question 3

The sponsor is requested to provide a brief summary of the major efficacy and safety findings from the Study PB-06-004.

Sponsor's response 3

An interim report for Study PB-06-004 was submitted with the initial submission (PM-2011-00478-3-3). The first round CER 1 provided an assessment of this study report under *Clinical Safety*. This study has been completed and the final study report (dated

December 2013) is completed. A summary of the major efficacy and safety findings from Study PB-06-004 were provided.

Delegate's question 4

The sponsor is requested to give a brief commentary on the patient in the high dose group who experienced a very severe autoimmune thrombocytopaenia, reported as a SAE not treatment-related. Please outline why the event was judged not to be treatment-related.

Sponsor's response 4

A brief commentary with patient details of the SAE of autoimmune thrombocytopaenia which was judged not to be treatment-related was provided.

The patient had low platelet counts prior to the initiation of taliglucerase treatment in the ERT naïve Study PB-06-001 and the platelets counts continued to be low in the extension Study PB-06-003. The failure of platelets to respond while other Gaucher parameters did respond to taliglucerase alfa treatment and the evaluation demonstrating autoimmune thrombocytopaenia clarified that the low platelet count was unrelated to taliglucerase alfa treatment.

Delegate's question 5

The sponsor is requested to inform the TGA whether the EU-RMP has been updated and to provide a summary of all changes which have been implemented in the most recent version, in particular of those changes which reference the use of taliglucerase in the paediatric population.

Sponsor's response 5

A copy of the updated EU-RMP was submitted to the TGA on 23 January 2014, in the sponsor's response to the RMP evaluation report, together with an amended ASA. The updated RMP and ASA documents are aligned with the agreed changes to be adopted in the sponsor's correspondence dated 30 November 2013. It is therefore considered the proposed condition of registration (number 1, see Delegate's overview above) is met.

The EU-RMP, *Summary of Changes in a Revised Risk Management Plan* includes a list of changes. This list references the use of taliglucerase alfa in the paediatric population.

Delegate's question 6

The sponsor is requested to inform the TGA of the status of all paediatric submissions to regulatory authorities world-wide at this time. In particular, the Delegate wishes to know whether any of those paediatric submissions contain any more data on the use of taliglucerase alfa in the paediatric population than was contained within either the original submission (PM-2011-00478-3-3) or the current submission. The data comparisons are to list not only any extra studies which may have been carried out in the paediatric population but to list any updated reports, e.g. updates of interim reports or reports of any ongoing and/or extension studies in the paediatric population.

Sponsor's response 6

A status update on the current paediatric submissions to regulatory authorities world-wide was provided.

The sponsor confirms that consistent with paediatric clinical evidence received by Health Canada and the US Food and Drug Administration, the TGA has received:

- 12 month paediatric data for Study PB-06-005, and
- 9 month paediatric data for Study PB-06-002.

TGA has not received the paediatric PK Study PB-06-006 data (report provided only to the US FDA) as the PK report was not available at the time of the resubmission application. The paediatric PK data are consistent with the adult PK data.

In relation to safety data, The TGA and Health Canada have received the SCS, including cumulative safety data from the sponsor's clinical database for ongoing studies through 01 May 2012, and cumulative safety data from the sponsor's safety database through 01 February 2013. The US FDA received cumulative safety data from the sponsor's clinical database for ongoing Study PB-06-006 through 31 March 2013, and cumulative safety data from the sponsor's safety database through 31 May 2013. A 120 Day Safety Update was also submitted to the US FDA which included additional safety data through 31 December 2013.

Delegates' question 7

The sponsor is requested to provide a list detailing firstly those studies whose reports have been submitted to the TGA but which require updating as in the case of ongoing or extension studies and secondly those studies whose reports have never before been submitted to the TGA. As flagged above, this information will aid the Delegate draft a relevant condition of registration relating to the submission of all outstanding reports.

Sponsor's response 7

A tabulated list of ongoing clinical studies and clinical studies not submitted to the TGA was provided.

Delegates' question 8

The sponsor is requested to provide a summary of the protocol for the proposed 10 year registry. Will entry to this registry be open to all Australian patients treated with taliglucerase alfa? If not, why not? How regularly will reports on the progress of this 10 year registry be provided to regulatory agencies, including the TGA?

Sponsor's response 8

A summary of the study protocol for the registry was provided. The registry will be available in countries with marketing approval for taliglucerase alfa. In Australia, the registry will be open to all patients initiated on treatment following the registration of taliglucerase alfa rpc. There are currently, 10 Australian patients receiving post-trial taliglucerase alfa treatment via the Special Access Scheme (SAS). It is the sponsor's intention that these 10 patients will not be enrolled in the registry since they were initiated on treatment prior to registration and extensive data has been collected on these patients during the course of their participation in the taliglucerase alfa rpc clinical trial program. Furthermore, it is the sponsor's intention to continue to supply these 10 patients under the SAS until Australian labeled stock becomes available upon reimbursement of taliglucerase alfa rpc under the Life Savings Drugs Program (LSDP).

In the USA, the registry enrolled the first patients in September 2013. An interim report will be issued in July 2019 and the final report issued in July 2024. Additional reports and/or observations will also be distributed to countries with market approval as requested.

Delegate's question 9

The Delegate seeks to know why bone involvement as measured by an exploratory parameter (QCSI measures of bone marrow fat fraction) has been reported in the PI when there was a higher level endpoint, albeit a tertiary endpoint, which measured various skeletal DEXA endpoints and which has not been summarised in the PI. Please explain this. Both endpoints showed trends only.

Sponsor's response 9

The sponsor agrees with the Delegate that the tertiary endpoint of DEXA measurement and the exploratory QCSI endpoint showed trends in Study PB-06-001. QCSI data was included in the PI because changes resulting from ERT can be more clearly observed in shorter time periods than seen with DEXA and longer-term DEXA data were not available. However, the sponsor will provide data for DEXA and QCSI in qualitative terms in the PI ensuring clarity that the results are trends only. Additionally, clarification will made that only Study PB-06-002 included inclusion/exclusion criteria related to bone manifestations of GD (exclusion criteria: No acute avascular necrosis event in the last year).

Conclusion

The sponsor believes the data submitted for Elelyso (taliglucerase alfa rpc) fully support approval of this medication for the long-term ERT for adult and paediatric patients with a confirmed diagnosis of Type 1 GD where the manifestations of GD may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia.

Advisory Committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered ELELYSO powder for injection containing 200 units of taliglucerase alfa rpc to have an overall positive benefit–risk profile for the amended indication;

> *ELELYSO is indicated for long-term enzyme replacement therapy for patients with a confirmed diagnosis of Type 1 Gaucher disease. The manifestations of Gaucher disease may include one or more of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopaenia.*

In making this recommendation the ACPM:

- Noted efficacy and safety have been reasonably demonstrated and the benefits of taliglucerase alfa outweigh the risks in the treatment of Type 1 GD.
- There are now sufficient data on glycosylation and immunogenicity profiles to reassure the Committee over that risk.
- The presence of IgG anti-taliglucerase antibodies (ADAs) did not appear to impair the safety or efficacy of taliglucerase alfa.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- The submission of the reports of any trials in the paediatric populations as soon as these become available.

Proposed PI and CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice:

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. Whether or not the indication should be widened to include paediatric subjects.

The ACPM advised that the indication should be widened to include paediatric patients despite limited data. Nonetheless the data are consistent with that reported in adults. These patients will be monitored very rigorously via the Life Saving Drugs Program and data regarding safety and efficacy will be collected by the Registry. The ACPM noted that the sponsor is in the process of making paediatric submissions to regulatory authorities in other jurisdictions.

2. Whether or not the reference to 'bone disease' should be removed from the proposed indications

The ACPM noted the sponsor has agreed that the indication should not include the sub-population of subjects with GD bone disease in the absence of relevant data.

3. Whether or not the proposed indications should refer to Gaucher Disease patients in general or more specifically to Type 1 Gaucher Disease, Type 1 referring to the non-neuropathic forms of the disease.

The ACPM agreed the proposed indications should refer specifically to Type 1 GD as this was the population enrolled in the trial.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Elelyso taliglucerase alfa rpc 200 units powder for injection, indicated for:

> *ELELYSO is indicated for long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of Type 1 Gaucher disease associated with at least one of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia.*

Specific conditions of registration applying to these goods

- The Elelyso European Risk Management Plan (RMP), version 4.0, dated 25 November 2013 with an Australian Specific Annex (Version 3.0, dated 16 January 2014), included with submission PM-2013-00303-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Specific conditions relating to batch release testing (details of these are beyond the scope of the AusPAR)
- The current storage temperature restrictions are to remain in place until a new [thermal] cycling study is submitted as a Category 3 application. In accordance with the sponsor's commitment provided in response to Question 15 of the Consolidated List of Questions, dated 30 November 2013, an additional [thermal] cycling study with one commercial batch will be performed to provide additional evidence on temperature excursions during transport.

- Within 3 months of the date of the approval letter of this submission, the sponsor is to submit a Category 1 application containing the reports of the studies in the table below:

Study Code	Study Description	Study Report Status
PB-06-004	Assessment of the safety of taliglucerase alfa treatment in patients whose Cerezyme dose was reduced or discontinued due to the shortage of Cerezyme supply.	Study Completed. Final Report: December 2013
PB-06-005	Phase III – 12-month, double-blind trial to assess the safety and efficacy of 2 doses (30 and 60 units/kg) in naïve children with Type 1 or 3 Gaucher disease	Final Report (amended*): January 2014
PB-06-006	Phase III – an extension study for paediatric subject who completed Studies PB-06-002 and PB-06-005.	PK Final Report: July 2013
PCL-13-006/R#	Assessment of the presence of antibodies to plant glycans on taliglucerase alfa in samples confirmed positive for antitaliglucerase alfa antibodies.	Final Report: January 2014

The submission is to be accompanied by a guide outlining any differences in data from that previously submitted to and evaluated by the TGA. It was agreed between the sponsor and the TGA delegate that this critical summary can be submitted in lieu of the clinical overview (Module 2.5) document

- The reports of the studies in the table below are to be submitted as Category 1 application(s) as soon as each becomes available or as soon as practicable thereafter:

Study Code	Study Description	Study Report Status
PB-06-003	Extended assessment of the safety and efficacy of taliglucerase alfa in both naïve Gaucher disease patients and patients with Gaucher disease previously under Cerezyme treatment.	Study Completed. Final Report under development
PB-06-006	Phase III – an extension study for paediatric subject who completed Studies PB-06-002 and PB-06-005.	Study ongoing
PB-06-007	Phase III – an extension study to assess the safety and efficacy of taliglucerase alfa in adult subjects completing PB-06-001 and enrolled in PB-06-003.	Study ongoing
Protocol No. B3031002 (Registry)	Phase IV - To gather data on the long term safety and effectiveness of taliglucerase alfa in the real world post-marketing setting	Study ongoing Interim report planned (5 year):

Study Code	Study Description	Study Report Status
		July 2019. Final report planned (10 year): July 2024.

Should the reporting period for the registry study (B3031002) be changed from its current 5-year frequency, the TGA is to be informed and is to be provided with these reports on completion at the new frequency.

Attachment 1. Product Information

The Product Information approved for Elelyso at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report 1

Attachment 3. Extract from the Clinical Evaluation Report 2

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