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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elelyso

taliglucerase alfa

Procedure No.: EMEA/H/C/002250

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
AEs	Adverse Events
Anvisa	Brazilian National Health Surveillance Agency
AS	Active Substance
AUC	Area under the plasma concentration curve
AUC_{last}	Area under the curve
BBB	Blood Brain Barrier
BMD	Bone mineral density
CBC	Complete blood count
CHMP	Committee for Medicinal Products for Human use
CHO	Chinese Hamster Ovary
CL	Clearance
C_{max}	Maximum plasma concentration
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRO	Contract research organization
CTM	Clinical Test Material
DEXA	Dual-energy x-ray absorptiometry
DNA	Deoxyribonucleic Acid
DSMB	Drug safety monitoring board
EAP	Expanded Access Program
EC	European Commission
ECG	Electrocardiograph
ECL	Electrochemiluminescent
EMA	European Medicines Agency
ER	Endoplasmic reticulum
ERT	Enzyme replacement therapy
EU	European Union
EWGGD	European Working Group on Gaucher disease
FDA	Food and Drug Administration
FP	Finished Product
GCD	Glucocerebrosidase
GCP	Good Clinical Practice
GD	Gaucher disease
GlcNAc	N-acetylglucosamine
GMP	Good Manufacturing Practice
IEF	Isoelectric Focusing
INN	International Non-proprietary Name
IPC	In-Process Control
ITT	Intent to treat
IV	Intravenous
KOLs	Key Opinion Leaders
KPP	Key Process Parameter
LC	Liquid Chromatography
LOCF	Last-observation-carried-forward
LPLV	Last Patient last Visit
MAA	Marketing Authorisation Application
Man/GlcNAc	Mannose/N-acetylglucosamine
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Authorities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple imputation
MN	Multiples of normal
MoH	Israeli Ministry of Health
MPA	Medicine Product Agency
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
MSPM	Murashige and Skoog Production Media

n	Number of values
NDA	New Drug Application
NGD	Neuronopathic Gaucher disease
NNGD	Non-neuronopathic Gaucher disease
NOR	Normal Operating Range
NP-HPLC	Normal Phase High Performance Liquid Chromatography
ODD	Orphan Drug Designation
PAR	Proven Acceptable Range
PARC/CCL 18	Pulmonary and Activation-regulated Chemokine (C-C motif ligand 18)
PD	Pharmacodynamic
PDCO	Paediatric Committee
Ph. Eur.	European Pharmacopeia
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PP	Per protocol
prGCD	Plant cell expressed recombinant human glucocerebrosidase
QCSI	Quantitative Chemical Shift Imaging
RfM	Request for Modifications
RMP	Risk Management Plan
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
SAEs	Serious adverse events
SAP	Statistical Analysis Plan
SD	Standard deviation
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SE-HPLC	Size Exclusion High Performance Liquid Chromatography
SME	Small and Medium size Enterprise
SmPC	Summary of Product Characteristics
SPA	Special Protocol Assessment
SRT	Substrate Reduction Therapy
$t_{1/2}$	Half-life
TGA	Taliglucerase alfa
T_{max}	Time of maximum plasma concentration
TSE	Transmissible Spongiform Encephalopathy
U	Unit
UK	United Kingdom
USA	United States of America
Vz	Volume of distribution during the terminal elimination phase
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Ltd. submitted on 25 November 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Elelyso, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 November 2009.

Elelyso was designated as an orphan medicinal product EU/3/10/726 on 23 March 2010. Elelyso was designated as an orphan medicinal product in the following indication: Treatment of Gaucher Disease.

The applicant applied for the following condition:

Elelyso (taliglucerase alfa) is indicated for long-term enzyme replacement therapy for the treatment of systemic symptoms in adult patients with a confirmed diagnosis of Gaucher disease.

The legal basis for this application refers to Article 8(3) of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No. 1901/2006, the application included an EMA Decision P/57/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/57/2010 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No. 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products Zavesca and Vpriv.

Derogations from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No. 847/2000, the applicant submitted data in support of the derogations to market exclusivity laid down in Article 8(3) of the Regulation (EC) No. 141/2000, which are:

- That the holder of the marketing authorisation for the orphan medicinal product (Vpriv) is unable to supply sufficient quantities of the medicinal product (Article 8(3)(b) of Regulation (EC) No 141/2000 provided for in Article 8(3)(c) of the Regulation (EC) No. 141/2000) and
- That the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior (Article 8(3)(b) of Regulation (EC) No 141/2000).

New active Substance status

The applicant requested the active substance taliglucerase alfa contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice / Protocol Assistance

The applicant did not seek scientific advice at the CHMP.

Licensing status

Elelyso has been given a Marketing Authorisation in the USA on 1 May 2012

A new application was filed in the following countries: Israel and Brazil.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **Pieter de Graeff**

- The application was received by the EMA on 25 November 2010.
- The procedure started on 15 December 2010.
- The CHMP adopted the CHMP assessment report for Elelyso on similarity with Zavesca or Vpriv on 17 February 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 March 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 04 March 2011.
- During the meeting on 14 April 2011 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 April 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2011.
- The summary report of the inspection carried out at the following site, Protalix Ltd, between 14-18 August 2011 was issued on 17 October 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 November 2011.
- During the CHMP meeting on 15 December 2011 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted written responses to the CHMP List of Outstanding Issues on 10 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 27 February 2012.

- During the CHMP meeting on 12 March 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 12-15 March 2012 the CHMP agreed on an additional list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP additional List of Outstanding Issues on 17 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the additional List of Outstanding Issues to all CHMP members on 06 June 2012 and the updated report on 18 June 2012.
- During the meeting on 18-21 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the CHMP, considered the benefit-risk balance of Elelyso favourable. However, the CHMP considered Elelyso to be similar to Vpriv for the same therapeutic indication and concluded that none of the derogations regarding orphan market exclusivity, as provided for by the Regulation (EC) No. 141/2000 apply and thus, recommended refusal of granting the marketing authorisation for Elelyso on 21 June 2012.
- The CHMP adopted a CHMP assessment report on the applicant's justifications on the applicability of the derogations laid down in Article 8(3) (b) and 8(3)(c) of Regulation (EC) No. 141/2000 in relation to a similar orphan medicinal product Elelyso on 21 June 2012.
- A revised CHMP opinion, CHMP assessment report and CHMP assessment report on the applicant's justifications on the applicability of the derogations laid down in Article 8(3) (b) and 8(3)(c) of Regulation (EC) No. 141/2000 in relation to a similar orphan medicinal product were adopted by the CHMP via written procedure on 3 July 2012.

2. Scientific discussion

2.1. Introduction

Elelyso (taliglucerase alfa) is intended for enzyme replacement therapy (ERT) of Gaucher disease (GD), which is a rare genetic disorder characterised by a functional deficiency of β-glucocerebrosidase activity. 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 degradative pathways when the activity of β-glucocerebrosidase is deficient. Tissue macrophages are the predominant cell type that accumulates excessive glucocerebroside under these enzyme deficient conditions and accumulation of excessive glucocerebrosides in lysosomal compartments of monocyte/macrophage-derived cells gives rise to the characteristic Gaucher cells: macrophages engorged with lipids with a crumpled-tissue-paper appearance and displaced nuclei. Formation of Gaucher cells causes enlargement of the liver and spleen, which may be massive and result in abdominal protuberance. Hepatocellular function is usually well preserved, although transaminases may be slightly elevated. Splenomegaly is associated with hypersplenism and pancytopenia, with anaemia and thrombocytopenia being most significant. Bone involvement is caused by accumulation in marrow macrophages, a decrease in osteoblast activity and bone mineralisation, and a relative increase in bone resorption. The resultant osteopoenia predisposes to vertebral compression and other pathological fractures. Pulmonary involvement is uncommon but manifests as interstitial lung disease or pulmonary hypertension when it occurs. During childhood, retarded growth and delayed developmental maturation are common.

Historically, GD has been classified into three subtypes:

Type 1 (non-neuropathic)

Type 2 (acute neuropathic)

Type 3 (sub-acute neuropathic)

However, the manifestation of symptoms varies significantly among patients and, often, a clear classification into these subtypes is difficult. In the recent classification adopted by treating physicians the GD population is classified according to the absence (non-neuropathic GD [NNGD]) or presence (neuropathic GD [NGD]) of complex neurological symptoms. The latter group is further subdivided into "acute" or "chronic" neuropathic disease. Acute neuropathic disease ("acute NGD") appears in newborns (≤ 1 year) with a very severe neurological presentation that results in the death of the patient within the first 2 years of age. In chronic neuropathic disease ("chronic NGD"), the neurological symptoms develop later and progress at a variable rate to a disease with neurological symptoms of varied severity. Under the previous classification system NNGD patients were Type 1 GD patients, acute NGD patients were Type 2 GD patients and chronic NGD patients were Type 3 along with any other patients with neurological symptoms that did not belong to the "acute" subgroup. NNGD accounts for 94% of GD cases. Acute NGD (about 1% of GD cases) includes patients with onset usually at one year of age with progressive bulbar involvement (stridor, squint, swallowing difficulty). The chronic NGD (about 5% of GD cases) again includes a heterogeneous group of patients. Certain patients have moderate systemic involvement associated with ophthalmoplegia as the only neurological symptom. Variable neurological signs are seen in more severe forms: supranuclear horizontal ophthalmoplegia, progressive myoclonic epilepsy, cerebellar ataxia, spasticity and dementia.

Currently, patients are treated with palliative therapy, which includes splenectomy, blood transfusions, and orthopaedic procedures, and bone marrow transplantation. Furthermore, the following medicinal products are authorised in the EU for the treatment of GD:

Cerezyme (imiglucerase) is not an orphan medicinal product and is indicated for long-term ERT indicated for Type 1 and 3 GD.

Vpriv (velaglucerase alfa) is an orphan medicinal product and is indicated for long-term ERT in patients with type 1 GD.

Zavesca (miglustat) is an orphan medicinal product and is a substrate reduction therapy (SRT), a glucosylceramide synthase inhibitor, which is approved as second-line therapy when ERT is not a therapeutic option for patients with type 1 GD.

Taliglucerase alfa is a recombinant glucocerebrosidase similar to the human lysosomal glycoprotein enzyme β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase). The active substance is purified from genetically modified carrot cells grown in pre-sterilised disposable bioreactors.

The mechanism of action is based on the ability of taliglucerase alfa to be specifically taken up by macrophages, the target cells in Gaucher disease. Following intravenous infusion, taliglucerase alfa is expected to target and penetrate macrophages through the mannose receptor and is delivered to the lysosome where it catalyses the hydrolysis of accumulated glucocerebrosides to glucose and ceramide.

The clinical development programme for taliglucerase alfa for the treatment of systemic symptoms in adult patients with a confirmed diagnosis of GD consists of one Phase 1 trial in healthy subjects and three Phase 3 safety and efficacy clinical studies in patients with GD, including 1 single pivotal completed study and 2 supportive ongoing studies. A Phase 2 study was not included in the clinical programme with taliglucerase alfa as it is a drug belonging to a class with a known pharmacological principle and a demonstrated mechanism of action, for which extensive dosing regimen experience is already available. An extension study was also initiated to collect long term data following treatment

with taliglucerase alfa. Further to the above clinical protocols, compassionate use programmes including an Expanded Access Protocol (EAP) study and named-patient compassionate use were also ongoing at the time of submission.

2.2. Quality aspects

2.2.1. Introduction

Taliglucerase alfa is a recombinant glucocerebrosidase similar to the human lysosomal glycoprotein enzyme β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase). The applicant has developed a plant cell-culture based expression system, using carrot cells as a host cell for the expression of the active substance. The expression construct has been designed with the aim of specific expression in the vacuole of the carrot cell, generating taliglucerase alfa with the desired glycosylation profile uptake into macrophages. The plant post-translational machinery produces proteins with mannose terminated glycans in the endomembrane system (plant secretory system). The ability to target proteins and to retain them in this compartment, allows the production of mannose-terminated glycoproteins. The protein is targeted into the plant secretory system by fusing a leader sequence and a vacuolar targeting signal to accumulate the protein in the vacuole. Taliglucerase alfa is a 506 amino acid enzyme, of which 497 amino acids encode for human glucocerebrosidase. This sequence 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.

Taliglucerase alfa is a glycosylated protein with approximately 7% of its molecular mass contributed by glycans. The amino acid sequence contains 5 potential N-linked glycosylation sites but only 4 are occupied by glycan chains (N21, N61, N148, and N272). Glycan analysis showed that all of the glycan structures have terminal mannose residues. These mannose-terminated glycans are specifically recognised by mannose receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

Elelyso is the invented name for taliglucerase alfa. Elelyso is a powder for solution for infusion supplied as sterile, non-pyrogenic, and white to off-white lyophilised powder in a glass vial with a rubber stopper and aluminium cap.

Each vial contains 200 units of taliglucerase alfa, with 6% overfill and the excipients Sodium citrate (buffering agent), citric acid (to adjust the buffer pH to 6.0), mannitol (tonicity-adjusting agent), and polysorbate 80 (stabilizer).. After reconstitution with water for injection, taliglucerase alfa is diluted in 0.9% sodium chloride solution and administered by intravenous infusion, over 1 - 2 hours.

2.2.2. Active Substance

Taliglucerase alfa (TGA) is a recombinant glucocerebrosidase analogue of the human lysosomal glycoprotein enzyme β-glucocerebrosidase that catalyses the hydrolysis of glucocerebroside to glucose and ceramide. The glycosylated protein is produced in genetically modified carrot cells.

Taliglucerase alfa has 4 sites with N-linked glycan structures with terminal mannose residues, important for internalization into the lysosomes of macrophages. Taliglucerase alfa is a 506 amino acid enzyme, of which 497 amino acids encode for human glucocerebrosidase. Two of the additional amino acids are due to a signal peptide; the seven others are involved in targeting TGA to the vacuole. Molecular mass is approximately 60,800Da to which glycans contribute ca. 7%.

Manufacture

Taliglucerase alfa is purified from genetically modified carrot cells. The production process is a two stage process:

- The upstream phase includes expansion of the recombinant carrot cells and expression of taliglucerase alfa;

The downstream purification process involves extraction, clarification and purification of the taliglucerase alfa protein. The purification process employs the standard techniques for protein purification by chromatography on multiple columns. This yields an active substance in aqueous solution, which is frozen prior to conversion to the finished product.

The active substance material is then filtered using a 0.2 µm filter and filled into bottles with HDPE screw closures, pre-sterilized with gamma irradiation. Prior to final formulation, the bulk active substance may be stored frozen for up to 24 months at -20 ± 5°C. Taliglucerase alfa AS will be shipped at not more than -15°C.

MCB & WCB

Establishment of the production cell line has been described in detail, including plasmid construction, transformation of the carrot cells and selection of producer clone. The origin of the carrot cell line was a carrot cultivar tuber grown for human consumption. The cell line was further used for plant transformation with the vector containing the taliglucerase alfa expression cassette.

A description of the cell bank used and the results of its testing, including specific virological tests genomic sequence analysis and genetic stability was provided. The consistency of this "fingerprint" has been confirmed during the production of the Master Cell Bank and Working Cell Bank, and in determination of the Limit of *in-vitro* Cell Age (LIVCA) for the manufacturing process.

The MCB for taliglucerase alfa production (10205MGCD) was prepared and cryopreserved (348 cryovials stored in liquid nitrogen). Cryopreservation methods for plant cell cultures are not well known; therefore a specific viable method was developed. Fifty vials were thawed and tested for viability, sterility and protein expression. MCB vials were also tested for plant specific carrot viruses and found negative. In addition, stability of protein coding sequence during culture to the end of production was established.

Manufacturing Process Controls

The overall process control strategy has been re-defined following the major concern raised in the List of Questions, with an improved description of the manufacturing process and the associated controls. Furthermore, several acceptance criteria were tightened following requests made throughout the procedure.

A clear overview of critical parameters was presented, following clarification of the terminology (acceptance criteria/ranges). The CPPs/KPPs/IPCs themselves are well defined and for most parameters the corrective actions if limits are exceeded is clearly described. In particular, the large number of parameters aimed at preventing microbiological contamination (for which the corrective action is 'rejection of batch') is noted, although the initial proposed bioburden limits were considered to be set too high. The bioburden control strategy for the entire manufacturing process was not conclusive with regard to the presented definitions of 'acceptance criterion' and 'acceptance range'. . According to the applicant, exceeding the acceptance range may result in rejection of the batch. An acceptance range exceeding an acceptance criterion is not acceptable and the applicant has

subsequently tightened many of the IPC limits and provided clarification that the rejection limits are based on the values for Normal Operating Range (NOR). The documentation was further updated to define the specifications rather than using confusing terminology such as NOR and Proven Acceptable Ranges (PAR). Following the applicant's review discussions and experience of operation of the commercial process, it was noted that divergence of the PARs and NORs occurred in only a few instances. Reduction in the upstream bioburden levels which could result in batch rejection make certain PARs invalid. The applicant therefore removed the PAR column in tables and renaming NOR column 'Acceptance Criterion', with corrective actions referring directly to the acceptance criteria. Two Critical Process Parameters have been identified during the purification process whose variability has an impact on the Critical Quality Attributes of taliglucerase alfa. The CPPs are, therefore, controlled within appropriate ranges to ensure that the process produces the desired active substance quality.

Manufacturing process validation

Process validation was performed at the commercial manufacturing site for the taliglucerase alfa active substance process, Protalix (Carmiel, Israel), according to process validation protocols. The purpose of the process validation studies was to demonstrate process control, reproducibility and acceptability of the taliglucerase alfa process.

Process validation studies were performed on the cell culture, harvesting and purification operations of three consecutive taliglucerase alfa active substance batches at commercial size

A significant increase in bioburden occurred in some validation batches after harvest as a result of incomplete cleaning and sanitisation of equipment. Corrective actions were implemented and in 11 additional harvest batches, bioburden levels were low. The sanitary performance of the taliglucerase alfa process has been demonstrated and revised bioburden IPC limits are presented. Improved procedures for bioburden control and further tightening of the IPC (rejection) limits for bioburden were given, to provide assurance that the bioburden levels are sufficiently controlled.

The pool hold times of intermediates were validated. In general, the purification process appears satisfactory, with removal of process-related and product-related impurities.

The applicant has supplied the information for retrospective and prospective resin re-use evaluation. A shipping validation report has been provided.

Characterisation

Elucidation of structure

The structure of taliglucerase alfa AS was evaluated by extensive testing performed on the three validation batches including the commercial reference standard manufactured by the commercial manufacturing process. The structure had been evaluated using X-ray crystallography, amino acid sequencing, peptide mapping, disulfide bond and free sulfhydryl content analysis. Glycan structure is important for the uptake of taliglucerase alfa by macrophages and characterisation of glycan structure and mannose content was also detailed in this section.

However, the characterisation section was considered incomplete at the time of the List of Questions and an extensive amount of new information was submitted in response to this concern. Orthogonal methods have been introduced and new or revised analytical methods have been developed and applied to further elucidate the protein structure and oxidation, deamination and similar product-related variants of taliglucerase alfa (TGA). Improved analytical assays which can better detect and

quantify product-related variants, including those formed by degradation, have been applied. The biological activity was evaluated by enzymatic activity using a synthetic substrate and determination of Michaelis-Menten kinetics for taliglucerase alfa using the same substrate.

The relevance of the mannan inhibition assay for inhibition of specific uptake of taliglucerase alfa by macrophages was questioned as a routine assay. The applicant has developed and validated an appropriate revised potency assay, macrophage uptake assay—which will be performed at active substance and finished product at release and stability. Information from individual batches has been provided for the provisional specification, which is rather wide, and the CHMP recommended the applicant to evaluate technical improvements to the cellular uptake assay to reduce the variability of this method. A revised specification range will be introduced after evaluation of release testing of at least 30 DS batches made by the commercial process and 15 DP batches produced from DS made by the commercial process, in addition to the relevant stability batches that have been tested at that time.

Impurities

The purity of the active substance is estimated by a combination of methods. The choice of analytical procedures is focused on the separation of the taliglucerase alfa product from product related substances (variants and impurities) and from process related impurities. Assays, including electrophoresis, RP-HPLC, capillary IEF, and Size Exclusion Chromatography are performed to assure the purity of taliglucerase alfa and characterize the product-related impurities. Process-related Impurities such as Host Cell Protein and Host Cell DNA are controlled at release, while clearance of other potential process-related impurities has been demonstrated.

Comparison with Cerezyme

A comparison of taliglucerase with imiglucerase (Cerezyme) has been submitted. The submission of these data is deemed to be in line with ICH Q6B recommendations on characterisation.

Taliglucerase is a recombinant analogue of the human enzyme. No international reference standard is available; a direct comparison with the human enzyme is technically challenging but a comparison with the commercially available recombinant cerebroglucerases: imiglucerase (Cerezyme) and velaglucerase (Vpriv) which have been compared previously with the human enzyme, is deemed sufficiently relevant.

Supportive comparison studies with Cerezyme were provided which showed similarity between these two molecules.

Specification

The active substance specification has been amended according to the various requests during the evaluation of the marketing authorisation application.

Release specification for the active substance includes control for appearance (Ph. Eur.), pH (Ph. Eur.), identification (peptide map) (SDS-PAGE – Western blot analysis), purity (RP-HPLC) (host cell protein by ELISA) (automated electrophoresis) (Capillary Isoelectric Focusing) (SE-HPLC), taliglucerase alfa content (RP-HPLC), specific activity (enzymatic activity and taliglucerase alfa assessment determination by RP-HPLC absorption at 280nm), enzymatic kinetics (Michaelis-Menten kinetics), cellular uptake (cell based assay), glycan structure analysis (NP-HPLC combined with glycosidase digestion), mannose content (mass spectrometry), total aerobic count (Ph. Eur.), bacterial endotoxin (Ph. Eur.), residual DNA and free sulfhydryl content (Ellman's reaction for thiol determination).

The information provided in the assay validation section in the dossier was inadequate, with only summary tables that were not fully explained. Details of the assay validation of the HCP assay, endotoxins, macrophage cellular uptake and kinetics by Michaelis-Menten was subsequently provided by the applicant. The macrophage uptake assay has replaced the cellular uptake inhibition assay and details of this new assay have been provided. All compendial and non-compendial analytical methods have been validated according to ICH guidance Q2 (R1) where appropriate.

Batch analysis data from 128 batches manufactured at industrial scale with the proposed manufacturing process were presented to support the proposed specification.

Reference standard

The reference standard is prepared from the active substance batches. A reference standard replacement protocol, including a protocol for determination of stability of the reference standard, has been submitted. Each new reference standard is qualified for use by testing against release specification and additional characterisation tests.

No international reference material is available. Therefore, the reference standard is prepared from the active substance batches. A reference standard replacement protocol, including a protocol for determination of stability of the reference standard, has been submitted. Each new reference standard is qualified for use by testing against release specification and additional characterisation tests. This protocol is deemed acceptable. The replacement of a reference standard will be the subject of a variation.

Stability

Stability data for three batches manufactured from the proposed commercial process is limited (up to 12 months available at -20 ± 5°C (long term) and 3 month at 5 ± 3°C(short term)), the applicant has provided data from five primary batches stored at -20°C ± 5°C for up to 36 months. This is considered supportive of the proposed shelf life of 24 months at -20°C ± 5°C, since comparability is demonstrated between the primary batches and the proposed commercial scale active substance.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the rapporteur and EMA.

Comparability exercise for Active Substance

During manufacturing development, a number of changes were made to the cell culture part of the upstream process; No significant changes were made to the downstream processing

The applicant did not provide the relevant data required within the manufacturing process development section in the initial dossier to support their argument that the changes made during process development did not impact the quality of the active substance. Furthermore, not all batches used in the (pre)clinical studies were released using the same battery of analytical methods.

To respond to this major objection, the applicant provided new comparability data and re-analysis of existing data to support the manufacturing changes between product used in the phase III pivotal trials and the proposed commercial product. The taliglucerase alfa activity appeared to be comparable

after the change. This suggests that improved expression levels and consistency of glycosylation following manufacturing changes do not have an impact on the enzyme kinetic parameters of taliglucerase alfa. The active substance batches appeared comparable before and after the changes were introduced, except for differences in the quantitative glycan profile. The glycan data shows a clear shift to a more homogeneous glycan distribution However, the glycan distributions, both before and after the process changes, contain the desired terminal mannose which is required for optimal uptake into the target cells by the mannose receptor.

A difference was noted in the uptake inhibition after the changes and, according to the expected mechanism of action for taliglucerase alfa, this change in uptake inhibition is likely to be related to the glycan differences. There were also differences in the new macrophage cellular uptake assay therefore it is recommended that further work is performed to reduce the variability observed in this potency assay. The clinical relevance of the observed differences in the glycan patterns pre-and post-change leading to differences in the new macrophage cellular uptake assay have been discussed and these should not impact clinical performance.

2.2.3. Finished Medicinal Product

The finished product, taliglucerase alfa powder for solution for infusion, is supplied as sterile, non-pyrogenic, white to off-white lyophilised powder in a Type I glass vial with a rubber stopper and aluminium cap, with the following detailed composition:

Name of Ingredients	Quantity per Vial (mg)	Function	Quality
Drug Substance			
Taliglucerase alfa	212 Units	Active ingredient	Manufacturer's specification
Excipients contained in the final product			
Mannitol	206.7	tonicity-adjusting agent	Ph. Eur.
Polysorbate 80	0.56	Stabiliser	Ph. Eur.
Sodium citrate[1] (as tribasic dihydrate)	30.4	Buffering agent	Ph. Eur.
Citric acid, anhydrous[2]	Q.S.	pH adjustment	Ph. Eur.
Water for Injections[3]	NA	Diluent Prior to Lyophilisation	Ph. Eur

[1] Introduced in DS manufacturing process
[2] For adjustment to pH=6. The amount depends on the pH of the solution
[3] Removed from the finished drug product during lyophilisation

The finished product is provided in 13.5 mL Type I glass vials, closed with rubber stoppers and secured with snap-cap aluminium seals. The nominal content of each vial is 200 units of taliglucerase alfa; a 12 units overfill (6%) is included to provide sufficient volume upon reconstitution. After reconstitution, taliglucerase alfa is diluted in 0.9% sodium chloride solution and administered by intravenous infusion, over 1 - 2 hours.

Pharmaceutical Development

The finished product formulation is qualitatively the same as the commercially available ß-Glucocerebrosidase (imiglucerase; (Cerezyme), Genzyme Corporation). The reason for using a similar formulation was to utilize existing safety data and precedence of a marketed product, which reduces the development risk.

There are no differences in the composition of taliglucerase alfa finished product formulation used over the course of clinical studies or for commercial use. The FP manufacturing principles were unchanged throughout the clinical development of the product. However, some changes have been made to the manufacturing process during development. These include:

1) The scale up of the formulation and lyophilisation process,

2) The optimization of the lyophilisation process, and

3) Difference in manufacturers

The lyophilisation cycle was optimised and transferred from Teva to Wasserburger Arzneimittelwerk GmbH (WA). The batch size was scaled up at this manufacturing facility. Media fill validation for this site has now been provided.

Comparability Exercise for Finished Medicinal Drug Product

The initial comparability section provided to support the manufacturing changes between taliglucerase alfa product used in the phase III pivotal trials and the proposed commercial product was inadequate; it was not clear whether finished product using taliglucerase alfa active substance manufactured using the commercial manufacturing process had been used for any of the Phase III studies. The applicant provided new comparability data and re-analysis of existing data to support the manufacturing changes between product used in the phase III pivotal trials and the proposed commercial product. The applicant also provided details of finished product batches using taliglucerase alfa active substance manufactured using the commercial process which have been used in Phase III studies so far. The final comparability section is adequate and comparability of taliglucerase alfa product used in the phase III pivotal trial (manufactured at Teva) with the proposed commercial product (manufactured at Wasserburger Arzneimittel) is considered demonstrated.

Manufacture of the product

The finished product is manufactured at Wasserburger Arzneimittelwerk GmbH (W.A.), Germany.

The main manufacturing process steps of taliglucerase alfa Drug Product consist of thawing of Drug Substance, formulation, sterile filtration, filling into vials, partial stoppering, lyophilisation and capping. The drug product manufacturing process is operated in GMP environments. With the initial documentation, the Applicant did not sufficiently demonstrate that the drug product manufacturing process was under control, and was able to ensure product quality and batch-to-batch consistency. Additional data was provided at D120 and D180 and the description of the different processing steps in the manufacturing of taliglucerase alfa Drug Product, the duration and temperature of the steps is now well documented. All the operating equipment and machines are prequalified. The manufacturing process is controlled in every preparation step. The in-process controls, parameters and qualified hold times are defined and the critical controls are identified.

Validation studies include filter validation, holding time validation, validation of compounding, filling and lyophilisation confirming the suitability of the drug product manufacturing process at this site.

The shipping has been qualified for three batches from Germany to Israel and further studies are planned.

Product specification

Release specification for the finished product include control for appearance/colour (visual inspection), water content (Ph. Eur.), Reconstitution time, pH after reconstitution (Ph. Eur.), appearance after reconstitution (Ph. Eur.), particulate matter after reconstitution (Ph. Eur.), Osmolality after reconstitution (Ph. Eur.), identification I (peptide map) (SDS-Page – Western blot analysis), content uniformity (Ph. Eur.), Purity (RP-HPLC) (Capillary isoelectric focusing) (Automatic electrophoresis) (SE-HPLC), taliglucerase alfa content (RP-HPLC), Potency (enzymatic activity), Enzyme kinetic (cell based assay), sterility (Ph. Eur.) and bacterial endotoxin (Ph. Eur.).

Analytical methods have been adequately validated and the specification limits are supported by data from seventeen batches representative of the commercial process. However, quality control for release of FP was not considered fully qualified since the transfer of non-compendial analytical assays for release and stability assay for Elelyso to the quality control testing site, Pfizer Ireland Pharmaceuticals, Grange Castle, Ireland was still ongoing and this was raised as a major objection. The applicant has provided acceptable data for the transfer of eight release and stability assays. For the cellular uptake assay limited data in relation to the transfer of this assay to the facility at Pfizer Ireland Pharmaceuticals, Grange Castle was provided, however this was deemed acceptable,

The justifications of the proposed commercial specifications for taliglucerase alfa finished product as provided by the applicant are largely acceptable. Some specifications have been tightened following requests by CHMP and some need reviewing once more batches have been manufactured and tested.

Stability of the product

Taliglucerase alfa finished product powder for solution for injection is stable when stored at 5 ± 3°C for the shelf life of 24 months. The applicant provided the results of the primary stability studies after 24 months storage, including data for eleven batches of which three were full scale validation batches. Only up to 9 month of stability data was available at long term condition (5 ± 3°C) for the full scale batches but the stability data of the primary stability batches (up to 36 months) were considered to be supportive to the proposed shelf-life.

Storage or temperature excursions of taliglucerase alfa Drug Product to -20°C, as suggested by the applicant, is acceptable and supported by appropriate data. Since the Applicant has not performed cycling studies of repeat freeze-thaw of the finished product, the labelling will include the precaution of "Do not freeze".

Based on the evaluation of two batches of pooled reconstituted finished product diluted with saline solution in infusion bags, reconstituted taliglucerase alfa finished product diluted into infusion bags is considered stable for at least 18 hours at 2-8°C.

The post-approval stability protocol and the stability commitment have been provided and are considered satisfactory. In accordance with EU GMP guidelines, any confirmed out-of-specification result of significant negative trend should be reported to the rapporteur and EMA.

Adventitious agents

Taliglucerase alfa is produced by a proprietary innovative technology where transformed carrot plant root cells, cultured in suspension in a closed bioreactor system, express the protein. The plant cell culture system is free of mammalian derived components which are not required for efficient plant cell growth and protein production. The carrot plant cells cultures are naturally and biologically protected from being infected by human or mammalian viruses or other pathogen due to host-pathogen specificity. Furthermore, plant viruses cannot be propagated in plant cells cultured in suspension. Finally, plant viruses pose no risk to humans

Based on this rationale and on the current scientific knowledge, the carrot cell culture line used for the production of taliglucerase alfa cannot be a host for viruses.

No raw materials of animal origin are used during the manufacturing process of both taliglucerase alfa drug substance and drug product. There are two components of biological origin that are use indirectly; one at the early stage of the MCB establishment, the other, issued from a non-TSE relevant species is used to manufacture a component of the production medium.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has provided satisfactory responses to all the major objections. A more detailed discussion of the complex semi-continuous process used for manufacture of taliglucerase alfa at commercial scale has clarified a number of questions which were initially raised regarding the active substance manufacturing process. Clarification regarding the active substance batch concept and fermenter 'production trains' has enabled a better understanding of how the manufacturing facility is utilised.

Improvement in bioburden control, with addition or tightening of in-process controls, has provided further assurance of process control. However, many of the issues raised in this regard have arisen because of unclear classification of the process controls; these were resolved by adapting the documentation.

Improved and optimised assays have been introduced, with appropriate validation data. These include an optimised RP-HPLC assay for purity and concentration determination of taliglucerase alfa, imaging cIEF for charged species and introduction of a macrophage uptake assay (to replace the cellular uptake inhibition assay). Further batches of active substance and/or finished product will need to be evaluated using these assays before the final specifications can be set; this is reflected in the recommendations. The validation activities at the finished product manufacturing site Wasserburger Arzneimittelwerk (WA) have been completed and the validation report confirms that this is acceptable.

The status of the site responsible for quality control testing (release and stability) and batch release, Pfizer Ireland Pharmaceuticals, Grange Castle, Ireland, has been resolved. The applicant has provided acceptable data for the transfer of eight release and stability assays. For the cellular uptake assay limited data in relation to the transfer of this assay to the facility at Pfizer Ireland Pharmaceuticals, Grange Castle was provided, however this was deemed acceptable, A revised specification range should be introduced after release testing with the improved assay of at least 30 batches of drug substance and 15 batches of the finished product manufactured using the commercial process.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable based on the information provided on manufacturing, testing and storage of both the active substance and the finished product. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

From a Quality point of view, the application for Elelyso is approvable.

2.3. Non-clinical aspects

2.3.1. Introduction

The originally proposed indication for Elelyso is the long-term enzyme replacement therapy for the treatment of the systemic symptoms in patients with GD. The active substance, taliglucerase alfa, is a glycosylated protein produced in genetically modified carrot cells by recombinant DNA technology. Taliglucerase alfa is a recombinant glucocerebrosidase, structurally similar to the human lysosomal glycoprotein enzyme β-glucocerebrosidase. The mechanism of action is based on its ability to be specifically taken up by the macrophages, the target cells in GD. Whilst recognising the stand alone nature of this application, it was also noted during the nonclinical development of taliglucerase alfa that it was considered that taliglucerase alfa and the existing therapy imiglucerase (Cerezyme) belong to the same pharmacological group. Key elements of the development were demonstration of the same mechanism of action (based on receptor-targeting) of taliglucerase alfa and imiglucerase, and assessing the safety of taliglucerase alfa in a series of appropriate toxicity studies sufficient to support the dossier.

2.3.2. Pharmacology

The active substance, taliglucerase alfa, is a 506 amino acid enzyme, of which 497 amino acids encode for human glucocerebrosidase. Additional amino acids were added to the native human glucocerebrosidase sequence to permit the efficient expression of active enzyme in carrot root cell cultures. Approximately 7% of its molecular mass is contributed by glycans. Glycan analysis showed that all of the glycan structures have terminal mannose residues. These mannose-terminated glycans are specifically recognised by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease. Taliglucerase alfa differs from imiglucerase in that the oligosaccharide chains have naturally exposed terminal mannose sugars. In comparison, imiglucerase requires post-purification enzymatic remodelling *in vitro* with different glycosidases in order to expose the terminal mannose residues required for cellular uptake by macrophages.

Primary pharmacodynamic studies

A summary of investigations to evaluate primary pharmacodynamics of taliglucerase alfa is presented in the table below.

Type of Study	Test System	Method of Administration	Testing Facility	Study No.
Primary Pharmacodynamics				
Enzyme activity	NA	In vitro	Protalix	Shaaltiel et al. 2007
Uptake by macrophages	Mouse macrophages	In vitro	Protalix	Shaaltiel et al. 2007
Uptake by macrophages	Human macrophages	In vitro	Protalix	prGCD uptake in human macrophages
Uptake by macrophages	Rat (NR8383) alveolar macrophage cell line	In vitro	Protalix	Taliglucerase uptake in macrophages from cynomolgus monkeys and rabbits
Uptake by macrophages	Rabbit, monkey and human macrophages	In vitro	Protalix	Taliglucerase uptake in macrophages from cynomolgus monkeys and rabbits

Primary pharmacodynamic studies included *in vitro* studies of enzyme kinetic parameters as well as macrophage uptake and inhibition of uptake for taliglucerase alfa. For reference, the applicant also included imiglucerase using mouse and human macrophages. The maintenance of enzymatic activity following uptake by macrophages was confirmed, as well as the role of mannose receptors in mediating the uptake. These *in vitro* data confirm that taliglucerase alfa exhibits a specific interaction with the Man/GlcNAc receptor present on enlarged macrophages (Gaucher cells). Furthermore, although not directly relevant to this stand alone dossier, it was noted that taliglucerase alfa exhibits similar enzyme kinetics to imiglucerase as also shown by the results in the table below.

Comparison of enzyme kinetics and uptake between imiglucerase and taliglucerase

Type of Study	Test System	Method of Administration	Concentration	Noteworthy Findings	Study No.
Enzyme activity	NA	In vitro	NA	Taliglucerase alfa Km = 20.7 ± 0.7 µM Vmax = 0.47 ± 0.08 µmol/min/mg [a] Imiglucerase Km = 15.2 ± 4.8 µM Vmax = 0.43 ± 0.06 µmol/min/mg [a]	Shaaltiel et al, 2007
Macrophage uptake	Mouse [b] peritoneal macrophages (thioglycolate-elicited)	In vitro	0, 1.6, 3.2, 6.4 U/ml	Taliglucerase alfa and imiglucerase Uptake by mouse macrophages with maintenance of enzyme activity after internalisation; uptake at 6.4 U/ml slightly higher for taliglucerase alfa; mannan (2 – 8 mg/ml) inhibited uptake	Shaaltiel et al, 2007
Macrophage uptake	Human macrophages	In vitro	0,1, 2, 4 U/ml	Taliglucerase alfa and imiglucerase Uptake by human macrophages with maintenance of enzyme activity after internalisation; uptake slightly higher for taliglucerase alfa; mannan (2 mg/ml) inhibited uptake (tested for taliglucerase alfa only)	prGCD uptake in human macrophages

NA = not applicable; prGCD = plant recombinant glucocerebrosidase
[a] Activity was determined with a fluorescent short-acyl-chain analogue of glucosylceramide, ie N-[6-[(7-nitrobenzo-2-oxa-1,3-diazol-4-yl) amino] hexanoyl]- glucosylsphingosine (C6-NBD-GlcCer) as a substrate; Vmax is expressed as µmol C6-NBD-Cer formed/min/mg.
[b] Strain not specified.

Taliglucerase alfa displayed a Vmax of 0.47 µmol C6-NBD-Cer formed/min/mg and a Km of 20.7 µM. For imiglucerase, Vmax was 0.43 µmol C6-NBD-Cer formed/min/mg and Km was 15.2 µM. Taliglucerase alfa and imiglucerase were both taken up by murine thioglycolate-elicited peritoneal macrophages when incubated for 90 minutes at 37° C at concentrations up to 6.4 units/ml. Uptake of taliglucerase alfa tended to be higher than the uptake of imiglucerase at higher concentrations. Both products maintained their enzymatic activity. Uptake of taliglucerase alfa and imiglucerase was progressively inhibited by the addition of increasing concentrations of yeast mannan (2-8 mg/ml) to the incubation medium, demonstrating that uptake is mediated by mannose (Man/GlcNac) receptors.

These *in vitro* data confirm that taliglucerase alfa exhibits a specific interaction with the Man/GlcNAc receptor present on enlarged macrophages. Furthermore, taliglucerase alfa exhibits similar enzyme kinetics to imiglucerase.

To assess the relevance of the nonclinical species used in the toxicology testing, an *in vitro* uptake assay was conducted using the rat alveolar macrophage cell line NR8383, and primary macrophages from rabbits and cynomolgus monkeys. In this assay, concentrations ranging from 1 to 4 U/ml were evaluated. Concentration-dependent uptake of taliglucerase alfa was observed in rat, rabbit, and cynomolgus monkey macrophages. When mannan was added to the incubation mixture (taliglucerase concentration of 1 U/ml), inhibition of uptake was observed. These data confirm that the species used in the nonclinical toxicology programme (mice, rats, monkeys, and rabbits) were relevant and, therefore, the safety data can be considered relevant for assessing potential adverse effects in

humans. However, the used *in vitro* concentrations are above the human serum concentrations (C_{max} 5 µg.ml ~ 0.13U/ml) and the CHMP has therefore requested information on the uptake and activity of taliglucerase alfa at clinically relevant concentrations. an additional *in vitro* experiment was conducted upon request of the Committee, results of which indicate that taliglucerase alfa is taken up and remains active in the target cells, macrophages derived from Gaucher disease patients, in the test system conditions. There are some limitations in the design of the experiment that prevent to draw conclusions on the uptake at clinically relevant concentrations in GD cells *in vivo* (i.e. selection of concentration at 17 µg/mL, low sample number). Notwithstanding these limitations, the results of this experiment are in line with the data by Shaaltiel *et al*. with regards to the uptake in macrophages derived from patients with Gaucher's disease and support the primary pharmacodynamic effect of taliglucerase alfa.

With respect to *in vivo* primary pharmacodynamic studies, these were not conducted. This was appropriately justified by the applicant, taking into account knowledge known about the effect of other members of the class and because the pharmacology and the receptor-targeting of taliglucerase alfa was considered to be adequately addressed by the described *in vitro* studies, and because the efficacy of taliglucerase alfa in ERT in Gaucher disease has been shown. Thus, sufficient information has been provided along with the justifications to accept this from a stand-alone application viewpoint.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies were not conducted because the uptake is receptor mediated on specific target cells and the activity of taliglucerase alfa as an enzyme is specific; no secondary pharmacodynamic effects are therefore anticipated. This justification is accepted by the CHMP.

Safety pharmacology programme

Specific secondary pharmacodynamic studies were not deemed necessary since the activity of taliglucerase alfa as an enzyme is specific and its mechanism of action is the same as for other approved ERT for GD, which has not provided cause for concern regarding potential effects on the central nervous system, cardiovascular system or respiratory system. Furthermore, information on potential effects of taliglucerase alfa on the mentioned organ systems was obtained from single and/or repeat-dose toxicity studies and no adverse effects related to taliglucerase alfa were recorded in the GLP-compliant toxicity studies.

Overall, behavioural observations such as unsteadiness, tremors, agitated behaviour, gasping respiration and/or excessive chewing due to excipients were reported in preliminary animal studies. The behavioural findings in cynomolgus monkeys were considered to be due to the high level of ethanol (18% (v/v)) in the pilot formulation. In marmosets, the findings were considered to be related to the high levels of excipients in the formulation (at least four-fold those in the clinical formulation). This was supported by the observation that when the study was repeated with dosing for 7 consecutive days at the same dose with excipient levels equivalent to the clinical formulation, no clinical signs were observed.

Electrocardiograms were collected pre-dose and towards the end of the dosing period in the 4-week repeat-dose toxicity study in marmoset monkeys and in the 4- and the 39-week repeat dose toxicity studies in cynomolgus monkeys. No effect was noted on RR, PR, QT (QTc) intervals, and QRS duration, or on heart rate. The No Observed Adverse Effect Levels (NOAELs) for adverse effects on the central nervous system, the respiratory system, and the cardiovascular system were equivalent to the highest dose level tested in monkeys:

• 55 mg/kg/day in the 4-week study in marmoset monkeys, associated with an $AUC_{0\text{-}100\ min}$ of 102858 µg.min/ml (males and females combined)

• 27.8 mg/kg/day in the 4-week study in cynomolgus monkeys, associated with an AUC_{all} of 123000 µg.min/ml (males and females combined)

• 27.8 mg/kg/dose in the 39-week study in cynomolgus monkeys, associated with an AUC_{all} of 107000 µg.min/ml (males and females combined)

These values of NOAEL represent a 5-fold multiple of the proposed maximum human administered dose of 66 mg/m2 (equivalent to 60 U/kg).

The CHMP agreed that including the safety pharmacology assessment as part of the toxicology programme is acceptable in this case. Information of potential effects on central nervous system, cardiovascular and respiratory parameters was collected in the single and repeat-dose toxicity studies conducted within the toxicology programme for taliglucerase alfa. According to the results of these studies, intravenous administration of taliglucerase alfa does not adversely affect the cardiovascular, respiratory or central nervous system in marmosets or cynomolgus monkeys.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted. In the context of enzyme replacement therapy and given the specificity of taliglucerase alfa as an enzyme, pharmacodynamic drug interactions are unlikely to occur. This justification is accepted by the Committee.

2.3.3. Pharmacokinetics

The pharmacokinetics programme for taliglucerase alfa consisted of toxicokinetic monitoring in the repeat-dose i.v. toxicity studies in marmoset and cynomolgus monkeys including a 39-week study mimicking the clinical treatment regimen (i.e. dosing every two weeks). No additional or dedicated pharmacokinetic studies were conducted.

Assays for taliglucerase alfa in monkey plasma and for antibodies in monkey serum were developed and validated or qualified prior to study initiation. Stability of taliglucerase alfa after several freeze/thaw cycles was sufficiently evaluated. There was no impact of the long-term frozen on stability.

The systemic bioavailability of taliglucerase alfa following i.v. infusion is immediate and the distribution is receptor-driven by mannose receptor uptake in key target organs. Toxicokinetic measurements indicate that C_{max} and AUC increase with increasing dose in a more than proportional manner, both after the first dose and after the repeated infusion. Exposure tended to be lower at week 39, but not at week 9, compared to exposure at day 1. Clearance tended to be marginally higher at week 39. However, at lower dose only, a decrease in clearance is observable with an increase of dose.

The initial approach to rely on biodistribution data of similar proteins was not considered sufficient by the CHMP. Glycosylation may affect the kinetics and the biodistribution of proteins. An experiment to compare the bio-delivery to vertebrae between taliglucerase alfa and velaglucerase alfa in mice was performed by the applicant. The results of this study suggested higher distribution of taliglucerase alfa than velaglucerase in vertebrae of mice. However, sufficient justification of the extent of biojustification data on taliglucerase alfa was provided and further distribution preclinical studies are not required, since if differences were identified in animals, the lack of a clear understanding of the mechanism underlying the differences would make translation of such observations to human difficult.

Overall, the balance of evidence indicates that the mannose receptor is the most important receptor responsible for the active distribution and clearance of taliglucerase. However, from the available data

it is not possible to preclude the role of another uptake receptor in the distribution of taliglucerase. Considering that an evaluation of the potential uptake of taliglucerase by other receptors or of the tissue distribution of taliglucerase was not provided, it cannot be assumed that the distribution is the same as for imiglucerase. In particular, differences in tissue distribution and trans-placental transfer cannot be ruled out between taliglucerase, velaglucerase, and imiglucerase, either mannose-driven or by another putative receptor. It is not considered appropriate to directly extrapolate data from approved products to bridge the gaps in the preclinical programme of taliglucerase alfa. As a consequence, the CHMP required the statement of the lack of pre- and post-natal development studies to be included in the SmPC (Latest version of the Product Information as submitted by the applicant but not adopted by the CHMP).

Metabolism and excretion studies were deemed unnecessary due to the anticipated breakdown of the enzyme to small peptides and amino acids. Justifications for the absence of stand-alone distribution, metabolism, excretion and pharmacokinetic drug interaction studies are acceptable to the CHMP. However, notwithstanding that the justification for the lack of excretion studies is acceptable; the statement that the clearance mechanisms are well known cannot be concurred. The results from the toxicokinetic measurements in the repeat dose toxicity studies suggest that the clearance of taliglucerase alfa is saturable and, to some extent, inducible after long term treatment.

Pharmacokinetic drug interaction studies were not conducted. Taliglucerase alfa is a protein and pharmacokinetic interactions with co-administered drugs subject to cytochrome P450-dependent metabolism are unlikely to occur.

2.3.4. Toxicology

Single dose toxicity

Overview of single dose studies

Study ID	**Species** (Number/Sex/Group)	**Dose** (mg/kg)	**Observed max non-lethal dose** (mg/kg)	**Major findings**
MET/003/AIT	Mouse: ICR(CD-1) 3/sex/group	0, 1.8, 9, 18	≥ 18	-
0071	Mouse: ICR(CD-1) 2/sex/group	18	≥ 18	-
HAO 003/043412	Monkey: cynomolgus 1/sex [a]	1.8, 9, 18	≥ 18	**≥ 1.8:** bruising at infusion site **9:** unsteady behaviour (f), excessive chewing (f) **18:** unsteady behaviour, grinding teeth (f)

[a]: *total number of animals used during the study.*

In a GLP-compliant study, a single i.v. bolus injection of taliglucerase alfa to male and female (CD-1) mice at dose levels of 1.8, 9 or 18 mg/kg did not result in mortality or test article-related clinical signs. No effect was noted on body weight. Gross necropsy revealed no noteworthy findings (study MET/003/AIT). The lack of systemic toxicity at 18 mg/kg was confirmed in a second (non-GLP compliant) study in mice, with evaluations extended to clinical pathology and histopathology of liver, kidney and spleen (study 0071). In a preliminary GLP-compliant escalating-dose study HAO 003/043412, a male and a female cynomolgus monkey received 1-hour intravenous infusions of taliglucerase alfa at dose levels of 1.8, 9, and 18 mg/kg, with a 3-day interval between doses. Adverse signs (unsteady behaviour, excessive chewing, teeth grinding) were noted at 9 and 18 mg/kg. These

were considered due to the high concentration of ethanol (18% (v/v)) in the formulation and the associated high volume used to achieve the 9 and 18 mg/kg doses. At 1.8 mg/kg (no clinical signs), the dose volume was 0.95 ml/kg whereas at 9 and 18 mg/kg (adverse clinical signs) dose volumes of 4.74 and 9.47 ml/kg, respectively, were administered. There were no other noteworthy findings in study HAO 003/043412.

Repeat dose toxicity

Repeated dose toxicity studies were performed in marmoset and cynomolgus monkeys, and included three pivotal GLP compliant studies. Prior to initiating the pivotal repeat-dose studies, two pilot studies were conducted in marmosets. In the 14-day study (HAO 005/040174), adverse clinical signs such as unsteadiness, loss of muscle tone, gasping respiration and agitated behaviour were observed. These observations were explained by the high concentration of excipients in the formulation (at least four-fold higher than in the clinical formulation). Similar effects were not noted in the 7-day follow-up study (HAO 008/050005), which used a formulation with excipient levels equivalent to the clinical formulation. The concentration of placebo constituents of the vials (i.e. mannitol, sodium citrate and polysorbate 80) were reduced by 80% compared to those used in study HAO 005/040174. There were no adverse signs seen during or after the administration, no effects on bodyweight, food consumption, haematology and blood chemistry parameters, and no findings at necropsy.

Overview of repeat-dose toxicity studies

Study ID	**Species** (Sex/Number/ Group)	**Dose** (mg/kg)	**Duration** (schedule)	**NOAEL** (mg/kg)	**Observations**
HAO 008/ 050005	Monkey: marmoset 1/sex	55	7 days (daily)	55	-
HAO 005/ 040174	Monkey: marmoset 1/sex	55	14 days (daily)	-	gasping respiration, retching, partially closed eyes, agitated behaviour, tremors, loss of body muscle tone, liplicking, unsteadiness and occasional red (blood) discharge from the nose. **injection site**:scabs, reddening bruising, histopathological lesions
HAO 004/ 052480	Monkey: marmoset 4/sex/group GLP compliant	0, 11, 55	29 days (daily)	-	**11:** ↑ spleen weight (f) **55:** ↑ spleen weight, ↓Hct, Hb, MCH, MCV **injection site**: scabs, reddening bruising, histopathological lesions (inflammatory, haemorrhagic)
1171-002	Monkey: cynomolgus 4/sex/group GLP compliant	0, 5.6, 27.8	28 days (daily)	5.6	**27.8:** Thyroid/parathyroid: ↓ weight, follicular cell hypertrophy/ hyperplasia (1 male) **injection site**: red skin discoloration, scabs, inflammation, haemorrhage

1171-001	Monkey: cynomolgus 4/sex/group GLP compliant	0, 5.6, 27.8	39 weeks (1 per 2 weeks)	27.8	- **injection site**: red discoloration, inflammation, haemorrhage

(Hct: haematocrit, Hb: haemoglobin, MCH: mean corpuscular haemoglobin, MCV mean corpuscular volume).

In the 4-week studies, taliglucerase alfa was administered on a daily basis, whereas in the 39-week study dosing mimicked the clinical regimen (once every two weeks) and took into account the long-term indication. Treatment of marmoset monkeys for 29 consecutive days at doses of 0, 11, and 55 mg/kg/day administered *via* a 20-minute infusion lead to a decrease in body weight and food consumption, which were attributed to the stress of the dosing procedure since they occurred in all groups including the controls. Increased spleen weight (males at 55 mg/kg/day and females at both doses) was also observed but without corresponding histopathological changes in the spleen and this was not considered to be a toxicologically significant finding.

There were no test article-related changes in ophthalmology, electrocardiography, haematology, clinical chemistry, or urinalysis parameters. The NOAEL was determined to be 55 mg/kg/day which was associated with a Day 29 $AUC_{0\text{-}100min}$ of 102858 µg.min/ml (males and females combined). In the 4-week cynomolgus monkey study 1171-002, animals were dosed for 28 consecutive days at 0, 5.6, and 27.8 mg/kg/day *via* a 1-hour infusion. The findings included thyroid changes at the high dose, which were not considered to be toxicologically significant due to low incidence and lack of statistical significance. The NOAEL was 27.8 mg/kg/day and was associated with a Day 28 AUC_{all} of 123000 µg.min/ml (values calculated from 0 to 1440 minutes; males and females combined).

When cynomolgus monkeys (n = 4/sex/group) were treated once every two weeks for 39 weeks (0, 5.6, and 27.8 mg/kg/day administered *via* a 1-hour infusion) the only test article related effect was anti-drug antibody formation. The NOAEL for this study was 27.8 mg/kg/dose which was associated with a Week 39 AUC_{all} of 107000 µg.min/ml (values calculated from 0 to 360 minutes; males and females combined). The NOAELs from the pivotal GLP-compliant repeat-dose study correspond to a 5-fold multiple of the proposed maximum human dose of 66 mg/m2 (equivalent to 60 U/kg).

Anti-taliglucerase alfa antibody formation was observed on Day 29 (HAO 004/052480) in the majority of marmoset monkeys at 11 mg/kg/day; values ranged from approximately 100 to 350 ng/ml in all animals. No antibodies were detected in marmoset monkeys treated with 55 mg/kg/day. Twenty-eight days of consecutive dosing in cynomolgus monkeys did not produce antibodies in any animal. Following 39-weeks of dosing every two weeks, antibodies were detected in a total of 13 samples: one low-dose female (months 6 and 9), two low-dose males (months 1, 3, 6, and 9 for one male and months 1, 6, and 9 for the other) and two high-dose males (month 9 for one male and months 3, 6, and 9 for the other). None of the antibodies detected in any of these studies was neutralising. The pattern of antibody response observed in the repeat-dose toxicity studies indicates that taliglucerase alfa has a low potential for immunogenicity in non-human primates. There was no consistency in the dose, gender, and time responses to treatment.

The CHMP noted that numerous different batches of the product were used in the toxicity studies; sometimes several different lots were used within the same study. It is unclear how the different batches reflect different processes of manufacturing and/or different contents in impurities. The Committee requested detailed information on the batches used in the toxicology studies, with clear reference to the process of manufacturing and impurity profile, in order to re-discuss whether some adverse effects are attributable to the excipients or potential process-related impurities. The requested data along with the information on the manufacturing and process related impurities (residual DNA and host cell proteins) were provided. Since multiple drug substance batches have been used to

manufacture a single drug product batch, a range was given where appropriate. Notably, in the two studies where the highest levels of residual DNA were measured (28-day and 39-week monkey studies) no adverse effects were reported, including clinical pathology and histopathology. In the same studies, host cell proteins were 0.02-0.03% in the drug substance batches tested. Therefore, the levels of the process impurities that can be regarded as toxicologically qualified are <0.02% for host cell proteins and <3.33 ppm for residual DNA, which are well above the specifications in the commercial formulation. One of the batches (K-39065) of material administered in the embryo-fetal studies to both rats and rabbits was also used in the clinical study PB-06-001. The process impurities were not measured in this batch. Only rats exhibited adverse clinical signs (swelling in the paws, limbs and/or face) whereas no clinical signs occurred in rabbits. This batch, as well as an additional batch for the high dose, were also administered to rabbits in the embryo-foetal study and to rats in the fertility study with clinical signs only occurring in rats. The fact that the same adverse reactions occurred at much lower levels of process impurities than in other toxicity studies suggests that they were not attributable neither to host proteins (0.003%) or residual DNA (<0.01 ppm), or otherwise the hypersensitivity would be species specific for rat. The CHMP considered the issue resolved.

Genotoxicity

Genotoxicity studies were not conducted for taliglucerase alfa. Since taliglucerase alfa is a protein, a direct interaction with DNA or chromosomes is not to be expected. In line with the ICH S6 Guideline, genotoxicity studies were not considered necessary and this is agreed by the CHMP.

Carcinogenicity

Carcinogenicity studies were not conducted. The pharmacological mechanism of action of taliglucerase alfa is highly targeted, being mediated by mannose receptors present on macrophages and is not associated with a risk for carcinogenicity. Histopathological evaluations in the 39-week toxicity study in cynomolgus monkeys did not reveal any (pre-)neoplastic changes. The clinical history of ERT in GD has not suggested any indication for a cause for concern. The weight-of-evidence therefore supports a lack of carcinogenic risk. In line with the ICH S6 Guideline and its addendum ICH S6 (R1), carcinogenicity studies were not considered necessary. This is acceptable to the CHMP.

Reproduction Toxicity

To assess the potential reproductive and developmental effects of taliglucerase alfa, a rat fertility and early embryonic development study was conducted along with embryo-foetal development studies in rats and rabbits. All studies were GLP-compliant and their overview is presented in the table below.

Overview of reproductive toxicity studies

Study ID	Species (number/ sex/group)	Dose (mg/kg)	Dosing schedule/ duration	Major findings	NOAEL (mg/ kg)
1171-004 Fertility and early em bryonic development	Rat, Sprague-Dawley (25/sex/ group)	0, 11, 55	3- and 4 day interval/ male: 4 weeks prior to mating, throughout mating until euthanasia (Day 51) female: 2 weeks prior to mating and throughout mating, GD 0, 3 and 7	**F0:** **?11**: material around nose **55:** swollen paws, limbs and face (nose, muzzle) **F1:** -	F0: 11 F1: 55
1171-003 Embryo-foetal development	Rabbit, NZW (23 females/ group)	0, 5.6, 27.8	GD 6, 9, 12, 15, 18	**F0:** - **F1:** -	F0: 27.8 F1: 27.8
1171-005 Embryo-foetal development	Rat, Sprague-Dawley (23 females/ group)	0, 11, 55	GD 6, 9, 12, 15, 17	**F0:** **55: death** (1 female GD 15) swollen paws, limbs and face (nose, muzzle) **F1:** -	F0: 11 F1: 55

Study 1171-004

Male and female Sprague-Dawley rats received taliglucerase alfa at dose levels of 11 or 55 mg/kg by slow bolus injection in the tail vein once every 3 or 4 days. Controls were given vehicle (mannitol, sodium citrate, polysorbate 80 NF in water for injection). Males were treated for 4 weeks prior to mating, throughout the mating period and post-mating until sacrifice on Day 51. Females were treated for 2 weeks prior to mating, throughout the mating period and on Gestation Days 0, 3 and 7. Females were euthanised on Gestation Day 13. Taliglucerase alfa did not affect fertility or reproductive performance indices, copulatory interval, gestation day 13 uterine implantation data or sperm analyses. There were no test article-related effects on parental body weights or body weight gain. The only observation was swollen limbs/paws and/or swollen face or muzzle at 55 mg/kg/dose, during the 30-90 minute post-dose examination. This finding was observed as early as after the first treatment and resolved before the next dose. The mechanism or reason for dose-dependency of this type of response is not clear. The NOAEL was determined to be 55 mg/kg/dose for reproductive toxicity and 11 mg/kg/dose for parental toxicity.

Study 1171-005

Pregnant Sprague-Dawley rats received taliglucerase alfa by slow bolus injection on Gestation Days 6, 9, 12, 15, and 17 at dose levels of11 and 55 mg/kg; Caesarean section was performed on Gestation Day 20. One control female died while being restrained for dosing on Gestation Day 9 and one high-dose female died following dosing on Gestation Day 15. Clinical findings seen in the high-dose female on gestation day 15 included decreased activity, difficulty in breathing, prostration, and pale appearance. Although no gross findings were noted at necropsy, a relationship with treatment could not be excluded for this animal. Other maternal effects were limited to clinical signs primarily occurring on treatment days at55 mg/kg/dose. These observations were similar to those noted in the fertility/early embryonic development study 1171-004. Taliglucerase alfa did not affect uterine implantation data, foetal body weights, foetal sex ratios, and external, visceral, or skeletal malformations or variations. The NOAEL was at least 55 mg/kg/dose for developmental toxicity and 11 mg/kg/dose for maternal toxicity in pregnant Sprague-Dawley rats.

Rabbit Study 1171-003

Pregnant New Zealand white rabbits (n = 23 time-mated/group) were given taliglucerase alfa by slow bolus injection on Gestation Days 6, 9, 12, 15, and 18 at dose levels of 5.6 and 27.8 mg/kg; Caesarian section was performed on Gestation Day 29. No test article-related maternal effects were recorded. Taliglucerase alfa did not affect uterine implantation data, foetal body weights, foetal sex ratios, and external, visceral, or skeletal malformations or variations. The NOAEL was at least 27.8 mg/kg/dose for both developmental and maternal toxicity in pregnant New Zealand white rabbits. The statistically significant change seen in these data in comparison to controls was an increase in additional sternebral ossification centres. This skeletal variation is seen commonly in this laboratory and although not seen in the concurrent controls, the maximum litter incidence from recent historical control data is In the absence of any other statistically significant changes in skeletal variations in the group from controls, the increase in this one variation, although statistically significant, was not considered toxicologically meaningful. The CHMP agreed with this conclusion and although these data suggest that treatment might affect the formation of ossification centres, there are no other observations which could be related to this apparent increase in ossification centres. The clinical relevance of this observation thus seems limited.

Discussion on Reproduction Toxicity

The CHMP noted that maternal adverse effects observed in the reproductive toxicity studies in rats suggest a histaminergic-type reaction shortly after dosing. Since the composition of excipients (i.e. mannitol, citrates, and polysorbate 80 NF) in the high dose vials appear to be the same as in the placebo vials, according to the original study reports(study 1171-005 and 1171-004), and the placebo treated animals did not show the same signs, drug-related hypersensitivity reactions cannot be excluded. Several different batches of test article have been used within a single study. Due to the lack of lack of measurements of the process impurities in some of development batches, no conclusions can be drawn on the causality of these adverse reactions. However, one of the batches used for the high dose and for which the process impurities are known, was administered to rabbits in the embryo-foetal study and rats in the fertility study as mentioned in section on repeat dose toxicity. The fact that this batch did cause the same adverse reactions while having much lower levels of process impurities than in other toxicity studies suggests that either they were not attributable to Since neither toxicokinetics nor anti-drug antibodies have been measured in the reproductive toxicity studies, their results should be interpreted with caution. Higher titres of anti-drug antibodies would be expected to be elicited in rats than in humans. Hence, the exposure of the embryo-foetus to taliglucerase could have been impaired due to neutralising antibodies. Published information on the outcomes of alglucerase and/or imiglucerase therapy on breastfeeding mothers and/or their breastfed infants is sparse. Enzyme ingested by infants *via* breast milk is likely to be degraded in the digestive system and, therefore, unlikely to reach the newborn's systemic circulation.

Overall, the Committee considers that there is insufficient information to recommend the use of taliglucerase during pregnancy and lactation. The proposed recommendations under section 4.6 of the SmPC reflect the necessary cautious approach (Latest version of the Product Information as submitted by the applicant but not adopted by the CHMP). Whilst this is a stand alone application, one might question whether there was relevant information from other members of the product class that might provide an indication of the human risk. In this context, it should be taken into account that structural differences between imiglucerase, velaglucerase, and taliglucerase, have an impact in their respective serum half-life and differences in tissue distribution and trans-placental transfer cannot be ruled out between taliglucerase, velaglucerase, and imiglucerase. Considering that the half-life of taliglucerase in humans is about 2 to 5-fold higher than the values published for the other two products used as Gaucher disease treatments, it seems likely that taliglucerase has more time than imiglucerace or

velaglucerase to interact with the mannose receptor present in the human placenta. Although reference is made to velaglucerase, the CHMP considers that results of the pre- and post-natal development studies with velaglucerase are not directly extrapolable to taliglucerase and hence, the SmPC states that pre- and post-natal studies have not been conducted with taliglucerase.

Toxicokinetic data

The pharmacokinetics programme for taliglucerase alfa included toxicokinetic monitoring in the repeat-dose i.v. toxicity studies in marmoset and cynomolgus monkeys including a 39-week study mimicking the clinical treatment regimen (i.e. dosing every two weeks). The results from the toxicokinetic measurements in these studies suggest that the clearance of taliglucerase alfa is saturable and, to some extent, inducible after long term treatment.

Local Tolerance

No separate local tolerance studies have been performed. Local effects were assessed in the repeat-dose studies. Local, injection site changes were noted in the repeat-dose studies in marmoset and cynomolgus monkey. These changes were related to the IV infusion technique and not to taliglucerase alfa since they occurred at the same incidence and severity in the vehicle control and drug-treated animals. In marmosets (daily dosing for 14 and 29 days) scabbing, reddening, and bruising at the injection site were observed. For cynomolgus monkeys, local effects were limited to red discoloration of the injection site in the 4-week study and no visible injection site changes in the 39-week study. Microscopic changes at the injection site were similar in both species and primarily included haemorrhage and inflammation. These data indicate no additional effects of taliglucerase alfa on the injection site.

Other toxicity studies

There was no evidence of immunotoxicity in the repeat-dose studies conducted in cynomolgus monkeys. The mannose receptor is crucial in eliciting the innate immune response to pathogens, and it is up-regulated during infections. The lack of increase in incidence of infections in the pre-clinical studies suggests that the immune system was not impaired by the temporary occupancy of the receptor by taliglucerase. Since the dosing interval for taliglucerase alfa is two weeks and the half-life (30 mins) is shorter than the doubling time of most bacteria and fungi, the temporary occupancy of the macrophage mannose receptor is short. There has also been no increased incidence of infections during the clinical use of taliglucerase alfa.

No signs of dependence or withdrawal have been reported in the toxicology studies. Dependence is not expected to be an issue for this type of product. The lack of metabolites studies is justified given the protein nature of the product.

The process impurities regarded as toxicologically qualified, based in the profile of the test article used in long term toxicity studies, are well above the specifications in the commercial formulation

2.3.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment has been conducted with taliglucerase alfa. The CHMP acknowledged that the lack of ecotoxicity/environmental risk assessment is justified given the protein nature of the product.

2.3.6. Discussion on non-clinical aspects

The nonclinical pharmacology programme consisted of a series of *in vitro* studies to evaluate primary pharmacodynamics of taliglucerase alfa. In their development programme, the applicant compared the activity of taliglucerase alfa with imiglucerase in some of these studies. In addition, the uptake of taliglucerase alfa by rat, rabbit, human and monkey macrophages was evaluated. These *in vitro* data confirm that taliglucerase alfa exhibits a specific interaction with the Man/GlcNAc receptor present in Gaucher cells. Furthermore, whilst not strictly relevant to this stand alone application, taliglucerase alfa exhibits similar enzyme kinetics to imiglucerase. Despite no *in vivo* pharmacodynamic studies have been conducted, there is sufficient non-clinical and clinical evidence to support the primary pharmacodynamic effect of taliglucerase alfa as ERT in GD. Secondary pharmacodynamic studies were not conducted because the uptake of taliglucerase alfa is receptor mediated on specific target cells and its activity as an enzyme is specific. Potential adverse effects on CNS, respiratory and cardiovascular systems were evaluated by monitoring of clinical signs and recording of ECG in single and/or repeat-dose toxicity studies. No indication of drug-related adverse effects on these organ systems was observed. Pharmacodynamic drug interaction studies were not conducted; given the specificity of taliglucerase alfa as an enzyme, these are unlikely to occur.

The pharmacokinetics programme for taliglucerase alfa consisted of toxicokinetic monitoring in the repeat-dose i.v. toxicity studies in cynomolgus monkeys including a 39-week study mimicking the clinical treatment regimen. No additional pharmacokinetic studies have been conducted. The lack of formal distribution studies was adequately justified by the applicant. The differences in tissue distribution and trans-placental transfer cannot be entirely ruled. Metabolism and excretion were deemed not necessary due to the anticipated breakdown of the enzyme to small peptides and amino acids. Thus, justifications for the absence of stand-alone distribution, metabolism, excretion and pharmacokinetic drug interaction studies are acceptable. Pharmacokinetic drug interaction studies were not conducted since taliglucerase alfa is a protein and interactions with co-administered drugs subject to cytochrome P450-dependent metabolism are unlikely to occur. The lack of information on tissue distribution and trans-placental transfer is reflected in the statement on the lack of pre- and post-natal development studies in the SmPC (Latest version of the Product Information as submitted by the applicant but not adopted by the CHMP).

A programme of single dose, repeat-dose, fertility and embryo-foetal development toxicity studies was performed to evaluate the safety of taliglucerase alfa. The single dose toxicity testing did not reveal noteworthy findings. In the repeat dose studies, the treatment Findings in the cynomolgus monkeys study included thyroid changes at the high dose, which were not considered to be toxicologically significant due to low incidence and lack of statistical significance. Similarly to the study conducted with marmoset monkeys, there were no significant effects on body weight, ophthalmoscopic observations, ECG parameters, clinical pathology parameters, or antibody analyses. When cynomolgus monkeys were treated once every two weeks for 39 weeks the only test article related effect was anti-drug antibody formation. None of the antibodies detected in any of these studies was neutralising and the observed pattern of antibody response indicates that taliglucerase alfa has a low potential for immunogenicity. Since neither toxicokinetics nor anti-drug antibodies have been measured in the reproductive toxicity studies, their results are interpreted with caution. Higher titres of anti-drug antibodies would be expected to be elicited in rats than in humans. Hence, the exposure of the embryo-foetus to taliglucerase could have been impaired due to neutralising antibodies. Published information on the outcomes of alglucerase and/or imiglucerase therapy on breast feeding mothers and/or their breast fed infants is sparse. Enzyme ingested by infants *via* breast milk is likely to be degraded in the digestive system and, therefore, unlikely to reach the newborn's systemic circulation. There is not sufficient information to recommend the use of taliglucerase during pregnancy and

lactation and appropriate statement is included in the SmPC. The lack of pre- and post-natal development studies was also included in the SmPC.

Studies on genotoxicity toxicity, carcinogenicity, peri/post-natal development, and in juvenile animals, were not conducted. The justifications based on scientific and regulatory guidelines, or on information available in the literature were accepted by the CHMP. There was no evidence of immunotoxicity in the repeat-dose studies conducted in marmosets and cynomolgus monkeys. Furthermore, dependence is not expected to be an issue for this type of product. The lack of metabolites studies and the lack of environmental risk assessment are justified given the protein nature of the product.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical programme for taliglucerase alfa is limited, but sufficient to support this marketing authorisation application because appropriate justifications have been provided for the lack of specific studies. Appropriate studies of mechanism of action (based on receptor-targeting) and potency were conducted, and the program focussed on assessing the safety of taliglucerase alfa in a series of adequate non-comparative toxicity studies. Overall, recognising the stand alone nature of this application, the CHMP concluded that the extent of the preclinical information together with the justifications for absence of certain studies is acceptable. The results from studies conducted with velaglucerase and imiglucerase, where reported, were deemed only supportive, and not necessarily directly extrapolable to taliglucerase alfa.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme for taliglucerase alfa for the treatment of systemic symptoms in adult patients with a confirmed diagnosis of GD consisted of one Phase 1 trial in healthy subjects (P-01-2005) and three Phase 3 safety and efficacy clinical studies in patients with GD, including one single pivotal completed study and two supportive ongoing studies. No Phase 2 study was included in the clinical programme with taliglucerase alfa as it belongs to a class of drugs with a known pharmacological principle and a demonstrated mechanism of action.

The pivotal Phase 3 study PB-06-001, was a multicentre, randomised, double-blind trial. The aim of the study was to assess the safety and efficacy of two parallel dose groups (30 and 60 U/kg) in untreated adult patients with GD with taliglucerase alfa given by i.v. infusion every two weeks for 9 months. The dose comparison (30 and 60 U/kg) was conducted as a post-hoc analysis, stemming from PB-06-001 and up to 9 and 12 months of treatment in the frame of PB-06-003.

Study PB-06-002 was a multicentre, open-label, switch-over Phase 3 trial to assess the safety and efficacy of taliglucerase alfa in up to 30 patients with GD treated with imiglucerase. The study was amended to include up to 30 patients as a result of the shortage of imiglucerase supply. Following recommendations from the Paediatric Committee (PDCO) on 9 April 2010, the protocol was further amended to include at least 5 patients aged 2-18 years within the total of 30 patients. Patients received i.v. infusion of taliglucerase alfa every two weeks at the same dose as their previous imiglucerase dose in the past 6 months or to the dose prior to the shortage of imiglucerase. The duration of the study was 9 months.

An extension study (Study PB-06-003) was initiated to collect long term data following treatment with taliglucerase alfa. Patients who completed 9 months of treatment in Protocols PB-06-001 and PB-06-002 could be enrolled in PB-06-003. Patients extended from PB-06-001 to PB-06-003 remained blinded

in order to evaluate clinical outcomes for at least 2 years, where it is expected that most of the patients will achieve disease stability.

Further to the above clinical protocols, compassionate use programmes including an Expanded Access Protocol (EAP) study, PB-06-004, and named-patient compassionate use were also ongoing. Creation of these programmes was triggered by the shortage of imiglucerase supply in mid-2009. The PB-06-004 treatment protocol provides expanded access to patients whose imiglucerase dose was reduced or discontinued due to the supply disturbance. It was initiated in the USA and Israel in November 2009 and is ongoing. Safety data collected from these programmes contribute to the assessment of the safety profile of taliglucerase alfa.

Furthermore, a historical analysis of the data on imiglucerase and alglucerase was conducted in order to put the efficacy of taliglucerase alfa into context, taking into account data obtained with taliglucerase alfa with the publicly available data regarding the efficacy of imiglucerase and alglucerase in the treatment of GD. No comparison was made to the orphan medicinal product velaglucerase licensed in August 2010.

No CHMP scientific advice was sought with respect to the clinical development programme of taliglucerase alfa. National scientific advice was sought after completion of the pivotal trial from several EU Member States. Key issues concerned the lack of a control group in the pivotal study, the strength of the statistical evidence, and the size of the safety database.

Safety data from supportive studies were included in the safety database. A post-hoc analysis on dose-effect response for the pivotal study PB-06-001 and extension study PB-06-003 were performed to strengthen the statistical evidence. In addition, post-hoc secondary efficacy analyses were performed in anaemic and hepatomegalic patients for the pivotal study PB-06-001 and post-hoc responder analyses were performed for the extension study PB-06-003.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled/ Treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
CLINICAL STUDIES									
Safety and PK	P-01-2005	Module 5, section 5.3.3.1	Primary: Evaluate the safety of three escalating doses of human taliglucerase alfa. Secondary: Evaluate the PK profile of taliglucerase alfa following IV administration in healthy volunteers.	Phase 1, Non-randomised, open-label, single-dose escalation. No treatment control.	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	Healthy subjects	3 single dose, 1 week apart	Completed: Full CSR
Safety and efficacy and PK	PB-06-001	Module 5, section 5.3.5.1	Assessment of the safety and efficacy of two parallel dose groups of taliglucerase alfa (30 and 60 U/kg) in naive patients with GD.	Phase 3, Multicenter, randomised, double-blind, parallel group trial 2 parallel dose groups. No treatment control.	Group 1: 30 U/kg Group 2: 60 U/kg IV Every 2 weeks	29/32 LPLV: September 2009	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	9 months	Completed: Full CSR
Safety and efficacy	PB-06-002	Module 5, section 5.3.5.2	Assessment of the safety and efficacy of taliglucerase alfa in patients with GD previously under Cerezyme treatment.	Phase 3, Multicenter, open-label, Switchover trial. No treatment control.	Same dose as imiglucerase dose Every 2 weeks	16/25	Patients with stable Gaucher disease currently treated with Cerezyme under a stable maintenance regimen	9 months	Ongoing; Abbreviated CSR Interim Analysis
Safety and efficacy	PB-06-003	Module 5, section 5.3.5.2	Extended assessment of the safety and efficacy of taliglucerase alfa in both naive GD patients and patients with GD previously under Cerezyme treatment.	Multicenter, double-blind* extension study. No treatment control.	Same dose as received during PB-06-001 or PB-06-002	26 (from PB-06-001) + 5 (from PB-06-002) =31	Eligible patients from PB-06-001 and PB-06-002	15 months	Ongoing; Abbreviated CSR Interim Analysis
Safety	PB-06-004	Module 5, section 5.3.5.2	Assessment of the safety of taliglucerase alfa treatment in patients whose Cerezyme dose was reduced or discontinued due to the shortage of Cerezyme supply.	Open-label, expanded access trial. No treatment control.	Same dose as imiglucerase before reduction or discontinuation due to drug shortage	26	Age 18 years or older Diagnosis of GD treated historically with imiglucerase	9 months	Ongoing; Short Report – *Ad Hoc* Safety Analysis
REPORTS OF ANALYSES OF DATA FROM MORE THAN ONE STUDY									
Efficacy	Dose separation *post-hoc* analysis PB-06-001 and PB-06-003	Module 5, section 5.3.5.3	Comparison between doses (30 and 60 U/kg).	Same as PB-06-001 & PB-06-003	Same as PB-06-001 & PB-06-003	Same as PB-06-001 & PB-06-003	Same as PB-06-001 & PB-06-003	Same as PB-06-001 & PB-06-003	Completed; *Post hoc* analysis report
Efficacy	Historical analysis	Module 5, section 5.3.5.3	Comparison of efficacy results obtained with taliglucerase alfa to publically available data for alglucerase and imiglucerase and therapeutic goals.	NA	NA	NA	NA	NA	Completed; Historical analysis report

2.4.2. Pharmacokinetics

Results of two clinical studies contributed to the information on pharmacokinetics: PB-06-01 (patients with Gaucher disease) and P-01-2005 (healthy subjects). During development of the product, no changes in the formulation occurred and the drug product manufacturing process principles remained constant using conventional drug compounding, aseptic filling, and lyophilisation procedures. The to-be-marketed formulation of taliglucerase alfa was used in the Phase 1 and 3 clinical studies.

Absorption

Taliglucerase alfa will be administered intravenously.

Distribution

Taliglucerase alfa pharmacokinetics is characterised by a very rapid clearance from plasma which is expectedly caused by uptake into phagocytic cells. Hence the plasma pharmacokinetics reflects distribution to phagocytes, and not the concentration at the active site within the cells. The mean volume of distribution of taliglucerase alfa in Gaucher disease patients was about 17 l at a dose of 30 U/kg and about 13 l at a dose of 60 U/kg. Organ distribution studies were not performed for taliglucerase alfa. As indicated before, cellular uptake of taliglucerase alfa is mediated by mannose receptors and its distribution to and subsequent uptake by tissues/target cells is receptor-driven. Taliglucerase alfa is not expected to cross the natural blood brain barrier. Plasma protein binding studies are considered not applicable for taliglucerase alfa, since the substance is not expected to significantly interact with plasma proteins.

Elimination

Following infusion completion, taliglucerase alfa plasma concentrations fell rapidly with a mean $t_{1/2}$ of 25 minutes. Clearance was about 30 l/h at a dose of 30 U/kg and lower at the dose level of 60 U/kg (about 20 l/h). The rapid clearance of taliglucerase alfa from plasma is consistent with the uptake of taliglucerase alfa into macrophages *via* mannose receptors. Taliglucerase alfa is a protein, which is considered to be degraded into small proteins and single amino acids by well known mechanisms. As such, metabolite studies or further elimination studies were not performed.

Dose proportionality and time dependencies

Taliglucerase alfa appears to exhibit dose proportional pharmacokinetics in the dose range investigated in healthy subjects, however, the results from the PK evaluation in the pivotal study demonstrates substantially more than proportional increase in the AUC with the higher dose. At the 60 U/kg dose, clearance was clearly lower compared at the 30 U/kg dose. Clearance was almost identical for both doses at both, week 1 and week 38. However, values were lower for the higher dose at both time points. This could perhaps suggest saturation of the uptake in phagocytes, as observed also in the nonclinical studies. However, taliglucerase appears to exhibit approximately dose proportional pharmacokinetics in the dose range of 15 - 60 U/Kg. There does not seem to be any significant time dependency in the pharmacokinetics. Taliglucerase alfa is not expected to accumulate.

Special populations

Data in special populations were not provided. The lack of data from patients with impaired renal or hepatic function is considered acceptable, considering that taliglucerase alfa is a protein. This is also the case for race, gender and weight. Taken into account the pharmacokinetic profile of taliglucerase alfa with rapid uptake into phagocytes and plasma concentrations that will not reflect the concentration at the effect site, the pharmacokinetics of taliglucerase alfa will not be useful to predict potential efficacy and safety differences in special populations, and the lack of data in these groups is therefore acceptable to the CHMP. Furthermore, taliglucerase alfa is not indicated in paediatric population. However, since there are data in study PB-06-001 on gender, the CHMP requested a comparison of the results in male and female subjects in order to evaluate whether there is a difference in

pharmacokinetics. In response, analyses of pharmacokinetic data based on gender were provided but no significant effect was observed.

Anti-taliglucerase antibodies: None of the healthy subjects in study P-01-2005 was positive for anti-taliglucerase alfa antibodies. In study PB-06-001, including Gaucher disease patients, 2 out of 32 subjects developed IgG antibodies to taliglucerase alfa during 9 months of treatment. Neutralising antibody tests were negative for both patients and no hypersensitive reaction was observed. For both subjects, pharmacokinetic data were available. Development of anti-taliglucerase antibodies did not appear to have an adverse influence on pharmacokinetics, as the obtained pharmacokinetics values in these subjects were within the range of values observed in the studies. Nevertheless, the number of patients with developed antibodies was low and pharmacokinetics is variable, which precludes a definitive conclusion.

Pharmacokinetic interaction studies

No interaction studies have been conducted with taliglucerase alfa, which is acceptable for an enzyme intended to be used in enzyme replacement therapy.

Pharmacokinetics using human biomaterials

No studies using human biomaterials were submitted.

2.4.3. Pharmacodynamics

Taliglucerase alfa is a recombinant human glucocerebrosidase intended as long-term ERT for the treatment of Gaucher disease and its pharmacotherapeutic rationale is the supplementation or replacement of the deficient beta-glucocerebrosidase in lysosomes. The pharmacodynamics of taliglucerase alfa has been evaluated in vitro in the nonclinical studies. Pharmacodynamic endpoints like platelet count and Hgb, as well as spleen and liver organ volumes can not be applied in studies with healthy volunteers, but are considered clinically relevant efficacy endpoints in phase III clinical trials. No specific clinical pharmacodynamic studies have been conducted in healthy volunteers. Available preclinical data as well as experience with alglucerase and imiglucerase are considered to provide an adequate rational for the clinical development of taliglucerase alfa.

Mechanism of action

Taliglucerase alfa is a plant cell expressed recombinant human glucocerebrosidase, naturally containing exposed tri-mannose residues, which is produced in transformed carrot cells. This is achieved by targeting taliglucerase alfa to specific subcellular organelles using a plant-specific C-terminal sorting signal. This targeting to the vacuoles takes advantage of the fact that the terminal residues in complex N-glycans in vacuolar glycoproteins are removed resulting in paucimannosidic type N-glycans that constitute a consensus 'vacuole-type' glycan, with naturally exposed mannose on all glycan structures. This high mannose form allows it to be effectively taken up by the phagocytic cells *via* mannose receptors. Preclinical studies established the mechanism of action, which is the similar to the currently authorised product imiglucerase.

Primary and Secondary pharmacology

The clinical programme with taliglucerase alfa was based on the fact that ERT is a class of drug with a known pharmacological principle and a demonstrated mechanism of action, for which extensive experience is available regarding the required dosing regimen. The pharmacodynamic effects

demonstrated *in vitro* were substantiated by the efficacy results obtained during the pivotal PB-06-001 clinical trial. No pharmacodynamic studies were carried out on either patients or healthy subjects. Due to the well known mechanism of action, the demonstrated pharmacological similarity to imiglucerase and the lack of surrogate parameters in healthy volunteers, this approach is acceptable.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic data obtained from studies PB-06-01 and P-01-2005 showed that the clearance and half-life appeared to vary between the healthy subjects and Gaucher patients studies, which may be due to the comparatively smaller sample size of the former. In addition, the infusion rates were different in some patients between the two studies, and therefore exposures were different between GD patients and healthy subjects, but the range of values at both the 30 and 60U/kg was wide with overlap of values between the two populations. The values of half-life, clearance and volume of distribution are consistent with the uptake of the substance into phagocytes. The lack of additional evaluation of elimination for taliglucerase is acceptable as this is an endogenous enzyme and would be expected to be degraded similarly. Pharmacokinetics in special populations, impaired renal or hepatic function, race, weight and elderly have not been investigated which is considered acceptable. No specific drug-interaction studies have been performed, but these are not expected. No apparent pharmacokinetic differences between male and female patients were identified.

Similar to other ERT, taliglucerase alfa appears to induce antibodies in patients treated. However, these seem to be overall low, since none of the healthy subjects were antibody positive in the phase I study and only 2 patients developed IgG antibodies in the pivotal trial but did not show neutralising activity. Nevertheless, this issue will be address via adequate surveillance of antibody formation.

Due to its mechanism of action and the lack of simple surrogate markers of effect, the pharmacodynamics of taliglucerase alpha can be evaluated in long-term efficacy studies. Given the specificity of the enzyme, no secondary pharmacodynamic effects are expected and the lack of data is thus acceptable. This also accounts for drug-drug interactions and neither in vitro interaction studies nor in vivo clinical drug interaction studies were conducted, which is acceptable to the CHMP.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered the pharmacokinetics of taliglucerase to be adequately assessed. There does not seem to be any significant time dependency in the pharmacokinetics. Pharmacokinetics in special populations, in patients with impaired renal or hepatic function, the effects of race, weight and age, and the specific drug-interaction studies were not performed, since significant effect is not expected for an enzyme. Similarly, no formal clinical pharmacodynamic studies were conducted in healthy volunteers. The clinical pharmacology development programme for taliglucerase alfa was considered adequate to support the marketing authorisation application.

2.5. Clinical efficacy

2.5.1. Dose response studies

No formal dose-response studies were performed, but two dose groups (30 U/kg and 60 U/kg) were included in the phase III pivotal efficacy and safety trial PB-06-001. Furthermore, dose selection was based on results from preclinical studies, clinical and laboratory assessments of safety and tolerability, as well as clinical activity. The phase I study showed linear kinetics and no safety issues for doses of

15 U/kg, 30 U/kg and 60 U/kg and the chosen dose was 60 U/kg (1.8 mg/kg), which is approximately 5 fold less than the animal NOAEL in animals adjusted to body surface area. The pharmacological basis for the dose selection relied on the principle that both imiglucerase and taliglucerase alfa are mechanistically similar and are intended for the same therapeutic indication according to dose escalation design. The higher dose (60 U/kg) was also chosen based on the safety and efficacy results obtained for imiglucerase. Consequently, no dose finding phase I or II studies were performed. The approach for dose selection is considered acceptable, given the similarities between taliglucerase alfa and imiglucerase and the extensive clinical experience with imiglucerase for more than 10 years.

2.5.2. Main studies

Study PB-06-001: A Phase III, Multicenter, Randomized, Double-Blind Trial to Assess the Safety and Efficacy of Two Parallel Dose Groups of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients With Gaucher Disease

Study PB-06-001 is considered pivotal for the clinical efficacy and safety evaluation of taliglucerase alfa. Thus, the main parts of the clinical efficacy chapter refer to the conduct and results of this pivotal study and data from other, supportive, studies are quoted as appropriate.

Methods

Study Participants

The patient population in study PB-06-001 included male and female subjects, 18 years or older. The diagnosis of GD was based on a leukocyte glucocerebrosidase activity level ≤3 nmol/mg.hr, which was ≤ 30 % of the mean activity of the reference range. The patients were required to have splenomegaly at least eight times the expected normal volume [measured volume divided by estimated normal volume (0.2% of body weight)] as determined by MRI volumetric analysis and to have thrombocytopenia (defined as platelet counts <120,000 per mm3) with or without anaemia (defined by haemoglobin at least 1 g/dl below normal range according to sex and age).

The main exclusion criteria included patients who had received ERT in the past or if they had not received ERT more than 12 months before entry they were required to have a negative anti-glucocerebrosidase antibody test at screening. Patients who had received substrate reduction therapy (SRT) in the past 12 months were also excluded. Other main exclusion criteria were the presence of HIV and/or, HBsAg, and/or hepatitis C infections; history of allergy to carrots; substrate reduction therapy (SRT) in the past 12 months; a positive anti-glucocerebrosidase antibody test; previous anaphylactoid reaction to Cerezyme or Ceredase.

The inclusion and exclusion criteria were considered by the CHMP as appropriate for this type of study.

Treatments

Patients in study PB-06-001 received i.v. infusion of taliglucerase alfa every two weeks. The individual dose for each patient was prepared according to patient's weight and the randomised treatment group (30 units/kg or 60 units/kg body weight) and for practical reasons the dose, in terms of total units, was rounded up to avoid the use of partial vials. Each dose was prepared by an unblinded pharmacist at each site. A dose adjustment check was performed every three months; if a patient's weight changed, the dose was adjusted according to the new weight. Human taliglucerase alfa vials were stored lyophilized at 2-8 C.

For initial infusions in all patients, human taliglucerase alfa was administered at a rate of 1.2 mL/min. If the rate of infusion was well tolerated, it could be increased up to 2.25 mL/min to deliver the 135 mL volume over one hour for all subsequent dosing. During the study, infusion rate was changed to occur over a 2-hour period to minimize the potential for increased risk of infusion reactions due to faster infusion rates.

Objectives

The primary objective of study PB-06-001 was to evaluate the efficacy and safety of taliglucerase alfa in untreated patients with significant signs and symptoms of Gaucher disease assessing the following parameters:

- - Percentage change in spleen volume from baseline to month 9 equals zero
- - Percentage change in spleen volume from baseline to month 9 is not equal to zero

Another objective included the determination of changes in secondary parameters (liver volume, haemoglobin, platelet counts, and biomarkers). Exploratory analyses were performed to assess the effect of taliglucerase on bone. Evaluation of safety of taliglucerase alfa treatment in patients with Gaucher disease was also undertaken. In addition, the pharmacokinetic profile in patients with Gaucher disease was determined, as discussed in section 2.4.2.

Outcomes/endpoints

The choice of the following study endpoints was considered appropriate by the CHMP:

Primary Efficacy Endpoints: The primary efficacy endpoint was the percentage change from baseline of spleen volume after nine months of treatment with taliglucerase alfa.

Secondary Efficacy Endpoints: The major secondary efficacy endpoints were the change from baseline of: haemoglobin, percentage change of liver volume, platelet counts.

The other secondary outcome measures were: biomarkers: chitotriosidase or pulmonary and activation-regulated chemokine (PARC/CCL18), proportion of patients with greater than 10% reduction in spleen volume at 9 months.

Tertiary endpoints: QCSI: a long-term follow-up of a small subpopulation of patients, change in bone mineral density measured with DEXA.

Safety: Safety measurements included adverse events, clinical laboratory evaluation, electrocardiogram and echocardiogram, pulmonary function tests, anti human taliglucerase alfa antibodies and hypersensitivity reactions. Adverse events were recorded at each visit. Complete blood count (CBC), blood chemistry and urinalysis were performed at Weeks 2, 4, 6, and 8 and then at every other visit (once a month) for 9 months. Anti-human taliglucerase alfa antibody was determined at every visit for the first 5 visits, and following that every other visit.

Sample size

With 12 patients in each treatment group (taliglucerase alfa 30 units/kg and taliglucerase alfa 60 units/kg), there was greater than 95% power to detect a change of 20% or more using a one-sample t-test (alpha=0.025, 2-sided test to allow for each group to be tested separately) to evaluate the primary outcome of percentage change in spleen volume after nine months. This calculation was based on the assumption that the standard deviation for the percentage change in spleen volume was 12%. Based on previous research, a normal spleen volume is expected to be approximately 0.12 L, and the patients in this protocol were expected to have spleen volumes 8 times this size. Thus, a 20%

reduction in spleen volume was anticipated to be equal to 0.192 L change in the mean spleen volume. To account for dropouts, 15 patients will be enrolled for each treatment group in order to ensure that at least 12 will have final measurements.

Randomisation

A unique screening number was assigned to all patients who signed the informed consent in study PB-06-001. After successful completion of the screening period, but prior to dosing, the eligible patient was randomised centrally and assigned a unique randomisation number, which included the site and patient number. Patients were randomly assigned to one of the two treatment groups in equal ratios, by site, using a computer generated randomisation code.

Blinding (masking)

The investigators, patients, clinical research organisations, central MRI reader, laboratory staff, and sponsor were blinded to the identity of the treatment in study PB-06-001. Blinded interim safety data were reviewed by an independent Data Monitoring Committee. Knowledge of the randomisation code was limited to the persons responsible for the creation of the randomisation code and implementation into the eCRF, preparation of the study medication (site pharmacist), and unblinded monitors and personnel responsible for product accountability. Unblinded study personnel did not have access to the clinical data and were not involved in the management of the study. The medication code could be broken only in the event of an adverse event that the investigator felt could not be adequately treated without knowing the identity of the study drug. The blinding method was considered acceptable by the CHMP.

Statistical methods

Three study populations were defined in the analyses in study PB-06-001:

- Intent-to-Treat (ITT): Patients who received at least one dose of medication and had at least the screening/baseline MRI evaluation.
- Per Protocol (PP) population: All ITT patients who completed 9 months of treatment and had no major protocol violations.
- Safety Population: Patients who received at least one dose of study medication

Efficacy evaluation: The primary efficacy analysis was based on two one-sample t-tests (one for each treatment group) to determine if the percentage change in spleen volume is different than zero using the ITT population. The analysis was also performed using the PP population. The primary efficacy analysis on the ITT population was performed using the missing data strategies to handle potential missing data. A multiple imputation approach was performed using all available observed data and the primary efficacy analysis was performed using the imputed data sets. Results were combined from the 100 imputation models to provide overall efficacy results. In addition, sensitivity analysis was performed using different missing data techniques. A mixed effects model including dose and time, with subject as a random effect, was fit to examine whether there was a difference between treatment groups. For each of the secondary endpoints, a one-sample t-test (% change in liver volume, mean change in haemoglobin and platelet count) was examined for each dose using the step-down approach. Hierarchical order was spleen volume followed by haemoglobin, liver volume and platelet count. Mean change from baseline was tested for each dose group at an alpha level of 0.025. Potential differences between treatment groups were analysed using a mixed effects model.

Safety evaluation: All adverse events occurring after randomisation or which were present prior to randomisation but worsened after treatment were classified by MedDRA System Organ Class/preferred

term stating number of adverse events, percentage of patients reporting adverse events and the number of serious adverse events. No statistical testing was performed.

Post-hoc analyses: Post-hoc analyses were performed to explore the secondary endpoints in subgroups of patients with anaemia or hepatomegaly, and to evaluate a possible dose effect, which studied using an ANCOVA model including dose group and the baseline value as continuous covariate. The reasoning behind this post-hoc analysis was to standardise statistical analytical methods for study PB-06-001 and PB-06-003 to facilitate side by side comparisons of efficacy results obtained at both 9 and 12 months after the start of treatment. Post-hoc analyses were performed for the primary and secondary efficacy endpoints. No adjustments for multiplicity were made. All secondary endpoints were analysed using observed data only.

The CHMP noted that the statistical analysis plan (SAP) was drawn up after inclusion of the last patient and near the end of the study period. It contains several deviations from the statistical section. Justification of the changes to the statistical analysis plan was not provided. These included a less strict alternative hypothesis for the primary endpoint and the secondary analysis using a step-down approach with platelet count being the last in hierarchical order planned after study end both point towards demonstrating efficacy. A major concern was therefore raised on the validity of these changes. In response, the applicant sufficiently justified the reasons for change in the SAP, providing some reassurance that the changes were not data driven. The step-down approach and the hierarchical order testing is appropriate, and although it would appear unusual to test platelet count as the last in order, based on the original analysis, the p-value was the lowest for platelet count and the endpoints would also have been met using the original SAP.

Results

Participant flow

Forty four patients were screened for eligibility in study PB-006-01 and 11 were excluded, mainly because inclusion criteria were not met. Thirty three patients were randomized and 32 received at least one dose of taliglucerase alfa. Three patients discontinued treatment, two due to adverse events and one due to pregnancy. One patient had an adverse event and received only a partial dose of study medication; this patient was excluded form the ITT population (ITT population; n=15 with 30 U/kg and n=16 with 60 U/kg). Two patients did not complete 9 months of treatment and twenty nine patients completed all 20 study visits (PP population; n=14 received 30 U/kg and n=15 received 60 U/kg).

Recruitment

Study PB-006-01 was conducted in the UK, Spain, Italy, Israel, South Africa, Canada, Serbia, Mexico, USA and Chile. The first patient was recruited in August 2007, the last patient in November 2008. The study ended in September 2009.

Conduct of the study

Following the start of the study PB-006-01, two amendments to the study protocol (version 4) were issued. Minor, country specific changes were issued during the first amendment. All country specific amendments were ultimately included in both versions of the protocol. Version 5 was not available for 8 sites. At these 8 sites, protocol version 6 was an amendment to version 4. Protocol 6 was available shortly after version 5. these were concluded not to affect the outcome of the clinical study.

Protocol deviations/violations: A total of 24 patients had protocol deviations; one patient with a major protocol violation (positive urine pregnancy test) and discontinued from the study after Visit 10. The majority of the deviations were visits outside of scheduled window or study procedures. Although the Committee noted that the number of patients with protocol deviations is relatively high, the majority of deviations is not considered to impact the outcomes of the study as they primarily relate to the time window of performance and do not affect primary or major secondary outcomes. Patients not meeting inclusion criteria for platelet counts were evenly distributed among dose groups and are not likely to affect the comparison between dose groups.

Baseline data

The following table summarises the overall demographic characteristics for the ITT population in the pivotal study. Both treatment groups had comparable demographic profiles. The results are similar to those observed in the safety and PP population. Fourteen patients had homozygous and 17 patients had heterozygous mutations; the distribution of mutations was evenly distributed between dose groups.

Baseline Demographic Profile of Patients – ITT population – study PB-006-01

	Taliglucerase alfa 30 U/kg (n=15)	Taliglucerase alfa 60 U/kg (n=16)	Overall (n=31)
Age (years)			
Mean (±SD)	36.3 (12.2)	36.0 (12.2)	36.1 (12.0)
Median	35.0	33.0	35.0
Range	19 to 74	19 to 58	19 to 74
Sex (n; %)			
Male	7 (46.7%)	8 (50.0%)	15 (48.4%)
Female	8 (53.3%)	8 (50.0%)	(16 (51.6%)
Race (n; %)			
Caucasian	15 (100%)	15 (93.8%)	30 (96.8%)
South African Black	0 (0%)	1 (6.3%)	1 (3.2%)
Gaucher disease genotype (n; %)	6 (40%)	6 (37.5%)	12 (38.7%)
N370S/N370S	9 (60%)	10 (62.5%)	19 (61.3%)
Other			

The time from diagnosis to first treatment ranged from 1 to 44 years for taliglucerase alfa 30 U/kg and less than 1 year to 33 years for taliglucerase alfa 60 U/kg. Two patients in the taliglucerase alfa 30 U/kg dose group had a history of ERT (imiglucerase) whereas in the taliglucerase alfa 60 U/kg dose group one patient had a history of ERT (alglucerase) and one patient of SRT (miglustat). Medical history, baseline vital sign measurements, and physical examinations appeared comparable between dosing arms. Electrocardiograms, echocardiography and pulmonary function test results for the safety population at the screening visit were comparable. The most commonly used concomitant medications were analgesics, antibacterials and antihistamines for systemic use. Almost all patients included in the study had non-neuronopathic disease, which has been noted by the CHMP and was subsequently reflected in the approved indication.

Numbers analysed

In total, 44 patients were screened, 33 were enrolled, 32 were evaluated for safety and 31 for efficacy in the pivotal study PB-006-01. One patient was randomised to the 60 units/kg group but did not

receive any dose of study medication. One patient was excluded from the ITT population who was randomised to the 30 units/kg group as they only received a partial dose of study medication.

Outcomes and estimation

Primary endpoint

The primary efficacy analysis in study PB-06-001 demonstrated that taliglucerase alfa treatment significantly reduced spleen volume from screening to the Month 9 time point as summarised in the table below, and at the Month 6 time point (taliglucerase alfa 30 U/kg, 22.21%; taliglucerase alfa 60 U/kg, 29.94%; p< 0.0001) in patients with GD.

Change in spleen volume from baseline to month 9 (ITT population – imputed values average) – study PB-006-01

Spleen volume (ml)	**Baseline**		**9 months**		**Percentage change from baseline to 9 months – imputed values average**	
	30 U/kg	**60 U/kg**	**30 U/kg**	**60 U/kg**	**30 U/kg**	**60 U/kg**
N	15	16	15	16	15	16
Mean	2,130.94	2,117.38	1,566.08	1,376.89	-26.91	-38.01
SD	1,154.72	1,356.17	900.17	1,055.81	7.79	9.38
Median	1,642.11	1,699.45	1,184.78	1,044.60	-27.85	-37.63
Range	886.41 to 4,901.13	913.65 to 5,41782	606.27 to 3,893.79	483.23 to 4,219.63	-42.60 to -15.58	-56.30 to -20.04

The differences between the two readers in spleen volume measurements were negligible; the majority of the readings showed less than 1% difference. There was no statistically significant difference observed in the mean spleen volume between the two dose groups at Months 6 and 9 (p=0.060). These results were consistent for both ITT and PP analyses populations regardless of whether the average combined imputation, or individual imputation model (1 to 100), or independent reader (1 and 2), or last observation carried forward (LOCF) method was used. The CHMP noted that the data did show efficacy of taliglucerase alfa and the dose response effect supports assay sensitivity.

Secondary endpoints

Haemoglobin

The mean haemoglobin values at baseline were at the lower limit of the normal range (taliglucerase alfa 30 U/kg, 12.2 g/dl; taliglucerase alfa 60 U/kg, 11.4 g/dl) and returned to normal values at the end of the study, i.e. at 9 months (taliglucerase alfa 30 U/kg, 14.0 g/dl; taliglucerase alfa 60 U/kg, 13.6 g/dl). As shown in the table below, a significant increase in mean haemoglobin level was observed between the baseline and the end of the study for both doses. Increase in mean haemoglobin level was also observed at 6 months for both doses.

Change in hemoglobin levels from baseline to month 9 (ITT population) – study PB-006-01

Hemoglobin (g/dl)	**Baseline**		**9 months**		**Change from baseline to 9 months**	
	30 U/kg	**60 U/kg**	**30 U/kg**	**60 U/kg**	**30 U/kg**	**60 U/kg**
N	14	16	14	15	16	15
Mean	12.2	11.4	14.0	13.6	1.6	2.2
SD	1.7	2.6	1.4	2.0	1.4	1.4
Median	12.3	11.2	13.7	14.2	1.3	1.6

Range	7.9 to 14.6	5.5 to 16.0	12.2 to 16.9	8.6 to 16.5	-0.1 to 5.8	0.5 to 5.1

There was no significant difference observed in mean haemoglobin values between the two dose groups at Months 6 and 9. Similar results were observed in the PP population analysis. Eight patients in the 60 U/kg dose group and two patients in the 30 U/kg dose group were anaemic at inclusion time (haemoglobin level < 11 g/dl for women and < 12 g/dl for men). In order to assess the effect of taliglucerase alfa in the clinically relevant group of anaemic patients, a *post hoc* subgroup analysis was carried out, on all 10 anaemic patients together, irrespective of dose group. Change in haemoglobin levels of patients defined as anaemic demonstrated an increase of 2.3 g/dl at 6 months and of 3.2 g/dl at 9 months for both dose groups combined.

Liver Volume

Significant reduction in liver volume from screening to Month 6 was observed in both dose groups (taliglucerase alfa 30 U/kg, 7.56%, p= 0.0020); taliglucerase alfa 60 U/kg, 7.51%, p= 0.0022). This was further reduced in both taliglucerase alfa dose groups at the end of the study (taliglucerase alfa 30 U/kg, 10.48%, taliglucerase alfa 60 U/kg, 11.11%). There was no significant difference observed in mean liver volume between the two dose groups at Months 6 and 9. These results are also consistent with the PP population analyses results. The % change in liver volume was analysed through a post-hoc analysis in the clinically relevant subgroup of hepatomegalic patients. Patients who entered the study with hepatomegaly (11 patients in the 30 U/kg dose group and 7 patients in the 60 U/kg dose group) defined as > 1.5 times expected liver volume (calculated as 2.5% of body weight) demonstrated a more significant decrease in liver volume at 6 months and 9 months (10.2% and 13.9%, respectively) for both doses together.

Platelet count

A significant increase in platelet count from baseline was observed in the 60 U/kg dose group at Month 9. Clinically relevant improvement (not statistically significant since the patients did not meet the pre-specified alpha level of 0.025) in platelet count was also observed for the taliglucerase alfa 30 U/kg dose group at Month 9 improvement as early as 6 months of treatment in both dose group. Significant increases in mean platelet count from baseline were also observed in taliglucerase alfa 60 U/kg treated patients compared to taliglucerase alfa 30 U/kg treated patients at Months 6 and 9. Similar results were noted for the PP population.

Change in platelet counts from baseline to month 9 (ITT population).

Platelet counts (cells per mm^3)	**Baseline**		**9 months**		**Change from baseline to 9 months**	
	30 U/kg	**60 U/kg**	**30 U/kg**	**60 U/kg**	**30 U/kg**	**60 U/kg**
N	15	16	15	16	15	16
Mean	75,320	65,038	86,747	106,531	11,427	41,494
SD	-		50,989	53,212	20,214	47,063
Median	56,00	53,500	73,000	108,500	10,000	38,000
Range	27,000 to 163,000	28,000 to 134,000	20,000 to 168,000	25,000 to 241,000	-25,000 to 59,000	-15,000 to 186,000

CHMP commented that although the data show efficacy of the highest dose group, a concern was raised with respect to the clinical efficacy of the lowest dose group, as discussed in section 2.5.3.

Plasma Chitotriosidase

Disease severity or response to taliglucerase alfa was also monitored by measurement of chitotriosidase levels prior to the dose administration and at Visits 7, 14 and 20. All patients achieved clinically relevant decreases in chitotriosidase levels at the end of the study, reflective of the severity

of the disease state. The mean level of chitotriosidase decreased in the ITT population by approximately 50% from baseline to the end of study.

Reduction in spleen volume by ≥10%

The proportion of patients reaching ≥ 10% reduction in spleen volume was set as one of the secondary endpoints. Spleen volume reduction ≥10% from the screening visit was observed in 100% of taliglucerase alfa 30 U/kg treated patients and in 93.8% of taliglucerase alfa 60 U/kg treated patients at Month 6. At the end of study, all patients in both dose groups (100%) had at least a 10% reduction in spleen volume. These results are also consistent with analyses performed on PP population. When using LOCF method, one taliglucerase alfa 60 U/kg treated patient did not achieve a 10% reduction in spleen volume at the end of study.

Tertiary endpoints

Lumbar spine, femoral neck and total hip DEXA scans at the screening visit and the end of study were presented by T score, Z score and bone mineral density (BMD). The majority of mean values of these measurements were within the normal range. Patients treated with taliglucerase alfa 60 U/kg tended to have lower mean scores in DEXA at the screening visit than the patients treated with 30 U/kg. A trend in improvement of the mean change of T and Z score for lumbar spine and femoral neck was observed after 9 months treatment in both study groups.

Changes in bone marrow fat fraction

Change in the bone marrow fat fraction measured by quantitative QCSI was assessed as an exploratory endpoint. The QCSI is a modification of the Dixon technique that quantifies the fat content in bone marrow with high reproducibility and sensitivity. The amount of fat in the bone marrow is represented as a fat fraction, which is decreased in patients with GD condition. A value for fat fraction of ≤ 0.23 is an indication of bone complications or "bone at risk". The optional lumbar spine QCSI assessment was performed at the screening visit and at the end of study. Ten patients (taliglucerase alfa 30 U/kg, n=5; taliglucerase alfa 60 U/kg, n=5) had QCSI performed at the screening visit and 9 patients had QCSI performed at the end of the study. One reading in the taliglucerase alfa 30 U/kg treatment group was not evaluable due to technical issues; therefore, only 8 patients (taliglucerase alfa 30 U/kg, 4; taliglucerase alfa 60 U/kg, 4) had QCSI performed at the end of study. The PB-06-001 study compared QCSI measurements from baseline to the 9 Month visit. The baseline data revealed that eight out of ten patients at baseline presented a fat fraction of ≤ 0.23, and that only two patients had a fat fraction > 0.23. All eight patients who had a measurement at 9 month, showed increases in the fat fraction with a value of ≥ 0.02 at the end of study. Of these, 7 patients showed a fraction increase ≥ 0.03, which was considered a true response to the ERT. Four of the eight patients had an increase of fat fraction ≥ 0.10, which was considered a high response. Overall, an increase in fat-fraction was observed in all patients using the QCSI technique within 9 months of taliglucerase alfa treatment. An improvement in "bone at risk" (fat fraction ≤ 0.23) was seen in the trial patient population such that at baseline only 25% (2/8) of the patients had a fat fraction > 0.23 and after 9 month of treatment this number increased to 75% (6/8) of the patients with a fat fraction >0.23. Taliglucerase alfa 60 U/kg treated patients showed greater fat-fraction increases than the taliglucerase alfa 30 U/kg treated patients.

Ancillary analyses

Dose separation *post hoc* analysis for taliglucerase alfa protocols PB-06-001 and PB-06-003

Since dose separation analyses were performed in studies PB-06-001 and PB-06-003 using different statistical methods, post-hoc analyses were performed to re-analyse the data using statistical methods consistent for both the 9 month time point of study PB-06-001 and the 3 month time point of study PB-06-003 (which is month 12 relative to the start of study PB-06-001). The objectives of these

analyses were to compare efficacy responses between the 30 U/kg and 60 U/kg doses of taliglucerase alfa after 9 and 12 months of treatment.

For the primary efficacy analysis performed on the ITT population both dosage groups demonstrated a significant reduction in spleen volume from baseline to the Month 9 and Month 12 visits. The taliglucerase alfa 60 U/kg dose group showed a statistically significant difference in mean spleen volume reduction at Month 9 and Month 12 compared to the 30 U/kg dose. Results are consistent with the analyses performed showing statistical differences between doses using raw mean values, LOCF or OBS methods for missing data. When evaluating the secondary efficacy, a significant reduction in liver volume from Baseline to Month 9 and Month 12 was observed in both dose groups when data are adjusted with baseline measures. There was no significant difference in the mean liver volume reduction between the two dose groups at Months 9 and 12. The results are consistent with the analyses performed using the raw mean values. Increases in mean platelet counts from baseline were observed at Month 9 and 12 in data adjusted with baseline measures. Increases in mean platelet count from baseline were observed in taliglucerase alfa 60 U/kg treated patients compared to taliglucerase alfa 30 U/kg treated patients at Months 9 and 12. There was a statistically significant mean difference between the taliglucerase alfa 60 U/kg and Month 9 and Month 12 in data adjusted with baseline measures. The results are consistent with the analyses performed using the raw mean values. An increase in mean haemoglobin level from baseline was observed in both dose groups at Month 9 and 12 when data are adjusted with baseline measures. There was no significant difference observed in the increased mean haemoglobin values between the two dose groups at Months 9 and 12. Disease severity or response to treatment was also monitored by measurement of chitotriosidase. Clinically relevant decrease in chitotriosidase level from baseline was observed in both dose groups at Month 9 when data are adjusted with baseline measures. There was no significant difference observed in the decreased mean chitotriosidase values between the two dose groups at Months 9. The results are consistent with the analyses performed using the raw mean values.

Evaluation of efficacy of taliglucerase alfa respective to historical data

A summary of efficacy data from the literature involving a selection of 14 publications obtained with Ceredase and Cerezyme and the therapeutic goals to be achieved with ERT was analysed as established by a group of experts in treating GD on the basis of their experience, specifically focusing on articles for which parameters were as close as possible to the clinical study population and endpoints included in the pivotal study PB-06-001 with taliglucerase alfa, as both it and Cerezyme have comparable mechanism of action. Both, the Range of Means (the minimum and maximum summary mean values) and the total range (the minimum and maximum individual-patient values) were extracted from the 14 papers selected. The spleen volumes at baseline in study PB-06-001 ranged between 8 to 54 MN. In the reviewed papers presented in the historical analysis, nearly all patients had enlarged spleens over 5 MN with a baseline Range of Means between 10 MN and 28.5 MN. The Total Range for baseline values in the historical review was 3.5-62 MN indicating patient heterogeneity within studies. Thus, the populations in Study PB-06-001 and the historical review have comparable baseline values. In all published studies for alglucerase and imiglucerase, reduction in mean spleen volume was observed. The Range of Means of percentage change from baseline deduced from the historical data after approximately 1 year of ERT with alglucerase and imiglucerase is -17.4% to - 38%. The results obtained after 9 months treatment with taliglucerase alfa therefore correspond with the mean and ranges estimated from the literature for 12 months therapy. This also accounts for liver response.

Furthermore, all studies with ERT have demonstrated improvement in haemoglobin levels in both, anaemic and non-anaemic patients, with a range of means of 10 to 24% increase in haemoglobin levels after up to 12 months of therapy. Expressed as percent change from baseline, 14.6% and 22.2%, haemoglobin increase was observed after 9 months of treatment with 30 and 60 U/kg of

taliglucerase alfa, respectively, and within the range of that reported in literature. With respect to the effect on platelets, the comparison of the results of the 9 months study PB-06-001 with the historical review results suggests a comparable effect with taliglucerase alfa.

The CHMP concluded that the historical data presented had several limitations related to, amongst others, the differences in standards of care over time and the large variation in baseline characteristics and efficacy results, complicating a comparison of the benefit-risk of taliglucerase alfa to standard ERT. Further responder analyses were therefore requested, as discussed in section 2.5.3.

Evaluation of efficacy of taliglucerase alfa respective to therapeutic goals

The therapeutic goals were defined by a group of Gaucher disease experts for ERT of a duration of at least 12 months and are not dose specific, thus included patients treated with a variety of doses and dosing schedules. The objectives of the analyses linked to therapeutic goals provided in the historical analysis were to assess the success of treatment with taliglucerase alfa in meeting these therapeutic goals for GD based on efficacy outcomes obtained after 12 months of treatment with taliglucerase alfa in the extension study PB-06-003. There were 65.4% (60 U/kg, 78.6%; 30 U/kg, 50.0%) taliglucerase alfa treated patients who achieved the therapeutic goal spleen volume ≤ 8 MN at month 12. There were 69.2% (60 U/kg, 92.9%; 30 U/kg, 41.7%) of taliglucerase alfa treated patients who achieved the therapeutic goal ≥ 30% reduction in spleen volume from baseline. With regards to the liver volume, there were 92.3% (60 U/kg, 92.9%; 30 U/kg, 91.7%) taliglucerase alfa treated patients who achieved the therapeutic goal liver volume ≤1.5 MN at month 12. There were 19.2% (60 U/kg, 21.4%; 30 U/kg, 16.7%) of taliglucerase alfa treated patients who achieved the therapeutic goal ≥ 20% reduction in liver volume from baseline. There were 92.3% (60 U/kg, 85.7%; 30 U/kg, 100.0%) taliglucerase alfa treated patients who achieved the therapeutic goal haemoglobin count ≥ 12 g/dl for male subjects ≥ 12 years old and ≥ 11 g/dl for others at month 12. The therapeutic goal for thrombocytopenia was defined to achieve a sufficient increase in platelets to prevent spontaneous bleeding; for splenectomised patients: to achieve normalisation of platelet counts; and for patients with an intact spleen: to achieve an increase of at least 1.5 fold in the first year of treatment. At month 12, here were 42.3% (60 U/kg, 64.3%; 30 U/kg, 16.7%) taliglucerase alfa treated patients who achieved the therapeutic goal for platelet counts (≥ 50% increase from the baseline value from study PB-06-001) at month 12 from baseline.

Responder analysis for both spleen volume and platelet count may support a clinical relevant efficacy of the highest dose, but the CHMP believes that analyses are considered exploratory only. Further responder analysis was therefore requested, as discussed in section 2.5.3.

Summary of main studies

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial PB-06-001

Title: A Phase III Multicenter, Randomized, Double-Blind Trial to Assess the Safety and Efficacy of Two Parallel Dose Groups of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease	
Study identifier	PB-06-001
Design	Multi-centre, randomized, double-blind, parallel group, dose-ranging trial

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		38 weeks not applicable not applicable
Hypothesis	The study was designed to test the null hypothesis that there was no percent change in spleen volume versus the alternative that the percent change in spleen volume was not equal to zero.		
Treatments groups	60 U/kg		Taliglucerase alfa 60 U/kg; N=17 randomized
	30 U/kg		Taliglucerase alfa 30 U/kg; N=16 randomized
Endpoints and definitions	Primary endpoint	Spleen volume	Percent change from baseline in spleen volume measured by MRI at 9 months
	Major secondary endpoints:	Hemoglobin Liver volume Platelet count	Change from baseline at 9 months Percent Change from baseline at 9 months Change from baseline at 9 months
Database lock	Not given		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat, 9 month			
Descriptive statistics and estimate variability	Treatment group	30 U/kg	60 U/kg	
	Number of subject	15	16	
	Spleen volume (ml)	1,566.08	1,376.89	
	SD	900.17	1,055.81	
	Platelet count (cells per mm^3)	86,747	106,531	
	SD	50,989	53,212	
	Hemoglobin level (g/dl)	14.0	13.6	
	SD	1.4	2.0	
	Liver volume (ml)	2,564.07	2,190.99	
	SD	559.57	376.70	

Effect estimate per comparison	Primary endpoint	Comparison groups	30 U/kg
		Mean percent change spleen volume from baseline (%)	-26.91

		SD	7.79
		P-value	P<0.001
			60 U/kg
		Mean percent change spleen volume from baseline (%)	-38.01
		Mean percent change spleen volume from baseline (%)	9.38
		P-value	P<0.001
Notes	Post-hoc comparison dose groups: Mean difference in change from baseline was 8.53% (95% CI: 1.38% to 15.67%).		
Analysis description	Major Secondary analysis (Change from baseline)		
	Taliglucerase alfa 60 U/kg statistically significantly increased mean platelet count of 41,494 cells/mm^3 from baseline to month 9 ($p<0.01$). The increase in platelet counts from baseline of 11,427 cells/mm^3 upon treatment with taliglucerase alfa 30 U/kg was not statistically significant ($p=0.046$). The mean increase in hemoglobin level from baseline to 9 months was 1.6 g/dl and 2.2 g/dl for taliglucerase alfa 30 U/kg and 60 U/kg, respectively and statistically significant for both groups. Both dosage groups demonstrated a statistical significant reduction in liver volume from screening to the month 9 visit; the estimated mean reduction was 10.48 for taliglucerase alfa 30 units/kg and 11.11% for taliglucerase alfa 60 units/kg.		

Analysis performed across trials (pooled analyses and meta-analysis)

The clinical programme with taliglucerase alfa included treatment of patients naïve to ERT for 9 months duration in the pivotal trial PB-06-001 and long term follow up in the PB-06-003. In addition, PB-06-002 has analysed the effect of switch from Cerezyme for duration of 9 months followed by long term follow up with patients eligible for PB-06-003.

Clinical studies in special populations

No clinical studies in special populations have been performed.

Supportive studies

Study PB-06-002

Study PB-06-002 was a Phase 3, multicentre, open-label, switchover study aiming to assess the safety and efficacy of switching treatment from Cerezyme to taliglucerase alfa in 30 patients with GD who have been receiving Cerezyme for at least 2 years at a stable maintenance regimen (dose unchanged) for at least the last 6 months. Stability of patients' GD disease was ensured. Haemoglobin and platelet count were measured every 2 weeks for a total of 6 measurements. Patients with stable disease were then switched from imiglucerase to taliglucerase alfa, performed every 2 weeks for a total of 20 infusions at a rate of approximately 1.3 ml/min. The starting dose of taliglucerase alfa was equivalent to each patient's imiglucerase dose in the past 6 months or to the dose prior to the shortage of imiglucerase. The total duration of treatment is 9 months. The dosage was increased to 60 U/kg if the patient experienced GD deterioration. The control for this study was the patient's historical clinical status while on Cerezyme therapy. The main efficacy criterion was the maintenance of patient's clinical

status over the treatment period after switching from Cerezyme. The efficacy was determined by the evaluation of the clinical deterioration of platelet counts, haemoglobin, spleen volume, liver volume. Other endpoints for efficacy included biomarkers chitotriosidase and PARC/CCL18. At the time of database freeze in 2010, 40 patients were screened, 28 were eligible for enrolment, 25 patients received taliglucerase alfa, and one patient voluntarily withdrew from the study before treatment. Sixteen (16) patients completed the study. Fifteen patients were included in the efficacy analysis. At the database freeze, the mean dose of taliglucerase alfa was 28.1 U/kg. An efficacy endpoint of this study was the enlargement of the liver or spleen from Baseline to Month 9 or sustained reductions in haemoglobin or platelet counts. The mean spleen volume decreased by 5.1%. One patient showed a greater than 20% increase in spleen volume from baseline at 9 months without clinically relevant deterioration in other efficacy endpoints. The mean liver volume decreased by a mean reduction of 1.4% and when compared to normal liver volume, it remained the same between Baseline and Month 9. Haemoglobin was normally measured at 9 visits. Haemoglobin at Baseline, Month 3, Month 6 and Month 9 are summarised in the table below. Haemoglobin appears to remain stable after switching from Cerezyme to taliglucerase alfa.

Summary of Haemoglobin Levels in Study PB-06-002 at Baseline, Month 3, 6 and 9

	Haemoglobin (g/dl)			
	Baseline*	Month 3	Month 6	Month 9
N	15	15	15	15
Mean	13.5	13.3	13.3	13.2
SD	1.7	1.6	2.0	1.7
Median	13.6	13.7	13.7	13.9
Range	10.7 to 16.1	10.6 to 15.6	10.0 to 16.2	10.3 to 15.7

SD: standard deviation; N: number * Baseline = Mean of the Evaluations in the Stability Period

Platelet count was measured at the local laboratory for the various visits. Platelet counts at Baseline, Month 3, Month 6 and Month 9 are summarised in the table below. Platelet count appears to remain stable after switching to taliglucerase alfa from Cerezyme.

The biomarkers chitotriosidase and CCL18 were measured every three months during the study. Four patients showed greater than 50% decreases in chitotriosidase level at the end of 9 months of treatment with taliglucerase alfa. The mean chitotriosidase level data support the stability of GD in these patients after switching from Cerezyme to taliglucerase alfa. A >10% mean decrease in mean chitotriosidase level from Baseline was observed at Months 3, 6 and 9 and a 10% mean decrease in mean CCL18 level from Baseline was observed at Month 9.

Study PB-06-003

The study PB-06-003 was a multicentre extension trial amended to extend the assessment of the safety and efficacy of taliglucerase alfa in patients with GD completing 9 months treatment in protocols PB-06-001 or PB-06-002. The duration of the treatment was of 64 - 128 weeks. Patients who completed protocol PB-06-001 and PB-06-002 received taliglucerase alfa as per the dosing schedule in the respective study. The efficacy parameters remained the same as those defined in PB-06-001 and/or PB-06-002. Safety monitoring including analysis of adverse events, clinical laboratory evaluation, electrocardiogram and echocardiogram, pulmonary function tests, anti-human taliglucerase alfa antibodies and hypersensitivity reactions. At the time of safety database lock in June 2010, 31 patients from 12 study sites (26 patients from study PB-06-001 and 5 patients from study PB-06-002) were enrolled treated in this extension study. Spleen volume was 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 of blinded treatment with taliglucerase alfa for patients derived from PB-06-001. In PB-06-003 study, 12 patients treated with 30 U/kg taliglucerase alfa had a 28.9% reduction in spleen volume and 14 patients treated with 60 U/kg had a 43.5% reduction after 12 months of treatment. The difference between the two doses in the effect on spleen volume was statistically significant. Liver volume was measured at Day 1, which corresponds to the final visit (Month 9) of the preceding trial, and at Month 3 of treatment, representing a total of 12 months of treatment with taliglucerase alfa for patients derived from study PB-06-001. In PB-06-003 study, 12 patients treated with 30 U/kg taliglucerase alfa had a 15.9% reduction in liver volume and 14 patients treated with 60 U/kg had a 13.2% reduction. There was no difference between the two doses in the effect on liver volume. Haemoglobin was measured every three months in this study. In study PB-06-003, 12 patients treated with 30 units/kg taliglucerase alfa had a 1.7 g/dl increase in haemoglobin level and 14 patients treated with 60 units/kg had a 2.2 g/dl increase. The effect at Month 3 appears also to be sustained at Month 6. Platelet counts are measured every three months. In the patients who continued treatment in PB-06-003, 12 patients treated with 30 U/kg taliglucerase alfa had a 15,425.0 per mm^3 increase in platelets and 14 patients treated with 60 U/kg had a 53,814.3 per mm^3 increase. Thus, the 60 U/kg dose of taliglucerase alfa improved platelet counts to a statistically significantly greater effect than the 30 U/kg dose after 12 months of treatment. The effect at Month 3 appears also to be sustained at Month 6. The QCSI was used to measure bone marrow fat fraction content as an exploratory endpoint, as in Study PB-06-001. The optional lumbar spine QCSI assessment was performed at Months 3 and 15 of PB-06- 003 corresponding to 12 and 24 months of total treatment. Overall, an increase in fat-fraction ≥ 0.02 from baseline was observed in all 8 patients but one within 9 months of taliglucerase treatment. An improvement in "bone at risk" was seen in the trial patient population; after 9 and 12 months of treatment, 75% (6/8) of the patients showed a fat fraction >0.23. Taliglucerase alfa 60 U/kg treated patients showed greater fat fraction increases than the taliglucerase alfa 30 U/kg treated patients.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The evaluation of the clinical efficacy of taliglucerase alfa included the conduct of the single pivotal trial PB-06-001, which was a dose controlled study. Study PB-06-002 was a switchover trial for patients previously on imiglucerase, and has used historical control data. The extension study PB-06-003 included patients from both trials. With respect to the dose selection in the pivotal trial, justifications were provided for not selecting a placebo controlled pivotal study design but choosing instead a single pivotal study with a dose control design instead of an active comparator. , The current approach to define the dose for the pivotal trial with taliglucerase alfa was based on the extrapolation from the extensive experience with imiglucerase ERT over the years, where 60 U/kg is widely accepted as the high dose to be effective and 30 U/kg is a distinctly lower dose. Additionally, after more than 10 years of experience with imiglucerase, the most effective dosing regimen of ERT was still a subject of debate between the Gaucher's experts and, no consensus on treatment optimal doses and their effectiveness was reached, except that 60 U/kg is considered a high but efficacious dose. Thus, the CHMP considered that for medical reasons and in the interest of the patients, the strategy to compare clinically relevant different doses of taliglucerase alfa - 30 and 60 U/kg - could be considered adequate. The dose selection was based on experience with Cerezyme and on the currently available national guidelines for the management of GD. Clinical experts in the GD field were consulted and agreed that further clarity of the optimal treatment dose would be most useful in clinical practice.

Efficacy data and additional analyses

In the pivotal study PB-06- 001, with respect to the primary endpoint, the mean changes from baseline in spleen volume were significantly decreased in both dose groups at both 6 and 9 months and the predefined primary endpoint was met at both time points. Changes were greater in the 60U/Kg dose comparatively, however, the difference between doses was not significantly different at both time points (p=0.060). The results appeared to be statistically robust, being consistent with both the ITT and PP analyses populations.

For the secondary endpoints, haemoglobin and liver volume showed significant changes in both dose groups at both 6 and 9 months however, the difference between doses was not significantly different at both time points. In contrast to the other secondary endpoints there was a significant difference between the changes from baseline between both dose groups at 9 months in favour of the higher dose with respect to the platelet count. Although platelet counts were increased with the lower dose the results were not statistically significant. Results of the post-hoc analysis suggested that changes were maximal in the subgroup of patients who had anaemia and hepatomegaly in both dose groups. Effects on plasma chitotriosidase values also showed a consistent decline in both dose groups which was more pronounced in the higher dose group. All patients achieved a 10% reduction in spleen volume at the end of the study.

With respect to the bone changes there seemed to be a notable difference in the mean Z scores between the two dose groups at baseline, with patients in the 60U/Kg dose group having much lower Z scores. It is not entirely clear why the lower dose group has shown increased changes compared to the 60U/Kg dose from baseline, unlike the secondary endpoints with anaemic and hepatomegaly patients showing the largest improvements from baseline. Nevertheless, after treatment fore nine months the mean Z score for the higher dose group appears to show marginal changes from baseline which nevertheless brings it within the normal range. Although absolute numbers are small, an increase in fat-fraction ≥ 0.03 from baseline was observed in all but 1 patient using the QCSI technique within 9 months. However, at baseline, only 2/8 of the patients had a fat fraction > 0.23 which increased to 6/8 after 9 months. Nevertheless, this proportion did not seem to have increased after 12 months. Thus, only 4 patients reached the threshold of >0.23, below which they would be considered to be as "bone at risk" group. As with other clinical endpoints, taliglucerase alfa 60 U/kg treated patients showed greater fat-fraction increases than the taliglucerase alfa 30 U/kg treated patients.

The results of the switchover trial PB-06-002 appeared to be consistent with those from the pivotal study. Overall, patients who were stable on their imiglucerase dose showed no signs of deterioration with respect to spleen and liver volumes, haemoglobin and platelet counts, after switching to the same dose of taliglucerase at the end of nine months. As far as the duration of efficacy is concerned, the results from the extension study demonstrate that effect duration with respect to all efficacy endpoints is maintained at month 3 of the extension study. However, similar to the trend seen with the pivotal study, there was a significant difference between the high and low doses with respect to the spleen volume at 12 months from baseline. This appeared to be due to the fact that values for spleen volumes at 9 and 12 months were approximately similar for the lower dose, whereas the higher dose showed a further reduction in the spleen volume at 12 months. There is therefore, some evidence of efficacy by the separation of doses in case of the absence of a placebo comparator with the implication that the higher dose would have been superior to placebo. No difference between doses was observed for the changes in liver volume where both doses showed further decreases. Haemoglobin values also showed a sustained rise both at month 3 and month 6 of the extension study. As observed in the pivotal study, the 60 U/kg dose of taliglucerase alfa improved platelet counts to a statistically significantly greater effect than the 30 U/kg dose after 12 months of treatment. However, firm conclusions on long term

efficacy cannot be drawn at this point in time. In this respect, the study did not show clear separation of doses with respect to all endpoints.

2.5.4. Conclusions on the clinical efficacy

Clinical data from the pivotal trial PB-06-001 show the efficacy of the highest dose of taliglucerase alfa (60 U/kg) in treatment-naïve adult patients with non-neuronopatic GD based on spleen volume and platelet count for the population included in the study. taliglucerase alfa is indicated in the treatment of Gaucher disease type 1 only.

The CHMP did not consider a specific measure necessary to address issues related to efficacy, but clinical efficacy data will be collected from the registry that is included as an additional pharmacovigilance activity in the RMP and discussed in section 2.6.2.

2.6. Clinical safety

The overall safety data for taliglucerase alfa is based on a completed Phase 1 study in 6 healthy subjects (P-01-2005), a completed pivotal Phase 3 study in 32 patients (safety population) naïve to enzyme replacement therapy (PB-06-001) and two ongoing studies: a study in patients switched from imiglucerase to taliglucerase alfa (PB-06-002) and an extension study (PB-06-003) enrolling patients who completed PB-06-001 and PB-06-002. In addition, an Expanded Access Programme (EAP) in the United States and Israel (study PB-06-004) and named-patient basis compassionate use programmes in several countries, e.g. UK, France, Germany, the Netherlands, Switzerland, Australia, Israel and Brazil, were ongoing at the time of MAA submission. It is of note that these programmes were triggered by the shortage of Cerezyme, which occurred in 2009. A formal safety review of data generated during clinical trials was conducted with a cut-off date of June 30, 2010 for all studies except PB-06-002, which has an August 15, 2010 cut-off date. The data include 89 subjects (6 healthy volunteers and 83 Gaucher patients under clinical trials). Although details of patients in compassionate programs are not available, the treating physicians are requested to report serious adverse events. None were reported to the date of the safety summary report. The overall safety population is summarised in the table below.

Overall safety population

Study ID (Phase)	**Design Control Type**	**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	Day 1: vehicle Day 8: 15 U/kg taliglucerase alfa Day 15: 30 U/kg taliglucerase alfa Day 22: 60 U/kg taliglucerase alfa	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	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 glucocerebr

Study ID (Phase)	Design Control Type	Study and Control Drug Dose, Route and Regimen	Subjects by Arm Completed/ Entered	Duration of Treatment	Study Population Inclusion Criteria
					osidase 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)	Open-label, Switchover trial	Same dose as imiglucerase dose	16/25	9 months	Patients with Gaucher disease currently treated with Cerezyme
PB-06-003 (Phase 3)	Double-blind* extension study	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	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 imigluceras e
CUPs	Open label	Same dose as imiglucerase before reduction or discontinuation due to drug shortage	74 at the time of data cut-off	Up to MA	Age 18 years or older Diagnosis of GD treated historically with imigluceras e

Patient exposure

Thirty-three patients were randomised to 30 U/kg (16 patients) or 60 U/kg (17 patients) in the pivotal study, PB-06-001. One patient withdrew from the study before being treated. Thirty two (32) patients (30 U/kg, 16; 60 U/kg: 16) were administered study medication at least once during the study. One patient received only one single partial dose [4.5 ml (60 U/kg dose group)] and withdrew due to a hypersensitivity reaction. A second patient developed hypersensitivity and withdrew at Week 22. One patient became pregnant and withdrew at Week 18. Thus, 29 patients completed the 9 months of treatment. In the switch-over study, PB-06-002, 25 patients have received treatment as of August 15,

2010. Sixteen patients have completed the study to date. No patients were withdrawn prematurely. As of June 30, 2010, 31 patients were enrolled in the extension study (PB-06-003) (from study PB-06-001, 26 patients; from Study PB-06-002, 5 patients), 9 of whom (from study PB-06-001) have completed total treatment duration of 24 months. Patients enrolled in PB-06-004 were treated with the same taliglucerase alfa dose as the imiglucerase dose received before reduction or discontinuation due to imiglucerase shortage. The overall summary of the patient exposure data as submitted initially is presented in the table below.

Total patient exposure to taliglucerase alfa in completed pivotal Phase 3 (PB-06-001), switchover (PB-06-002) (as of August 15, 2010), ongoing extension (PB-06- 003) studies and expanded access programme (PB-06-004) (as of June 30, 2010)

		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	9	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

Considering the information on patient exposure, the Committee expressed their concerns about the low number of patients exposed to taliglucerase alfa and the lack of sufficient long-term data. The CHMP concluded that the profile emerging form the overall safety database is not different from that based on the initially submitted information and corresponds with the safety profile known from other ERTs in Gaucher disease. Given the relative small population studied to date and the life-long treatment, the CHMP agreed to a commitment to continue following the patients for safety purposes. Accordingly, the major objection was considered resolved with a pharmacovigilance activity included in the Risk Management Plan for Elelyso.

Adverse events

In the pivotal study PB-06-001, 23 out 32 patients who received taliglucerase alfa also experienced 137 AEs (30 U/kg, 65; 60 U/kg, 72) as summarised in the table below. Eight of these patients (30 U/kg, 3; 60 U/kg, 5) experienced 28 events (30 U/kg, 12; 60 U/kg, 16) which were considered by the investigator as treatment-related. All AEs were mild or moderate in intensity and the majority of the events resolved without sequelae by the end of the infusion. Four patients experienced 6 AEs that were ongoing until the end of study that did not impact their continuing study drug treatment. These events were definitely not treatment related and include hypertension, arthralgia, swelling, varicose veins, hyperuricemia and hypertriglyceridemia. No deaths or SAEs occurred during the study. The safety profile was comparable between the two dose groups. The most commonly experienced AE for both dose groups was headache, pharyngitis and upper respiratory tract infection; all AEs resolved without sequelae by the end of the study.

Summary of AEs in all Studies Pertinent to Safety in Gaucher Patients as of June 30, 2010 (Except Otherwise Stated)

Parameter	PB-06-001		PB-06-002 (August 15, 2010)	PB-06-003 (June 30, 2010)			PB-06-004 (June 30, 2010)	Overall
				Derived from PB-06-001		Derived from PB-06-002		
	30 U/kg N=16	60 U/kg N=16	11-60U/kg N=25	30 U/kg N=12	60 U/kg N=14	12-29 U/kg N=5	13-65 U/kg N=26	N=83
AE	65	72	135	64	85	1	104	526
Mild or moderate AE	65	72	132	64	81	1	103	518
Severe or very severe AE	0	0	3	0	4	0	1	12
Serious AE	0	0	3	0	1	0	1*	5
AE probably or definitely not related to treatment	53	56	115	50	75	1	42	392
AE definitely, probably or possibly related to treatment	12	16	20	14	10	0	62	134

AE: adverse event; N: number of patients

* A severe adverse event was marked as serious at the time of data cut-off for this analysis, but has since been corrected.

It is of note, the AEs do not appear to be more likely in patients switching from imiglucerase (PB-06-002 and PB-06-004) than occurred in patients who were naïve to ERT. The analysis of the overall population up to 33 months does not reveal unexpected safety findings.

Overall Analysis of Adverse Events: Overall, 83 taliglucerase alfa treated patients experienced 526 AEs. Among those AEs, 134 events were considered by the investigator at least possibly treatment related. Almost all AEs were mild or moderate in intensity. An overview of the experienced events is given in the table below.

Number of patients with common treatment-related AEs – Studies PB-06-001, PB-06-002, PB-06-003 and PB-06-004.

N=83 patients		**Mild**	**Moderate**	**Total**
SYSTEM ORGAN CLASS	PREFERRED TERM			
Eye disorders	Blepharitis	1 (1.2%)	0 (0.0%)	1 (1.2%)
Gastrointestinal disorders	Abdominal pain	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Diarrhoea	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Frequent bowel movements	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Lip swelling	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Nausea	2 (2.4%)	0 (0.0%)	2 (2.4%)
	Oesophageal pain	0 (0.0%)	1 (1.2%)	1 (1.2%)
General disorders and administration site conditions	Asthenia	2 (2.4%)	0 (0.0%)	2 (2.4%)
	Chest pain	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Chills	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Fatigue	3 (3.6%)	1 (1.2%)	4 (4.8%)
	Feeling hot	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Infusion related reaction	5 (6.0%)	0 (0.0%)	5 (6.0%)
	Infusion site pain	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Lethargy	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Local swelling	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Oedema peripheral	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Pain	1 (1.2%)	0 (0.0%)	1 (1.2%)
Hepatobiliary disorders	Gallblader disorder	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Hepatic cyst	1 (1.2%)	0 (0.0%)	1 (1.2%)
Immune system disorders	Hypersensitivity	2 (2.4%)	2 (2.4%)	4 (4.8%)
Investigations	Weight increase	2 (2.4%)	0 (0.0%)	2 (2.4%)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (1.2%)	1 (1.2%)	2 (2.4%)
	Back pain	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Joint stiffness	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Muscle spasms	1 (1.2%)	0 (0.0%)	1 (1.2%)
Nervous system disorders	Burning sensation	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Dizziness	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Headache	4 (4.8%)	1 (1.2%)	5 (6.0%)
Renal and urinary disorders	Glycosuria	1 (1.2%)	0 (0.0%)	1 (1.2%)
Reproductive system and breast disorders	Gynaecomastia	1 (1.2%)	0 (0.0%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	2 (2.4%)	0 (0.0%)	2 (2.4%)
	Rhinorrhoea	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Sneezing	1 (1.2%)	0 (0.0%)	1 (1.2%)
Skin and subcutaneous tissue disorders	Drug eruption	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Erythema	3 (3.6%)	0 (0.0%)	3 (3.6%)
	Pruritus	4 (4.8%)	0 (0.0%)	4 (4.8%)
	Rash	1 (1.2%)	0 (0.0%)	1 (1.2%)
	Skin irritation	1 (1.2%)	0 (0.0%)	1 (1.2%)
Vascular disorders	Flushing	2 (2.4%)	0 (0.0%)	2 (2.4%)

All events: The most common treatment-emergent AEs (occurring in more than 5% patients) independently of their relation to treatment, for all studies combined include headache (20.5%), arthralgia (16.9%), fatigue (12.0%), nasopharyngitis (12.0%), back pain (9.6%), upper respiratory infection (9.6%), influenza (8.4%), infusion related reaction (7.2%), nausea (7.2%), pharyngitis (7.2%), pharyngolaryngeal pain (7.2%), cough (6.0%), erythema (6.0%), pain (6.0%), pruritus (6.0%), pyrexia (6.0%), urinary tract infection (6.0%).

Related events: Common treatment-related AEs included infusion related reaction (6.0%), headache (6.0%), hypersensitivity (4.8%), fatigue (4.8%), pruritus (4.8%), and erythema (3.6%) were the most frequent events associated with taliglucerase alfa infusions.

During the evaluation of the adverse event's profile of Elelyso, the Committee expressed their concern regarding the assignment of the causality of AEs. In response to this concern, verification and a plausible explanation for the assignment of the relationship to the study drug was provided and the CHMP considered the response satisfactory. Furthermore, the lack of safety data during the stabilisation period in study PB-006-002 was also explained. The main reason for this was the very low number of patients treated during stabilisation period. The remaining patients were off treatment with imiglucerase.

Serious adverse event/deaths/other significant events

Four serious adverse events (SAEs) were reported in the clinical trials, but none was considered by the investigator as treatment related (please refer to the table below). No deaths were reported during the studies.

Number of subjects with SAEs observed in studies PB-06-001, PB-06-002, PB-06-003 and PB-06-004

Patients from:		PB-06-001 and PB-06-003				PB-06-002 and PB-06-003		PB-06-004		Overall	
	Relation to treatment	30 U/kg N=16		60 U/kg N=16		12-60U/kg N=25		N=26		N=83	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Blood and lymphatic system disorders (Autoimmune thrombocytopenia)	No	0	(0.0)	1	(6.3)*	0	(0.0)	0	(0.0)	1	(1.2)
Musculoskeletal and connective tissue disorders (Back pain)	No	0	(0.0)	0	(0.0)	0	(0.0)	1**	(3.8)	1**	(1.2)
Renal and urinary disorders (Nephrolithiasis)	No	0	(0.0)	0	(0.0)	1	(4.0)	0	(0.0)	1	(1.2)
Reproductive system and breast disorders (Pelvic prolapse)	No	0	(0.0)	0	(0.0)	1	(4.0)	0	(0.0)	1	(1.2)
Respiratory, thoracic and mediastinal disorders (Epistaxis)	No	0	(0.0)	0	(0.0)	1	(4.0)	0	(0.0)	1	(1.2)

Note: Adverse events occurring during treatment in the extension study (PB-06-003) are reported under the patients' original protocol and treatment group.

*The SAE was reported in the extension study PB-06-003

** A severe adverse event was marked as serious at the time of data cut-off for this analysis, but has since been corrected to non-serious.

The number of patients experiencing related adverse events in the pivotal study PB-06-001 is summarised in the table below.

Number of subjects with AEs definitely, possibly, or probably related to treatment by MedDRA System Organ Class / preferred term (safety population)

		PB-06-001	
System Organ Class / Preferred Term		30 U/kg n=16	60 U/kg n=16
		N (%)	N (%)
Gastrointestinal disorders			
Abdominal pain	Mild	1 (6.3)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)
	Total	1 (6.3)	0 (0.0)
General disorders and administration site conditions			
Feeling hot	Mild	1 (6.3)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)
	Total	1 (6.3)	0 (0.0)
Immune system disorders			
Hypersensitivity	Mild	0 (0.0)	1 (6.3)
	Moderate	1 (6.3)	0 (0.0)
	Total	1 (6.3)	1 (6.3)
Musculoskeletal and connective tissue disorders			
Arthralgia	Mild	0 (0.0)	1 (6.3)
	Moderate	0 (0.0)	0 (0.0)
	Total	0 (0.0)	1 (6.3)
Muscle spasms	Mild	1 (6.3)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)
	Total	1 (6.3)	0 (0.0)
Nervous system disorders			
Dizziness	Mild	1 (6.3)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)
	Total	1 (6.3)	0 (0.0)
Headache	Mild	0 (0.0)	1 (6.3)
	Moderate	1 (6.3)	0 (0.0)
	Total	1 (6.3)	1 (6.3)
Renal and urinary disorders			
Glycosuria	Mild	0 (0.0)	1 (6.3)
	Moderate	0 (0.0)	0 (0.0)
	Total	0 (0.0)	1 (6.3)
Skin and subcutaneous tissue disorders			
Pruritus	Mild	1 (6.3)	1 (6.3)
	Moderate	0 (0.0)	0 (0.0)
	Total	1 (6.3)	1 (6.3)
Skin irritation	Mild	0 (0.0)	1 (6.3)
	Moderate	0 (0.0)	0 (0.0)
	Total	0 (0.0)	1 (6.3)

Immunological events: No infusion related reactions were observed in study P-01-2005 in healthy volunteers. The most frequent events were headache, infusion related reaction, nausea, hypersensitivity, and flushing. The most frequently reported events assessed by the investigator as at least possibly related to the study drug were headache, infusion related reaction and hypersensitivity. The majority of the events were mild in severity and none were severe. Two patients experienced hypersensitivity reactions. Thirty-eight patients reported 111 AEs during or after 98 infusions; most of the AEs were considered by the investigator at least possibly related to taliglucerase alfa. The most common AEs reported as related to the infusions were headache, asthenia or fatigue, dizziness, infusion related reaction, and pruritus.

Anti-human taliglucerase alfa antibodies: No anti-human taliglucerase alfa antibodies were detected in the 6 healthy volunteers in study P-01-2005. When evaluating data from the Gaucher disease patients, the bio-analytical plans for analysis of antibody response to taliglucerase alfa treatment in each study indicate that the analysis and reporting of the results is based on completed patients (completed

dosing per protocol or prematurely withdrawn). Therefore, antibody analysis has not been performed for patients who are still being treated in a study and will be done at study completion. In PB-06-001, 32 patients were tested for immunogenicity to taliglucerase alfa and one patient in each dose group (taliglucerase alfa 30 U/kg, 10-001; taliglucerase alfa 60 U/kg, 12-024) demonstrated positive IgG antibody titers to human taliglucerase alfa. Neutralising antibody test results were negative for both patients. One patient experienced five AEs at various visits (vomiting, flushing, influenza, lymphadenopathy, and hypertension) during the study but did not develop a hypersensitivity reaction during the study. The patient completed the study and had a positive IgG antibody response at the end of study. This patient was further enrolled to the extension study PB-06-003 and developed a fixed drug eruption starting after 62 weeks. Fixed drug eruptions are delayed hypersensitivity reactions mediated by T cells and there may not be an association with antibody development. A different patient did not develop a hypersensitivity reaction but experienced two AEs at two different visits (glucosuria and influenza) during the study. The patient completed the study and had a positive IgG antibody response at the end of study. This patient was also enrolled to the extension study PB-06-003 and is tolerating the infusions well.

During the evaluation procedure the Committee raised questions on the general safety and immunological events, especially those occurring in study PB-06-001. Data on patients treated with dose 60 IU/kg were also to be submitted separately from the remaining patient group and a discussion on the possible differences between taliglucerase alfa and other treatments was to be provided. Following the receipt of the responses the CHMP considered that the frequency of antibody development is not different from that mentioned for imiglucerase. The antibody formation for velaglucerase appears to be somewhat lower, however due to different analyzing methods this information should be interpreted with caution. For taliglucerase alfa, the presence of a positive antibody status appeared to have no effect on efficacy or safety outcomes. Results published for velaglucerase and imiglucerase lead to the same conclusion. The clinical relevance of the antibody formation will receive special attention in the long term follow-up and this was included in the RMP. Furthermore, the role of different plant glycan structures was discussed. There is currently a lack of strong evidence to suggest the association between plant glycan structures and immunogenicity and the potential immunogenicity of plant glycans has yet to be conclusively established. The established immunogenicity testing programme will continue along with the evaluation of the anti-taliglucerase antibodies generated in patients to determine specificity for the plant-derived glycans on taliglucerase alfa. In the post-marketing setting, the routine pharmacovigilance and risk minimisation activities (including Targeted Medical Event review, Periodic Safety Update Reports and suitable labelling) will be adequate to monitor and ensure patient safety concerning adverse effects related to unusual immunogenicity. The proposed measures to address the above concerns are reasonable and agreed by the CHMP.

Safety related to drug-drug interactions and other interactions

Drug interactions are not expected with taliglucerase alfa due to the nature of the substance and were not assessed. This information is adequately reflected in Section 4.5 of taliglucerase alfa SmPC (Latest version of the Product Information as submitted by the applicant but not adopted by the CHMP).

Laboratory findings

Laboratory haematology and biochemistry: The majority of the laboratory haematology and biochemistry parameters remained at normal levels from screening or improved to normal levels by the end of study. One taliglucerase 60 units/kg treated patient had elevated ALT, which was 3 times above the higher limit of normal (40 IU/L), however this patient returned to 52 IU/L at Visit 20. No

significant decrease in erythrocyte sedimentation rate was seen at the end of study (taliglucerase 30 units/kg, 11.9 mm/hr; taliglucerase 60 units/kg, 15.3 mm/hr).

Electrocardiogram (ECG) and Echocardiography: ECG results for the safety population were measured at baseline, visits 7, 14 and 20. There were no clinically significant changes from baseline observed at these visits. Nine patients had abnormal echocardiography results at the screening visit. Six were evaluated as normal by the end of the study and 3 patients remained abnormal at the end of study.

Pulmonary Function Test: There were no apparent mean value changes from screening to the end of study in all PFT parameters tested.

Bone Disease: No patients experienced bone pain or fractures during the study. Evaluation of DEXA showed stable to slightly improved bone density and QCSI showed improvement in bone marrow fat fraction.

Vital Signs: Vital sign parameters were monitored at each infusion visit for 210 minutes, every 15 minutes during the infusion up to the first 2 hr time period, with continued monitoring for three additional 30 minute periods. No adverse events were reported associated with patients' vital sign measurements. Changes in vital signs during taliglucerase were not analyzed, but no adverse events were reported for significant changes not related to hypersensitivity reactions.

Patients switched from imiglucerase: The majority of the laboratory haematology and biochemistry parameters remained at normal levels from screening through the end of study. 7 patients reported normal liver function at baseline and liver function tests above normal (2 with ALT, 1 with AST, 4 with bilirubin levels) during treatment. Two patients in the pivotal study reported liver function values more that 3 times ULN. The Committee has therefore requested that a thorough discussion of these events is provided. In response, a plausible explanation for the increase in hepatic enzymes in the small number of patients was given, however, there does not seem to be a discernible cause in others. While it is accepted that minor elevations can occur in some GD patients without concomitant morbidity, it would be prudent to keep hepatic enzymes under review initially until more data is available. Therefore, monitoring of liver enzymes is included in the RMP and elevated liver enzymes will be evaluated as a specific safety concern.

Safety in special populations

Because of the small number of patients in each population group, the subgroup analyses were not performed.

Discontinuation due to adverse events

Overall, two patients (taliglucerase alfa 30 U/kg and 60 U/kg) discontinued from study PB-06-001 due to a hypersensitivity reaction. In the same study PB-06-001, one patient was discontinued due to pregnancy. The CHMP requested further details with respect to the withdrawals and study discontinuation and based on the response provided, this issue does not raise any significant concerns.

Post marketing experience

There is no post marketing experience with taliglucerase alfa since at the time of the evaluation this product has not been marketed in the EU.

2.6.1. Discussion on clinical safety

In the pivotal study PB-06-001, the absence of a comparator arm makes the comprehensive assessment of the safety profile of taliglucerase somewhat complicated. Nevertheless, there does not seem to be a clear cut dose relationship with the adverse events, except for few events, which include headache. In this respect it is notable that for infusion reactions the occurrence of headache in the same patient has had a differing causality assigned. The incidence of antibodies presence appears to be remarkably low in comparison with other enzyme replacement therapies since only two patients were found to be IgG positive with no neutralising activity. Although two cases of hypersensitivity occurred, one was in a patient who had a pre-dose IgE antibody and also later reacted to imiglucerase. While both patients who suffered hypersensitivity episodes were withdrawn from the study, no patients were withdrawn due to any other adverse events. The CHMP considered it reassuring that there were no SAEs or deaths in the pivotal study. Overall, there do not seem to be unexpected findings from the data submitted.

In the switchover study the number of infusion reactions considered related to treatment appeared to be increased in the group of patients who had transitioned from imiglucerase treatment. Nevertheless, the Committee noted that these tended to be mild. Other common adverse event included nasopharyngitis. Three SAEs were reported; neither of them was considered related to the study medication, and there were no deaths or premature withdrawals from the study. However, it was not entirely clear if safety data was collected during the stabilisation period in the switch study. In response to the Committee's concern, plausible explanation for the lack of safety data during the stabilisation period in study PB-006-002 was provided; namely that there were very few patients treated during stabilisation and the remaining patients were off treatment with imiglucerase.

The incidence of patients who were positive for antibodies appears to be comparatively low since only one patient was positive for IgG but showed no neutralising activity. Overall, there were no unexpected findings from the study. It is notable that in the patients who were extended from study PB-06-002, there were no further adverse events, although the patient numbers are small and preclude firm conclusions. There were no clear-cut differences in the dose groups in patients whose treatment was extended from the pivotal trial. Although there was one SAE of immune thrombocytopenia, this was not considered related to study medication. As with other studies there were no premature study withdrawals.

For taliglucerase alfa, the presence of a positive antibody status appeared to have no effect on efficacy or safety outcomes. The clinical relevance of the antibody formation will be an issue of special attention in the long term follow-up and has been included in the RMP. The information currently available in the SmPC refers to the fact that the persistence of cross-reactivity cannot be excluded. Neither, however, can the cross-reactivity be demonstrated. The proposal to warn against a possible cross-reactivity is agreed to be the appropriate approach. Further routine pharmacovigilance and risk minimisation activities are also in place. Long term safety will be monitored through the maintenance of a registry, which is agreed by the CHMP as an additional pharmacovigilance activity in the RMP.

Indirect comparison using publicly available data for currently available ERT suggest that the frequency of antibody formation is comparable or somewhat higher with taliglucerase alfa. However, comparisons are hampered by different analysing methods between studies.

In the expanded access as well as in the compassionate use programme, there have been no unexpected findings. No SAEs or deaths have been reported and there were no withdrawals due to adverse events.

In general, laboratory parameters were unremarkable; the majority of the laboratory haematology, biochemistry, vital signs or other parameters remained at normal levels. A few patients showed increases in the ALT levels, though less than considered clinically significant. The patient numbers are small and there appeared to be a dose relationship. In this respect two healthy volunteers showed slight elevation in bilirubin levels during the study. It is notable that no patients were prematurely withdrawn due to these adverse events, other than the two who showed hypersensitivity. In other patients treatment was continued despite hypersensitivity under cover of pre-medication.

Infusion reactions did not appear to raise significant issues and were easily managed without treatment having to be discontinued in the majority of patients.

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC (Latest version of the Product Information as submitted by the applicant but not adopted by the CHMP).

2.6.2. Conclusions on the clinical safety

The overall safety results indicate that taliglucerase was generally well tolerated with minor side effects that were self-limited and resolved with no treatment. No serious adverse events were attributable to the product administered intravenously once every 2 weeks at doses up to 60 mg/kg. Although at the time of the MAA submission the safety database seem somewhat small and the CHMP raised an objection in this regard, further submitted safety information in form of the interim follow up data from studies PB-06-001 and PB-06-002 suggest that the emerging safety profile for taliglucerase alfa corresponds with that known for other ERTs in the treatment of Gaucher disease. Nevertheless, considering the limited size of the studied population to date and the proposed life-long treatment for taliglucerase alfa, the CHMP recommended on a commitment to continue the follow up of patients. Accordingly, the CHMP considers an appropriate measure to be put in place and obliged the applicant to set up a registry to obtain information regarding long term efficacy and safety, formation of antibodies, their impact on efficacy and safety of taliglucerase treatment, cross-reactivity with other ERT's and the dose dependence of the adverse events as well as hepatic enzymes. The follow-up should be at least five years. This is added as an additional pharmacovigilance activity in the RMP of Elelyso. Furthermore, the clinical relevance of the antibody formation will receive special attention in the long term follow-up and this was included in the RMP as a pharmacovigilance activity.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan. References are made to SmPC (Latest version of the Product Information as submitted by the applicant but not adopted by the CHMP).

Table 1. Summary of the risk management plan

Safety concern	Pharmacovigilance activities	Risk minimisation activities
Important Identified Safety Concerns		
Hypersensitivity	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.3 Contraindications Hypersensitivity to the active substance, to other glucocerebrosidase enzymes, or to any of the excipients listed in Section 6.1. SmPC Section 4.4 Special warnings and precautions for use Infusion-related reactions and hypersensitivity Hypersensitivity reactions are possible, therefore appropriate medical support should be readily available when taliglucerase alfa is administered. Infusion-related (i.e. occurring during or shortly after infusion), and hypersensitivity reactions have been reported with taliglucerase alfa. If a severe allergic reaction occurs, immediate discontinuation of the taliglucerase alfa infusion is recommended. Patients who experience infusion-related reactions or signs and symptoms of hypersensitivity can however usually be managed successfully and have therapy continued by slowing the infusion rate, treating with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions.

Infusion-related reactions	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.2 Posology and method of administration Method of administration After reconstitution and dilution, the preparation is administered by intravenous infusion over a period from 2 to minimum 1 hour. Duration of infusion may be adjusted as tolerated by the patient. SmPC Section 4.4 Special warnings and precautions for use Infusion-related reactions and hypersensitivity Hypersensitivity reactions are possible, therefore appropriate medical support should be readily available when taliglucerase alfa is administered. Infusion-related (i.e. occurring during or shortly after infusion), and hypersensitivity reactions have been reported with taliglucerase alfa. If a severe allergic reaction occurs, immediate discontinuation of the taliglucerase alfa infusion is recommended. Patients who experience infusion-related reactions or signs and symptoms of hypersensitivity can however usually be managed successfully and have therapy continued by slowing the infusion rate, treating with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions
Important Potential Safety Concerns		
Immunogenicity	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.4 Special warnings and precautions for use Antibody response Patients have developed IgG antibodies to taliglucerase alfa. Although numbers were small, more hypersensitivity events have been observed in association with a positive antibody response than in the absence of an antibody response. Antibodies may play a role in adverse reactions found with the use of taliglucerase alfa. To further evaluate the relationship, in cases of severe infusion-related reactions and in cases of lack of or loss of effect, patients should be tested for the presence of antibodies and the results reported to the company.
Off-label paediatric use	Routine pharmacovigilance.	Prescribing information from the SmPC section 4.2 Paediatric population The safety and efficacy of Elelyso in children aged 2 – 18 years have not yet been established. Currently available data are described (see section 5.1) but no recommendation on a posology can be made.

Prolonged activated partial thromboplastin time	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	Labelling with respect to prolonged activated partial thromboplastin time is not considered necessary because this outcome is a feature of Gaucher disease and has been observed during enzyme replacement therapy but has been reported as an adverse event only once during clinical studies in patients treated with taliglucerase alfa.
Elevated liver enzymes	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	Labelling with respect to elevated liver enzymes is not considered necessary because this outcome is considered to be largely due to the underlying disease or comedications.
Important Missing Information		
Pregnancy and lactation	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	Prescribing information from the SmPC section 4.6 Pregnancy Reproduction studies of taliglucerase alfa have been performed in rats and rabbits at doses up to 5 times the maximum human dose on a mg/m² basis and have revealed no evidence of impaired fertility or harm to the fetus due to taliglucerase alfa. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, caution should be exercised when prescribing to pregnant women.
Paediatric population	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.2 Posology and method of administration Paediatric population The safety and efficacy of Elelyso in children aged 2 – 18 years have not yet been established. Currently available data are described (see section 5.1) but no recommendation on a posology can be made.
Elderly population	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.2 Posology and method of administration Elderly (≥65 years old) During clinical studies 8 patients aged 65 or older were treated with Elelyso. This limited data set does not indicate a need for a dose adjustment in this age group.
History of allergy to carrots	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.4 Special warnings and precaution for use Allergy to carrots The occurrence of allergic reactions in those with known carrot allergies is currently not known and has not been studied in clinical trials. Therefore caution should be exercised in treating such patients. If infusion-related reactions or hypersensitivity occur, patients should be managed as described above.

Presence of neuronopathic Gaucher disease	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	Prescribing information from the SmPC section 5.1. SmPC section 5.1 Pharmacodynamic properties. Neuronopathic Gaucher disease Patients with severe neurological symptoms were excluded from clinical studies.
Anaphylactoid or infusion-related reaction to previous ERT	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC Section 4.4 Special warnings and precautions for use Infusion-related reactions and hypersensitivity Hypersensitivity reactions are possible, therefore appropriate medical support should be readily available when taliglucerase alfa is administered. Infusion-related (i.e. occurring during or shortly after infusion), and hypersensitivity reactions have been reported with taliglucerase alfa. If a severe allergic reaction occurs, immediate discontinuation of the taliglucerase alfa infusion is recommended. Patients who experience infusion-related reactions or signs and symptoms of hypersensitivity can however usually be managed successfully and have therapy continued by slowing the infusion rate, treating with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions.
Potential drug-drug interactions	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC section 4.5 Interaction with other medicinal products and other forms of interaction No interaction studies have been performed.
History of pre-existing hepatic impairment	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC section 4.2 Posology and method of administration Renal or hepatic impairment No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of taliglucerase alfa.
History of pre-existing renal impairment	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC section 4.2 Posology and method of administration Renal or hepatic impairment No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of taliglucerase alfa.

History of pre-existing cardiovascular disease	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	Labeling with respect to pre-existing cardiovascular disease is not considered necessary since there is no evidence for an effect of taliglucerase or other enzyme replacement therapy on cardiovascular outcomes.
Experience in Patients on Long Term Therapy	Routine pharmacovigilance. A post-approval system for follow-up of taliglucerase alfa-treated-patients in a patient registry will be established.	SmPC section 4.8 Undesirable effects The safety of Elelyso has been evaluated in over 120 patients with Gaucher disease. Elelyso was administered in doses of 11-73 units/kg body weight every other week for lengths of treatment up to 39 months. SmPC section 5.1 Pharmacodynamic properties Twenty-six (26) previously treatment naïve patients continued to be treated with Elelyso in an extension of this study [pivotal study PB-06-001] in a blinded manner for a total treatment duration of 24 months and showed continued improvement in efficacy

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The applicant shall continue to collect safety data on immunogenicity and its effect on safety and efficacy as part of routine pharmacovigilance activity and as part of the registry.	Data will be made available in the PSURs an in the registry reports.
The applicant shall set up a Registry to obtain information regarding long term efficacy and safety, formation of antibodies, their impact on efficacy and safety, cross-reactivity with other ERT's and the dose dependence of the adverse events as well as hepatic enzymes. The follow-up should at least span 5 years.	Study reports will be submitted annually, synchronised with the PSUR submission, as a separate document, with the key findings summarised in the PSUR.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Taliglucerase alfa is a recombinant version of an endogenous enzyme which is deficient in patients with Gaucher's disease. Accordingly, the mechanism of action and pharmacodynamic effects are well known. There is abundant evidence on dosage used in clinical practice with comparable ERTs.

In the pivotal study the mean changes from baseline in spleen volume were statistically significantly decreased in both dose groups at both 6 and 9 months and the predefined primary endpoint was met. Overall, changes were greater in the 60 U/Kg dose than in the 30 U/kg group. The results appeared to be robust and consistent with the ITT and PP analyses populations. For the secondary endpoints, haemoglobin and liver volume showed significant changes in both dose groups at both 6 and 9 months, although the difference between doses was not significantly different. In contrast, there was a significant difference between the changes from baseline between both dose groups at 9 months in favour of the higher dose with respect to the platelet count. Although platelet counts were increased with the lower dose, the results were not statistically significant. The preliminary results from the extension study provide assurance that after one year of treatment, there is limited evidence of dose separation. The switch study provided supportive evidence that there is no significant clinical deterioration in patients who were switched from imiglucerase. The findings for the biomarkers were consistent with the results for the primary and secondary points. Using historical data, the results for the main parameters assessed for taliglucerase alfa in study PB-06-001 and supplemented by the additional 3 months data from study PB-06-003 appear to be within the ranges established in the historical data reviewed. This would suggest approximately comparable efficacy of taliglucerase alfa compared to alglucerase/imiglucerase.

Results of the studies were reviewed by a panel of Gaucher experts. It was estimated that 81% of patients with splenomegaly and 96% of patients with hepatomegaly achieved therapeutic goals after 12 months of treatment. Although patients included those with splenomegaly and thrombocytopenia, as per inclusion criteria, only 58% had hepatomegaly and 32% anaemia at baseline, with over 90% reaching treatment goals. As observed in the clinical studies, the 60 U/Kg dose showed a greater effective response in spleen volume and platelet count than that observed in patients treated with taliglucerase alfa 30 U/kg.

Uncertainty in the knowledge about the beneficial effects

The demonstration of efficacy of taliglucerase alfa relies on one single pivotal study including a limited number of 31 treatment-naïve patients. This pivotal study was performed without a comparator arm, but included a high and low dose control. This could potentially limit the evaluation of the magnitude of effect in the light of currently available ERT. A comparison of the dose groups was not planned. Nevertheless, if there is obvious separation between the doses, this would indicate that the higher dose is clinically superior to the lower dose, thus indirectly implying that it would have been superior to placebo. Indeed, the results of the requested reanalyses showed clear evidence of superiority of the

high dose over the low dose at 9 and 12 months for the outcome related to spleen volume. In addition, a better response was seen for the higher dose than the lower dose in terms of effect on platelets. Nevertheless, the lower dose allows for adjustments to be made on an individual basis based on achievement and maintenance of therapeutic goals for patients with stable disease.

The use of historical data provides some supportive evidence. It is noted that the period when the studies were conducted may be different with implications for the response to treatment due to a difference in the standard of care as well differences in the exclusion and inclusion criteria. Nevertheless, further historical comparison with recent data on velaglucerase using similar responder rates provided satisfactory reassurance that the results with taliglucerase are comparable to those of velaglucerase, which in some part addresses the lack of active comparator.

The limited number of patients with type 3 Gaucher disease in the pivotal and switchover studies resulted a recommendation for the use of taliglucerase in the treatment of type 1 of Gaucher disease only. The beneficial effects in patients with acute or chronic neuropathic disease are not known yet. Additional long-term follow up data will provide reassurance on the long-term efficacy in patients with stable disease.

Risks

Unfavourable effects

In the results of the pivotal study PB-006-01, there does not seem to be a clear dose relationship with the adverse events, except for few events which include headache. The incidence of antibodies appears to be around 50% and only 3 patients were found to have neutralising activity. Although two cases of hypersensitivity occurred, one was in a patient who had a pre-dose IgE antibody and also later reacted to imiglucerase as well. While both patients who suffered hypersensitivity episodes were withdrawn from the study, no patients were withdrawn due to any other adverse events. It is reassuring to note that there were no SAEs or deaths in the pivotal study. Overall, there did not appear to be any unexpected findings from the data submitted.

In the switchover study the number of infusion reactions which were considered related to treatment appeared to be increased for patients who had transitioned from imiglucerase**,** however these tended to be mild. Although there were 3 SAEs, these were considered unrelated to study medication and there were no deaths or premature withdrawals from the study. Overall, there were no unexpected findings from the study.

In the extension study, there was one SAE of immune thrombocytopenia, this was not considered related to study medication. Similarly, no unexpected findings were identified in the expanded access or the compassionate use program. No SAEs or deaths have been reported and as with other studies there were no withdrawals from the study due to adverse events.

Uncertainty in the knowledge about the unfavourable effects

The lack of a comparator for the pivotal study limits the assessment of safety which is further compounded by the small number of patients and the small size of the safety database, due to the rarity of the disease. The overall safety and immunogenicity data for studies PB-06-001 and PB-06-002 confirm that the safety profile of taliglucerase appears to be similar to that observed with other ERTs. It cannot be concluded if the low incidence of antibodies observed relates to the rather high assay cut-off point. Additionally, the immunogenicity data indicated that there was no impact on efficacy and safety. Results submitted indicate no difference in immunology compared to imiglucerase and velaglucerase.

The overall safety data are reassuring and allow a positive benefit-risk outcome. The immunogenicity of taliglucerase alfa will be closely monitored via post-authorisation measure stated in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Changes in the spleen and liver volume as well as haemoglobin and platelet counts including biomarkers are considered to be relevant and sensitive clinical favourable effects. Hypersensitivity, infusion reactions and immunogenicity are important unfavourable effects which can impact negatively on efficacy and safety with implications for compliance both in the short term and long term.

Benefit-risk balance

Clinically relevant changes in the spleen and liver volumes as well as haemoglobin, platelets and biomarkers were demonstrated which were statistically significant, sustained and consistent in all the studies. Changes appear to be comparable to historical data with velaglucerase.

Overall safety results indicate that taliglucerase was generally well tolerated with minor side effects usually resolved without the need for a major treatment. The most commonly observed symptoms of infusion-related reactions were headache, pruritus, and hypersensitivity. These can be usually managed by slowing the infusion rate or stopping and resuming treatment with decreased infusion rate. If a severe allergic reaction occurs, immediate discontinuation of the taliglucerase alfa infusion is recommended.

There were no unexpected effects and no serious adverse events were attributable to the product administered intravenously once every 2 weeks at doses up to 60 mg/kg. There were no deaths. The safety profile of taliglucerase alfa appears acceptable and overall comparable to that of standard ERT. The incidence of infusion related reactions appears somewhat lower. Accordingly, the benefits observed outweigh the risks involved with taliglucerase alfa and therefore, the benefit /risk balance is considered positive.

The conclusion on the positive risk-benefit balance of Elelyso by the CHMP is subject to following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (Draft Summary of Product Characteristics, section 4.2 in the latest version of the Product Information as submitted by the applicant but not adopted by the CHMP).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

However, the CHMP considered Elelyso to be similar to Vpriv for the same therapeutic indication and concluded that none of the derogations regarding orphan market exclusivity, as provided for by the Regulation (EC) No. 141/2000 apply and thus, recommended refusal of granting the marketing authorisation for Elelyso.

The grounds for refusal can be found here.

Discussion on the benefit-risk balance

The lack of a comparator arm in the pivotal study was compensated by the use of a dose control. No formal analysis of dose separation was planned. A post hoc dose separation analysis of the pivotal study as well as the extension study showed that after 9 and 12 months of treatment with taliglucerase alfa, a 60 U/kg dose resulted in a statistically better response than 30 U/kg dose for spleen volume and platelet count, but not however, for liver volume, haemoglobin, or chitotriosidase activity. Inconsistent results were obtained for the lowest dose of taliglucerase alfa 30 U/kg and the efficacy of this dose as starting dose was not acequated. Initiation of less effective treatment in this chronic progressive disease may have serious implications for the patient in the long-term. Therefore the 60 U/kg dose is the recommended starting dose and the 30 U/kg dose can only be considered for those patients who have achieved and maintained the therapeutic goals while treated with 60 U/kg. This is in line with the dose recommendations for velaglucerase. Infusion reactions did not appear to raise significant issues and were easily managed without treatment having to be discontinued in the majority of patients. The incidence of immunogenicity appeared to be remarkably low. The safety profile of taliglucerase seems acceptable but evaluation of the safety population is limited by the low number of patients exposed to taliglucerase alfa and the lack of sufficient long-term data, which will be provided via fulfilment of the agreed pharmacovigilance activities.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Elelyso is not similar to Zavesca within the meaning of Article 3 of Commission Regulation (EC) No. 847/200, but it is similar to Vpriv.

Derogations from market exclusivity

The CHMP by consensus is of the opinion that the following derogations from market exclusivity claimed by the applicant do not apply:

- for the derogation laid down in Article 8(3)(b) of Regulation (EC) No. 141/2000 that the marketing authorisation holder for Vpriv is unable to supply sufficient quantities of the medicinal product and

- for the derogation laid down in 8(3)(c) of Regulation (EC) No. 141/2000 that that the medicinal product, although similar to Vpriv, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Eleyso

- indicated for long-term enzyme replacement therapy for adults with a confirmed diagnosis of Type 1 Gaucher disease -

is favourable. However, the CHMP considers Elelyso to be similar to Vpriv for the same therapeutic indication and considers that none of the derogations regarding orphan market exclusivity, as provided for by the Regulation (EC) No. 141/2000, apply. Therefore, the CHMP recommends the refusal of granting the Marketing Authorisation for Elelyso (taliglucerase alfa).

The grounds for refusal can be found here.

Furthermore, the CHMP, in light of the negative recommendation, was of the opinion that it is not appropriate to conclude on the new active substance status at this time.