Assessment report

for

VPRIV

International Nonproprietary Name:

velaglucerase alfa

Procedure No. EMEA/H/C/001249

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shire Pharmaceuticals Ireland Ltd. submitted on 30 October 2009 an application for Marketing Authorisation to the European Medicines Agency for VPRIV, 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 Agency/CHMP on 25 September 2008.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

A - Centralised / Article 8(3) / New active substance.

The applicant applied for the following indication:

Long-term enzyme replacement therapy (ERT) for paediatric and adult patients with type 1 Gaucher disease.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

1.1.1. For new centralised dossiers orphan medicinal products

The applicant Shire Pharmaceuticals Ireland Ltd. submitted on 30 October 2009 an application for Marketing Authorisation to the European Medicines Agency through the centralised procedure for VPRIV, which was designated as an orphan medicinal product EU/3/10/752 on 09 June 2010. VPRIV was designated as an orphan medicinal product in the following indication: Treatment of Gaucher disease. The calculated prevalence of this condition was 0.3 in 10,000 persons EU population.

The applicant applied for the following indication: treatment of type 1 Gaucher disease.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of VPRIV as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

1.1.2. Information on paediatric requirements

Pursuant to Article 7, of Regulation (EC) No 1901/2006 the application included an Agency Decision (P/245/2009) for the following conditions :

- For Gaucher Disease, Types 1 and 3 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver;

- For Gaucher Disease, Type 2 on the granting of a (product-specific) waiver.

1.1.3. Information relating to orphan market exclusivity

1.1.3.1. Similarity

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

1.1.4. Licensing status:

A new application was filed in the following countries: USA, Canada

The product was not licensed in any country at the time of submission of the application.

VPRIV has been given a Marketing Authorisation in the United States of America on 26 February 2010.

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: **Harald Enzmann** Co-Rapporteur: **Kristina Dunder**

- The application was received by the Agency on 30 October 2009.
- Accelerated Assessment procedure was agreed-upon by CHMP on 22 October 2009.
- The procedure started on 23 December 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2010.
- During the meeting on 19-22 April 2010, 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 22 April 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 May 2010.
- Pre-approval GMP inspections of three sites responsible for the manufacture of VPRIV drug substance and drug product have been conducted:
  1. Shire Human Genetic Therapies, Inc. 205 Alewife Brook Parkway, Cambridge, USA (site responsible for active substance manufacture and storage), performed on 15th-17th June 2010;
  2. Eminent Services Corporation - 7495 New Technology Corporation, Frederick, MD, USA (site responsible for the storage of finished product unlabelled vials), performed on 18th June 2010;
  3. Cangene BioPharma Inc. (former Cheasapeake Biological Laboratories) - Baltimore, MD, USA (site responsible for the manufacture of the finished product), performed on 21-22 June 2010.
  The results of the 3 inspections were circulated on 23 June 2010.
- The Rapporteurs circulated the Initial Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 June 2010.
- The Rapporteurs circulated the Updated Joint Assessment Report based on the responses to the List of Questions and applicant's clarifications on 21 June 2010.
- During a meeting of a Biological Working Party on 15 June 2010, experts were convened to address questions raised by the CHMP.
- During the meeting on 21-24 June 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to VPRIV on 24 June 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2010.
- During the meeting on 21-24 June 2010, the CHMP adopted a report on similarity of VPRIV with Zavesca dated 11 June 2010.

2. Scientific discussion

2.1. Introduction

VPRIV (velaglucerase alfa) is intended for enzyme replacement therapy (ERT) in type 1 Gaucher disease.

Gaucher disease (GD) is a rare lysosomal storage disorder caused by mutations in the GBA gene, which encodes a lysosomal enzyme called β-glucocerebrosidase (GCase) that catalyzes the breakdown of glucosylcerebroside (GlcCer). The ensuing deficiency in GCase activity leads to intracellular accumulation of the substrate, GlcCer, primarily in macrophages. Because of the burden of GlcCer storage and the resulting macrophage activation, a number of pathological consequences arise, primarily in the spleen, liver, bone, lung, and brain.

There is a considerable degree of variability in the clinical signs and symptoms of GD. From a clinical perspective, GD has been classified into three subtypes:

- Type 1 (nonneuropathic)
- Type 2 (acute neuropathic)
- Type 3 (sub-acute neuropathic)

Type 1 GD is the most common subtype affecting an estimated 30,000 people worldwide, and patients display a wide range of symptoms, including splenomegaly, hepatomegaly, anaemia, thrombocytopenia, bone complications. Type 2 GD presents in infancy and is characterised by a rapid neurodegenerative course with widespread visceral involvement. Failure to thrive and stridor due to laryngospasm are commonly observed, and death due to progressive psychomotor degeneration occurs within the first 2 to 3 years of life. Type 3 GD presents around preschool age and is characterised by visceral and bony involvement, in addition to neurological symptoms such as abnormal eye movements, ataxia, seizures, and dementia. The neurological symptoms usually appear later in life, and patients may survive until their third or fourth decade.

Beside the palliative therapy, such as splenectomy, blood transfusions, and orthopaedic procedures, as well as occasionally bone marrow transplantation, there are currently two commercially available therapies for the treatment of GD.

- Imiglucerase is an Enzyme Replacement Therapy (ERT) which is approved as first-line therapy for Type 1 and Type 3 GD in the EU;
- Miglustat is a substrate reduction therapy (SRT), a glucosylceramide synthase inhibitor, which is approved as second-line therapy when ERT is not a therapeutic option.

The goal of these therapies is to reduce storage of GlcCer in affected tissues of GD patients. ERT achieves this by increasing GCase levels through administration of a macrophage-targeted recombinant GCase, while SRT lowers GlcCer levels by inhibiting the ceramide specific glucosyltransferase responsible for GlcCer biosynthesis.

Velaglucerase alfa , is a human GCase that is produced by gene activation in a human cell line. It is being developed as a long-term ERT for patients with type 1 Gaucher disease. It is secreted as a monomeric glycoprotein of approximately 63 kD containing 5 potential N-linked glycosylation sites, 4 of which are occupied. Regulatory and structural DNA sequences are inserted at specific upstream positions of the human GCase gene, thereby activating the endogenous human gene to produce velaglucerase alfa in a human cell line. Natural GCase is expressed as a highly sialyated glycoprotein that contains complex carbohydrate chains and is poorly internalised by phagocytic cells. Velaglucerase alfa is manufactured to contain predominantly high mannose-type-linked glycans. This high mannose form allows it to be effectively taken up by the phagocytic cells via mannose receptors. Velaglucerase alfa drug product is a lyophilised powder for solution.

The clinical development program comprised of several clinical studies enrolling a total of 113 patients with a confirmed diagnosis of type 1 Gaucher disease. Selection of dose and dose regimen has primarily been based on preclinical assessments. Patients with type 2 or type 3 Gaucher disease were excluded. The clinical programme studied treatment-naïve patients as well as patients transitioned from imiglucerase. Efficacy assessment for studies in treatment-naïve patients focused on

improvements in the Hgb, platelet count, and liver and spleen volumes. Efficacy assessment for patients transitioning from imiglucerase focused on maintenance of improvement obtained.

The claimed indication is:

VPRIV is indicated for long-term enzyme replacement therapy (ERT) for paediatric and adult patients with type 1 Gaucher disease.

The approved indication is:

VPRIV is indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

2.2. Quality aspects

2.2.1. Introduction

Velaglucerase alfa is a purified recombinant form of the naturally occurring human lysosomal enzyme glucocerebrosidase that cleaves glucocerebroside to glucose and ceramide. It is produced by gene activation technology in a human cell line. The deduced amino acid sequence of recombinant velaglucerase alfa is identical to the one based on the reported genomic sequence of human glucocerebrosidase.

VPRIV is the invented name of velaglucerase alfa drug product. VPRIV is a sterile preservative-free lyophilised powder presented in a glass vial and closed with a rubber stopper. The drug product is a lyophilised powder for solution presented in two strengths: 200U filled in a 5 mL vial and 400U filled in a 20 mL vial.

The final formulation of the drug product is 2.5 mg/mL velaglucerase alfa in 50 mM Na citrate, containing 5% sucrose and 0.01% vol/vol polysorbate 20, at pH 6.0 after reconstitution.

2.2.2. Active substance

Velaglucerase alfa is a glycoprotein, which belongs to the family of glycosyl hydrolases and hydrolyses the glycolipid glucocerebroside to glucose and ceramide.

It is produced by gene activation technology in an HT-1080 human fibroblast cell line and contains the same amino acid sequence as the naturally occurring human lysosomal enzyme glucocerebrosidase. The enzyme is expressed as fusion protein with the human growth hormone signal peptide which triggers secretion of the 523 amino acid polypeptide chain into the medium. Upon secretion, the signal peptide is cleaved resulting in a 497 amino acid chain identical to the protein backbone of naturally occurring glucocerebrosidase. The relative molecular mass of velaglucerase alfa is 63 kDa, of which the glycostructures constitute 7 kDa.

Velaglucerase alfa contains 5 potential N-glycosylation sites, one of which (N462) is unoccupied. Velaglucerase alfa contains predominantly high-mannose-type N-linked glycans facilitating the uptake of velaglucerase alfa into the macrophages via the mannose receptor. Two disulfide linkages are built near the N-terminus involving 4 cysteines whereas 3 further cysteines remain as free thiols.

2.2.2.1. Manufacture of the Active Substance

Cell Culture and Harvest

The cell culture process starts with a vial(s) of working cell bank (WCB) which is thawed and expanded in shaker flasks and single-use bioreactors before inoculation of the 500 L production bioreactor. After

inoculation of the production bioreactor, the culture is continuously perfused with growth media until the required cell density for production is reached.

After a defined cell density has been reached, the bioreactor is perfused with production medium. Harvests are collected then concentrated.

Purification

The velaglucerase alfa purification process consists of three subsequent orthogonal chromatographic steps followed by diafiltration and concentration steps. All columns are run in a bind/ elute mode.
The drug substance is frozen and stored at -65 to -85 °C.

The purification process is adequately described and proper in-process controls (IPCs) are set.

Control of critical steps

The manufacturing process controls are divided into operational and performance parameters and classified as critical, key or non-key.

- Critical Operational Parameter: An input process parameter that should be controlled within a meaningful, narrow operating range to ensure that drug substance quality attributes meet their specifications.
- Non-critical Operational Parameter: All input process parameters that fall outside the definition for critical operational parameter are non-critical. These parameters are divided into key and non-key parameters.
  - Key Operational Parameter: An input process parameter that should be carefully controlled within a narrow range and is essential for process performance. A key operational parameter does not affect critical product quality attributes.
  - Non-key Operational Parameter: An input process parameter that has been demonstrated to be easily controlled or has a wide acceptable limit.

Critical parameters are specified by acceptance ranges/ limits, whereas action limits are foreseen for key performance parameters. Acceptance ranges and action limits for the operational parameters have been identified in down-scaled runs, partly by design of experiment (DOE). However, several acceptance limits established for the commercial process were requested to be tightened as they were not considered sufficiently justified by the three validation runs. These will be addressed by the applicant as a post-authorisation commitment.
Down-scaled chromatography models were used for process characterisation, establishment of acceptance criteria for IPCs, spiking (to remove host cell DNA impurities) and recovery studies. Bioburden is controlled throughout the process by action limits at several process steps. The applicant commits to implement new acceptance criteria for the critical process intermediates bulk harvest and unpurified bulk within six months after approval.

The operational ranges for the key parameters identified for the cell expansion process, bioreactor growth and harvest collection phases are considered legally binding. Linear velocity and collection set points are also considered key operational parameters. Any changes of the respective operational ranges will be submitted as type II variation.

Three consistency runs were performed for cell culture and purification demonstrating that the process delivers drug substance of consistent quality when operational parameters are kept at the center values of the predefined ranges.

Control of materials

Compendial raw materials are employed where available. Non-compendial raw materials are tested according to respective in-house specifications. The recombinant human insulin used for cell culture is produced by yeast fermentation.
Filter and chromatographic resin materials used during the manufacture of velaglucerase alfa are purchased by qualified manufacturers. They do not contain any materials of animal origin.

2.2.2.2. Manufacturing Process Development

During velaglucerase alfa development, several manufacturing process changes were introduced. The material used in clinical phase I/ II was derived from a perfused bioreactor with serum-containing

adhesion cultures. From phase I/II to further clinical development, the commercial process was introduced being a serum-free suspension culture (i.e. all animal-derived components were removed).

In order to control consistency of product characteristics throughout process development up to the final stage of the manufacturing process comparability exercises were performed with representative lots of each stage:

Comparability of preclinical material and phase I/II material

No physicochemical comparability data have been provided of batches manufactured at this early stage of process development. Significant change with regard to product characteristics would normally not be expected as the main characteristics of the process potentially impacting the product characteristics, such as serum-based media and adherent culture were maintained.

Comparability of phase I/II and commercial material

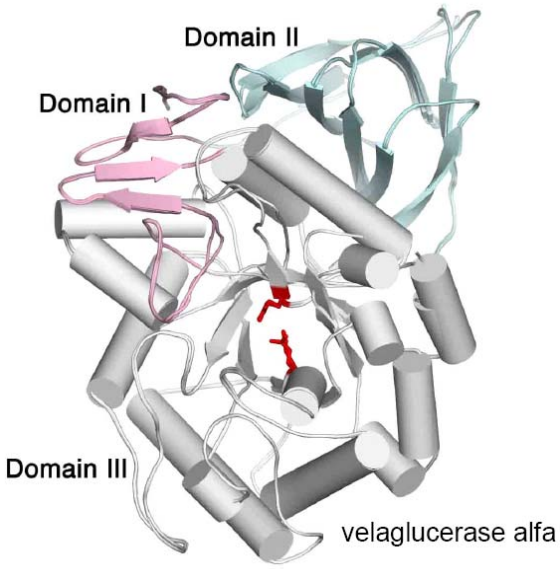
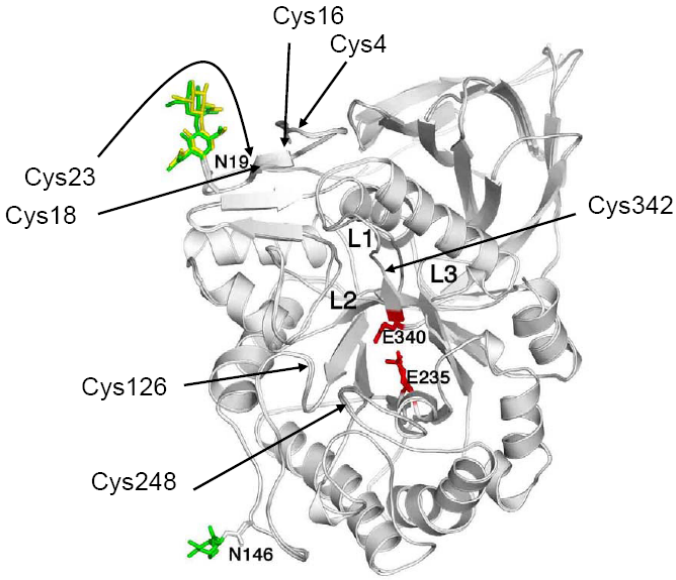
Comprehensive information has been provided to summarise the changes observed in product characteristics upon change from phase I/II material to initial commercial material. A subsequent change to the manufacture of commercial material was introduced and a comparability programme performed to support the change. No deviations were observed from any of the acceptance criteria set so comparability of the material is considered supported.

2.2.2.3. Characterisation

An extensive characterisation programme has been conducted mainly on reference standard lots. State-of-the-art analytical methods and additional high level methodological approaches were applied to gain insight into structural features of velaglucerase alfa.

The primary sequence was verified by combination of liquid separation with mass spectrometric detection. Absence of N- and C-terminal variability has been confirmed.

Secondary structure measurements confirmed that alfa helix and beta sheet represent the predominant structural elements in velaglucerase alfa. This finding has been supported by elucidation of the three-dimensional crystal structure. The studies revealed that velaglucerase alfa crystallises as a twin-molecule with each part consisting of three domains I, II and III. Domain III, the largest one contains the catalytic site. The crystal structure also confirmed two disulfide bonds in domain I derived from the close vicinity of the respective two pairs of cysteines in the crystal. Three remaining cysteines located at singular positions in domain III remain unpaired. In accordance with the results on secondary structural elements, velaglucerase alfa appears as an overall rigid molecule with particular short sections within the structure acting as flexible loops to allow necessary conformational arrangements for the catalytic site. These investigations are considered very valuable to understand the basic architecture of this molecule and verify a high level of purity of velaglucerase alfa.
The X-ray crystal structure of velaglucerase alfa has also been elucidated.

	
X-ray crystal structure of velaglucerase alfa Domain I, pink (residues 1-29 and 383-414); domain II, blue (residues 30-75 and 431-497) and domain III, grey (residues 76-381 and 416-430). Catalytic residues (Glu235, Glu340) are shown as red sticks at the centre of the molecule.	**Characteristics of velaglucerase alfa** Glycosylation sites detected in molecule A are shown in green. Three loops near the active site are labelled L1 (residues 345-350), L2 (residues 393-399) and L3 (residues 312-319). Free cysteines (Cys126, Cys248, Cys342) and disulfide linked cysteines (Cys4-Cys16, Cys18-Cys23) are also shown.

Of 5 potential N-glycosylation sites within the primary structure of velaglucerase alfa, 4 are occupied. The structural variability of N-glycans of velaglucerase alfa is limited, because of the company's strategy to retain as much N-glycans as possible in the premature oligomannose structure.

Overall glycosylation analysis is considered comprehensive taking into account the satisfactory responses to requests for clarification and verification of particular structural aspects The molecular weight of velaglucerase alfa has been characterised using a different analytical methods. Whereas standard methods such as Matrix assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) determined the non-glycosylated MW as 55.7 kDA and the glycosylated MW as ~63 kDa, methods that address the native molecule in solution (e.g. size exclusion HPLC (SEC) also including Multi-Angle Laser Light Scattering (MALLS), sedimentation velocity analytical ultracentrifugation detection (SV-AUC), sedimentation equilibrium analysis (SE)) revealed that the situation is more complex. The latter analytical methods indicated that molecular subfractions of velaglucerase alfa readily self-associate and re-dissociate. The extent of association depends on the protein concentration in solution. As a result the mean molecular weight is slightly elevated (up to 80 kDa) as compared to the monomeric MW of 63 kDa.

The biological activity of velaglucerase alfa has been addressed by enzymatic activity assays, a binding kinetics assay and *in-vitro* cellular (i.e. macrophages) uptake assays. Cellular uptake of velaglucerase alfa into macrophages ensuring delivery of the replacement enzyme to the lysosomes was verified. The data on biological activity are considered satisfactory.

Forced degradation studies have been conducted on velaglucerase alfa. At the same time the study served to demonstrate the stability indicating potential of the methods applied. Overall aggregation

and oxidation appear as the major susceptibility categories that may subsequently also impact biological activity. In this respect the Company is asked to provide further data supporting a potential correlation.

A comprehensive summary has been provided on potential impurities present in velaglucerase alfa arising from the process or product. Adequate control of these impurities is ensured by orthogonal analytical methods capable to detect the molecular variants where considered necessary.

2.2.2.4. Control of the Active Substance

Specifications

Velaglucerase alfa active substance is released according to defined release specifications.

The drug substance specification has been amended according to the various requests during the marketing authorisation procedure. References to the analytical methods were included for each test parameter. All analytical methods have been appropriately validated.

Release specifications for the drug substance include controls for appearance, peptide mapping, free thiol content, host cell protein, reversed phase HPLC, SDS-PAGE (Silver staining), size exclusion HPLC, cellular uptake bioassay, specific activity, protein concentration, bacterial endotoxin, bioburden, glycan mapping, osmolality, pH and polysorbate.

Drug substance specification will be re-evaluated in total on a data basis of additional commercial scale lots.
A number of acceptance limits have been tightened based on the currently available data base and these acceptance limits will be reconsidered again in the future when more data is available. Overall the presentation of method validation data is considered comprehensive and satisfactory.

Reference Standards

The reference standard has been qualified following batch release testing criteria and additional characterisation tests acceptance criteria including a comparison to the previous reference standard. A suitable procedure for future qualification of reference standards has been provided.

2.2.2.5. Stability of the Active Substance

The shelf life was established based on data from commercial process batches. 36 months of stability studies have been completed for 3 clinical lots of velaglucerase alfa drug substance. Further 9 – 12 months data are available of ongoing stability studies on several additional lots. Similarly 6 months data are available for the 3 process validation lots.
The submitted stability data support the proposed shelf life of 36 months at long term storage conditions between -65 and -85°C.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules of Governing Medicinal Products in the European Union), any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.2.6. Adventitious Agents

Multiple levels of control have been established throughout the velaglucerase alfa manufacturing process to minimize the risk of microbial or adventitious virus contamination. Testing of the cell banks and routine testing of the unprocessed bulk as proposed by the applicant is deemed sufficient.

For cell culture no animal derived material is used. The virus reduction data presented by the applicant show that the purification process contains several steps, which are considered effective for eliminating potential viral contamination. For some model viruses (Bovine Diarrhoea Virus (BVDV), Porcine Parvovirus (PPV)) the column steps only contribute moderately to virus clearance, however nanofiltration has been shown to be an effective step. The company has committed to add to the virus validation studies for one of the column steps.

2.2.3. Finished Product

The drug product VPRIV is a sterile lyophilised powder presented in the two strengths of 200U and 400U per vial corresponding to 5mg and 10 mg drug substance, respectively. The drug product is composed of velaglucerase alfa and the excipients sucrose, citrate buffer pH 6.0 and polysorbate 20. The concentration of the excipients is identical for both strengths:

Velaglucerase alfa drug product composition

Names of ingredients	Nominal content per 200U/vial	Nominal content per 400U/vial	Function	Reference to standards
Velaglucerase alfa	5 mg (200Unit)	10 mg (400Unit)	Active ingredient	In-house monograph
Sucrose	100 mg	200 mg	Lyoprotectant	NF, Ph Eur
Sodium citrate, dihydrate	25.88 mg	51.76 mg	Buffer salt	USP, Ph Eur
Citric acid, monohydrate	2.52 mg	5.04 mg	Buffer salt	USP, Ph Eur
Polysorbate 20	0.22 mg	0.44 mg	Stabilizing agent	NF, Ph Eur

The container closure system consists of Ph.Eur. type I glass vials and butyl rubber stoppers with a fluoro-resin coating.

Prior to use, the lyophilised powder is reconstituted by addition of 2.2 ml (200U) or 4.3 ml (400U) of WFI to enable withdrawal of a nominal volume of 2 or 4 ml, respectively, containing 2.5 mg protein per mL. The reconstituted drug product is further diluted in 0.9% sodium chloride prior to application. Considering the recommended dose of 60 U/kg, several vials are needed for one administration which is applied every other week as a 60-minute intravenous infusion. The components of the drug product solution are demonstrated to be suitable to ensure sufficient velaglucerase alfa stability in the liquid as well as the lyophilised product. All clinical studies were performed with VPRIV drug product formulation as intended for commercial production.

2.2.3.1. Manufacture of the Finished Product

The production process consists of formulation, sterile filtration, filling and lyophilisation procedures. Suitable IPCs are introduced and their action limits or acceptance criteria are considered justified and adequate. The set-points of the operational parameters for the compounding step were adequately evaluated by appropriate process development studies. The acceptable ranges of the critical parameters of the lyophilisation process were confirmed by using design of experiment (DOE) in a lab-scale lyophiliser. Furthermore, the loading of the manufacturing lyophiliser, the holding times during drug product processing, the duration of the lyophilisation steps and the overall maximum process time from start via sterile filtration to the completion of fill were evaluated at commercial scale with regard to velaglucerase alfa stability and are considered justified.

The process validation approach including the number and the size of the validation batches chosen is in accordance with the EU requirements. All validation batches complied with the established in-process and release specifications as well as additional process monitoring data. Based on the results the commercial manufacturing process of VPRIV 200U/vial and 400U/vial can be considered validated.

2.2.3.2. Pharmaceutical Development

Comparability studies were performed to support slight process modifications implemented during VPRIV finished product development. The studies confirm comparability for 400U/vial before and after process modification and demonstrate no significant difference between drug product quality of 400U/vial and 200U/vial at release and under stress conditions after process adaptation. All batches used in the pivotal clinical studies were produced according to the commercial production process.

2.2.3.3. Control of the Finished Product

Specifications

The drug product release specification have been defined.

Release specifications for the drug product include controls for appearance, SDS-PAGE (Western), Reversed Phase HPLC, Size Exclusion HPLC (SE-HPLC), specific activity, content uniformity, bacterial endotoxin, sterility, moisture content, osmolarity, particulates, pH, polysorbate.

In general, the drug product release specification is considered adequate to control drug product quality. As required, a test for quantity of velaglucerase alfa and a specification limit for the SE-HPLC impurity peak was added to the testing programme. The Company commits to re-evaluate the specification limits when more batch data are available. The test methods are either identical to the procedures used for drug substance analysis or comply with the Ph. Eur. For the colorimetric activity assay, historical data will be evaluated and/or additional studies will be performed as a post-authorisation commitment to provide required precision for drug product analysis in the presence of sucrose. Identity testing in drug product analysis was adequately validated. Totally, release results of 19 drug product batches have been presented which all met the drug product specification.

13 drug product batches were used in the pivotal clinical studies. The impurity profiles of these batches have been evaluated retrospectively, in particular the product-related proteins. The MAH confirmed that the batches used in the clinical studies had been stored for about 24 months prior to use. Taking into account the trend in the impurity profile that had been observed during stability studies together with the method impreciseness calculated it is considered proven that drug product batches with an amount of up to the maximum impurity limits were used in clinical trials. In consequence, the amounts of product-related proteins are deemed qualified up to their specification limits.

2.2.3.4. Stability of the Finished Product

Stability studies have been conducted with clinical and validation batches. Drug substance from the previous and current processes were used for production of the drug product stability batches.

The design and testing program of the stability studies are acceptable. A re-evaluation of the acceptance criteria of the shelf life specification is requested as post-authorisation commitment.

The long-terms stability data are considered adequate to support a shelf life of 36 months for VPRIV 400U/vial. For VPRIV 200 U/vial, a shelf life of 18 months at 5±3°C is acceptable based on the updated stability data.
Stability data of studies under accelerated and stress conditions demonstrate a decrease of the main peaks after HPLC analysis over the time. ConcomitantSE-HPLC impurity peaks increase, whereas no significant change of the amount of aggregates was observed. Photodegradation of VPRIV can be prevented by storage of the vials in the outer package as confirmed by appropriate photostability studies.

A post approval stability protocol is provided. The parameters and their acceptance criteria are identical to the proposed drug product shelf life specification. Stability studies after approval will be only conducted at storage temperature of 5 ±3°C.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules of Governing Medicinal Products in the European Union), any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Conclusions:
The proposed drug product shelf lives are 36 months for the 400 U/vial and 18 months for the 200 U/vial at the long term storage condition of at 5±3°C, as supported by the available stability data.

In-use stability
Drug product stability after reconstitution and dilution with sterile WFI was evaluated, also about the end of shelf life. The following storage instructions are included in the SmPC:
'Chemical and physical in use stability has been demonstrated for 24 hours at 2°C to 8°C under protection from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and must not exceed 24 hours at 2°C to 8°C.'

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Adequate information regarding the manufacturing process of the drug substance was provided by the applicant. The used human cell line was sufficiently characterised and is considered suitable for the production of velaglucerase alfa. The three validation/conformance batches at commercial scale for cell culture and purification support the consistent performance of the drug substance manufacturing process when the critical and key operational parameters are met at the center values of the proposed acceptable ranges. Thus, the validation of the whole ranges of acceptance criteria is considered supported by the results of the down-scale process characterisation studies. The classification of some operational parameters as "key" was confirmed by the Company as well as the introduction of bioburden rejection limits at distinct steps.

Characterisation of velaglucerase alfa was performed at a high level yielding valuable insights into the structural features of the molecule and thus a satisfactory detailed picture on the nature of velaglucerase alfa. Further clarification on the various association states in solution including potential distinction between these stages was hampered by the limited stability of these fractions towards sample handling procedures. Drug substance batches produced by the commercial process displayed consistent velaglucerase alfa quality well in accordance with the proposed specifications. Analytical procedures used for lot release and the corresponding validation reports are considered adequate and the necessary clarification required in this respect was provided with sufficient detail. A shelf life of 36 months at long term storage conditions can be supported based on satisfactory stability data.

Multiple levels of control have been established throughout the velaglucerase alfa manufacturing process to minimize the risk of microbial or adventitious virus contamination. For cell culture no animal derived material is used. Testing of the cell banks and routine testing of the unprocessed bulk as suggested by the applicant is deemed sufficient. Virus reduction data show that the purification process contains several steps, which are considered effective for eliminating potential viral contamination. Although for some model viruses (BVDV, PPV) the column steps only contribute moderately to virus removal, the overall strategy for virus clearance is deemed adequate, as nanofiltration has been shown to be an effective step.

Information on the development of the drug product has been presented in a satisfactory manner. The manufacturing process was demonstrated to be sufficiently under control to consistently produce drug product of the defined quality. Based on the analytical procedures applied, the tests carried out at drug product release confirmed consistent product quality. For bioburden prior to sterile filtration a rejection limit has been defined. The impurity profiles of all batches used in the pivotal clinical studies were evaluated. Based on these data evidence is provided that drug product batches with an amount of up to the maximum limit for impurities had been used in clinical trials. Thus, the product-related impurities determined by use of SE-HPLC are considered as being qualified at their specification limits. Based on stability data provided so far, no significant drug product instability can be observed. A shelf life of 36 months (400 U vial) and 18 months (200 U vial) is justified. Furthermore, it was demonstrated by appropriate tests, that photodegradation of velaglucerase alfa drug product can be avoided by storage in the outer package.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In general, the development, manufacture, characterisation and control of drug substance and drug product as described in the quality dossier, Modules 2.3 and 3, are considered adequate to produce velaglucerase alfa of sufficient quality in a consistent manner. With regard to virus safety the overall strategy as described by the applicant is considered adequate.
All quality concerns identified during the assessment of the dossier have been solved by the Company satisfactorily. Quality follow-up measures have been identified and are listed in section 2.11.

2.2.6. GMP compliance

Pre-approval GMP inspections of three sites responsible for the manufacture of VPRIV drug substance and drug product have been conducted:

- *Shire Human Genetic Therapies, Inc. 205 Alewife Brook Parkway, Cambridge, USA* (site responsible for active substance manufacture and storage).
A pre-approval inspection of this site with focus on locations used for velaglucerase alfa production was requested as parts of this manufacturing plant were not covered by the last routine inspection. This inspection took place on took place on 15-17 June 2010 and the site was found to be in compliance with EU GMP.

- *Eminent Services Corporation - 7495 New Technology Corporation, Frederick, MD, USA* (site responsible for the storage of finished product unlabelled vials). This inspection took place on 18th June 2010 and the site was found to be in compliance with EU GMP.

- *Cheasapeake Biological Laboratories (CBL) - Baltimore, MD, USA (*site responsible for the manufacture of the finished product).
A pre-approval inspection was considered necessary for this site, as the lyophilisation process intended for the VPRIV drug product production was not covered by the recent inspection. This inspection took place on 21 – 22 June 2010 and the site was found to be in compliance with EU GMP pending submission and assessment of an appropriate corrective action plan by the manufacturer. The manufacturer has committed to submit the appropriate corrective action plan and the MAH committed to ensure that the corrective action plan will be implemented by 30 September 2010.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-neuronopathic Gaucher disease (GD) is characterized by an enzymatic deficiency to biodegrade glucocerebrosides. The cell population mostly affected by this deficiency are macrophages which accumulate glucocerebrosides derived from cell membranes of phagocytosed cells and turn thereby into so called Gaucher cells or storage cells. Velaglucerase alfa is a biotechnologically generated β-glucocerebrosidase, engineered to be taken up via the mannose-receptor of macrophages after IV administration. Velaglucerase alfa is the third in a line of enzymes designed as therapy for this disease after alglucerase and imiglucerase. Velaglucerase alfa is structurally similar to imiglucerase.
Preclinical development programme for velaglucerase alfa is aimed to support the use of this product for the treatment of GD and consists of pharmacodynamic, pharmacokinetic and toxicological studies.

2.3.2. Pharmacology

The pharmacology programme is limited but considered to be adequate for this type of product, i.e. recombinant endogenous enzyme.

2.3.2.1. Primary pharmacodynamic studies

A mouse model of Gaucher disease (D409V/null Mouse) was used to compare the effect of velaglucerase alfa with imiglucerase. This animal model was chosen because it has features similar to human type 1 Gaucher disease (GD), namely accumulation of "storage cells" (glucocerebroside-laden macrophages) in the lung, liver and spleen early in the pathogenic process, and a lack of pathology in the brain.

Three separate studies (751-1U0-09 1222, -1223, -1224) were conducted, using essentially similar protocols but different enzyme doses (5, 15 and 60 units/kg, respectively). Animals were dosed intravenously with velaglucerase alfa, imiglucerase or saline once a week for 4 or 8 weeks. The measured endpoints included tissue accumulation of glucosylceramide (GC) in several visceral organs and presence of lipid-laden macrophages (storage cells), since these are among the earliest defects observed in human GD, and are thought to be causative of later disease sequelae. Wild type mice were used as controls.

The D409V/null mouse appears to be a relevant animal model of GD type I (non-neuronopathic GD). In this animal model, two characteristics of GD, elevated glucocerebroside levels in the liver and spleen, and appeareance of storage cells (Gaucher cells) in the liver, were effectively counteracted at doses even much lower than the clinically intended one. Furthermore, velaglucerase alfa and imiglucerase act similarly and comparably in this animal model. This series of experiments provides a reasonable proof that velaglucerase alfa has similar effects *in vivo* as imiglucerase. However, no conclusions about the long term efficacy can be drawn. The CHMP requested information on the exact procedure for the determination of the number of storage cells in various tissues and on the processing of histological slides and the additionally provided information was considered satisfactory. Data on binding of imiglucerase to the isolated recombinant human mannose receptor in the same experimental setting were also requested with the view to examine whether there is a difference between velaglucerase alfa and imiglucerase in binding behaviour to the mannose receptor. It was acknowledged that due to the artificial *in vitro* test system, non-physiological binding between the soluble receptor molecules and mannose residues of enzyme immobilized in high density onto a surface might occur. Effective cell uptake of velaglucerase alfa has been shown before in a cell based assay. Animal data with a mouse model of Gaucher disease (D409V/null mouse) have shown that velaglucerase alfa activity *in vivo* is overall indistinguishable from activity of imiglucerase. Clinical data as well have demonstrated efficacy of velaglucerase alfa. Therefore, the apparently lower affinity between the human mannose receptor and velaglucerase alfa compared to imiglucerase suggested by the *in vitro* binding data is considered to be of little relevance and superseded by *in vivo* animal and clinical data.

2.3.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed. This approach was based on ICH S7A Guidance, Safety Pharmacology Studies for Human Pharmaceuticals. Considering the high similarity between velaglucerase alfa and imiglucerase and due to the clinical and preclinical experience with imiglucerase, the conduct of secondary pharacodynamics studies is considered dispensable.

2.3.2.3. Safety pharmacology programme

No separate safety pharmacology studies were conducted but cardiovascular safety was evaluated in a 6-month rhesus monkey toxicity study (TKT-1U0-00-003). The animals received doses of up to 15 mg/kg i.v. every other week. ECG examinations were performed prior to the study and during weeks 12 and 24 (on a non-dosing day), and from recovery animals during week 28. The ECGs were recorded and qualitatively evaluated.

Examination of the ECGs from all monkeys at the pre-study, week 12, 24 and 28 time-points did not reveal any velaglucerase alfa related effects on ECG parameters (PR, QRS and QT intervals) including any evidence of QTc prolongation or abnormalities in waveform morphology or heart rhythm. In addition, there were no adverse effects on clinical chemistry, heart weight, or macroscopic/microscopic findings in the heart related to velaglucerase alfa. In this study, IV bolus doses up to 17 mg/kg, i.e., 11-fold the highest anticipated clinical dose (1.5 mg/kg; IV infusion) did not have any effects on the cardiovascular system of rhesus monkeys.

Core batteries of CNS and respiratory safety measurements were not addressed as endpoints in general toxicity studies or as dedicated studies. However, in all of the general toxicity or developmental and reproductive toxicity studies conducted, no clinical observations of velaglucerase alfa -related effects on cardiovascular, CNS or respiratory parameters were noted. It is therefore acceptable that no separate safety pharmacology studies are considered necessary.

2.3.2.4. Pharmacodynamic drug interactions

No specific pharmacodynamic drug interaction studies were performed. Due to the clinical and preclinical experience with imiglucerase no pharmacodynamic interaction studies for velaglucerase alfa are considered necessary.

2.3.3. Pharmacokinetics

All pharmacokinetic studies used the intravenous route. Single dose pharmacokinetic parameters, e.g. absorption patterns, were determined in rats and dogs and multiple dose measurements were made as a part of the 6-months repeated dose toxicity study in rhesus monkeys. Combined distribution and excretion were studied in the rat. In addition, pharmacokinetic studies in rats and rhesus monkeys were conducted to assess the comparability of velaglucerase alfa produced in roller bottle and bioreactor cell cultures. Overall, the extent of the nonclinical pharmacokinetic programme is adequate; no metabolism studies were conducted, which is acceptable for this kind of product.

Three methods were used for determination of the kinetics of velaglucerase alfa: determination of enzyme activity, radiochemical labelling and detection of velaglucerase alfa, and the detection of anti-velaglucerase alfa antibodies in serum.

After single dose IV administration, serum elimination followed 1st order kinetics in rats at all doses tested (based on determination of enzymatic activity). In dogs at the low dose 1st order kinetics were observed as well, but at the high dose 1st order elimination kinetics were observed starting 20 minutes post administration. After repeated dose IV administration every other week in Rhesus monkeys, serum elimination followed 1st order kinetics at all doses tested. Whereas C_{max} was dose proportional, AUC increased more than in a dose-proportional manner in all three species.

Two distribution studies (TKT-1U0-01-001 and -008) with ^{125}I-labelled velaglucerase alfa were conducted in S-D rats. The animals were given bolus IV injections at nominal doses of 1 and 10 mg/kg

(3-5 µCi/ animal), collecting tissue samples at various time points and determining radioactivity by liquid scintillation spectroscopy. Only 6% of the radioactivity is found in the blood. Other tissues with high initial ^{125}I (velaglucerase alfa)-concentrations at this dose are lungs, spleen bone marrow and kidneys. If a ten times higher dose (10 mg/kg) is administered, the portion distributed to the liver is reduced from 70% to 24 %, whereas at this high dose the portion found in the blood is increased from 6% to 38%. Such pharmacokinetic behaviour indicates a saturation of an uptake mechanism, which is in agreement with saturation of the assumed mannose-receptor mediated uptake mechanism.

Serum half-life of velaglucerase alfa was determined to be in the range of minutes (based on determination of enzymatic activity). At the low dose a serum half-life from 2.3 to 3.6 minutes (rats) to 4.0 to 4.7 minutes (monkeys) was calculated. At higher doses, longer serum half-lives were observed, with a maximum value of 11 minutes determined in monkeys at a 20 fold higher dose. In Cynomolgus monkeys a serum half-life of 7-8 minutes has been reported in the Cerezyme EPAR. Therefore, pharmacokinetics in plasma appears to be comparable between velaglucerase alfa and imiglucerase.

Regarding tissue elimination in the rat (determined using radiolabelled velaglucerase alfa), a terminal half-life of about 17 hours for the liver and 13 hours for the spleen was calculated. Due to these terminal tissue-half-lives and due to the protein nature of velaglucerase alfa, accumulation of velaglucerase alfa in humans with IV administration every other week is therefore not expected to occur.

Radioactivity of ^{125}I-radiolabelled velaglucerase alfa in the rat was nearly completely excreted via urine within 48 hours post IV administration.

No pharmacokinetics interaction studies were submitted and this is considered acceptable for this type of product.

2.3.4. Toxicology

Velaglucerase alfa was tested in a series of toxicology studies using bolus IV dose administration. These studies included an acute study, 3- and 6-month studies in Sprague Dawley (S-D) rats, and a 6-month study in rhesus monkeys. All studies in the toxicology program were conducted according to current Good Laboratory Practices (GLP) unless indicated.

Toxicology Program for Velaglucerase alfa

Study Type/ Duration	Study Number	Species	Number	Dose Levels (mg/kg)
Single-dose toxicity	**TKT-1U0-00-004**	S-D rat	5/sex/group	0,1.1, 5.7, 23
Repeat-dose toxicity				
3 months	**TKT-1U0-00-005**	S-D rat	5/sex/group	0,0.84, 3.4, 17
6 months	**TKT-1U0-00-006**	S-D rat	10/sex/group	0, 0.84, 3.4, 17
6 months	**TKT-1U0-00-003**	Rhesus monkey	5/sex/group	0, 0.84, 3.4, 17
Reproductive and developmental toxicity				
Male fertility	**SHGT-1U0-06-010**	S-D rat	25 M/group	0, 1.5, 5, 17
Fertility and early embryonic development	**SHGT-1U0-06-011**	S-D rat	25 F/group	0, 1.5, 5, 17
Embryo-fetal development	**SHGT-1U0-06-013**	S-D rat	25 F/group	0, 1.5, 5, 17
Embryo-fetal development	**SHGT-1U0-06-015**	NZW rabbit	23F/group	0, 1.5, 10, 20

Prenatal and postnatal development, including maternal function	**SHGT-1U0-06-016**	S-D rat	25/sex/group	0, 15. 5, 17
Other studies				
Histamine/Complement release (non-GLP)	**SHGT-1U0-06-017**	S-D rat	4M/group	17
Local tolerance and antigenicity were evaluated in Study Nos. **TKT-1U0-00-005, TKT-1U0-00-006**, and **TKT-1U0-00-003.**				

2.3.4.1. Single dose toxicity

In the single dose toxicity study TKT-1U0-00-004, the animals received a single bolus IV dose of velaglucerase alfa via the tail vein and were sacrificed on either Day 2 or Day 15. Toxicological evaluations included mortality, clinical observations/physical examinations, body weight, clinical pathology, organ weights, gross necropsy, and histopathological examinations. The study revealed no specific toxicity up to the highest dose tested 20 mg/kg bodyweight (corrected to 23 mg/kg). However, some experimental shortcomings were identified. Due to an incidental clotting of blood samples on day 2, three animals/group/sex were additionally included in the study to replace the lost animals. Based on the information provided, the CHMP concluded that the inclusion of the additional animals seems to be acceptable in order to avoid unnecessary replication of the study, which is also favourable from the animal welfare perspective. The results upon physical examination, body weight, body-weight gain and organ weight gain were not affected. Although the statistical impact of the haematology and coagulation parameters after 24 hours may be affected, it is acknowledged that these parameters were also obtained in the repeated dose toxicity studies with no specific findings and, thus the matter does not raise further concern.

2.3.4.2. Repeat dose toxicity (with toxicokinetics)

The repeated dose toxicity studies were performed in rats and monkeys for up to 6 months duration and an additional recovery period. Velaglucerase alfa was administered every second week via a bolus IV route. Details of the repeat toxicity studies and summary of the results are presented in the table below.

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg b.w./ twice weekly)	Major findings
TKT-1U0-00-005	SD Rat/♂♀/10	0, 0.84 3.4, 17 mg/kg b.w., IV, twice weekly, Lot (RE200-001)	3 months	17 mg/kg b.w.	No death, **0.75 mg/kg:** serum urea nitrogen ♂↓, serum albumin ♂↑, antibody formation (7/10) **3 mg/kg**: facial swelling (1 ♂) serum albumin ♂↑ , serum urea nitrogen ♂↓, serum albumin ♂↑, antibody formation (6/10) **15 mg/kg:** facial swelling (♂ 5/5, ♀2/5), swollen paws (♂ 4/5, ♀5/5), serum urea nitrogen ♂↓, ♂ pH ↑ ,antibody formation (1/10), no further treatment related changes except injection side reactions in all groups

TKT-1U0-0006	SD Rat/♂♀/ **0, 3.4, 17 mg/kg b.w.: 10/group,** **0.84 mg/kg bw: 5/group**	0, 0.75, 3.0, 15 mg/kg b.w., IV every 2 weeks. Two different lots of drug substance (RE200-001 and RE200-02)	6 months (24 weeks) 4 weeks recovery	17 mg/kg	1 death, 1 animal euthanized "in extremis", **0 mg/kg:** swollen paws/muzzle or red paws/muzzle (15/20 at dose No. 13) etc., urine blood 1 ♂ 1 ♀ (week 24), 1 ♀ (week 28), antibody formation (1/20) **0.84 mg/kg:** swollen paws/muzzle or red paws/muzzle (9/10 at dose No. 13) etc. ; Clinical Biochemistry: [Ca^{2+}]♀ ↑ (week 25); urine (blood): 1 ♂, 1 ♀ (week 24), 1 ♀ (week 28); antibody formation at week 24 (5/10) **3.4 mg/kg**: 1 ♂ death (day 169 after blood sampling), swollen paws/muzzle or red paws/muzzle etc., (19/20 at dose No. 13), convulsion (3/20 day 43, 85 and 85); Haematology: LUC ♂↑ (week 25), MONO ♂ ↓ (week 29), WBC ♂ ↓ (week 29), BASO ♀↑ (week 29) ↑ Clinical Biochemistry: [Na^{2+}] ♀↑ (week 25), GLU ♀↑, urine (blood): 6 ♂ , 1 ♀ (week 24) , 1 ♀ (week 28); antibody formation at week 24 (13/20) **17mg/kg:** 1 ♂ death (day 1, animal replaced), 1 ♂ euthanized (day 29), swollen paws/muzzle or red paws/muzzle (15/20 at dose No. 13), etc., haematology: APTT ♀ ↑ Clinical Biochemistry: TRI ♂ ↓ (week 25), [Cl^-]♀ ↑ (week 25), [Na^+]♀ ↑ (week 25) [Ca^{2+}]♀ ↑ (week 29), blood in urine 1 ♀ (week 24) 1 ♀ (week 28); antibody formation at week 24 (10/19)
TKT-1U0-00-003	Monkey/rhesus/♂♀/ **0, 3.4, 17 mg/kg bw: 5/ group, 0.84 mg/kg: 4/group**	0, 0.84, 3.4, 17 mg/kg bw., i.v., twice weekly two different lots of drug substance (RE200-001 and RE200-02)	6 month, 4 weeks recovery	17 mg/kg	No death, no substance related changes, **17 mg/kg b.w :** antibody formation with no correlation to decrease in AUC values

In the rat studies of 3 months (TKT-1U0-00-005) and 6 months (TKT-1U0-00-006), the main findings were transient swelling of paws, limbs and muzzle that occurred shortly after the injections administration and disappeared within 24 hours. In the 3-month rat study TKT-1U0-00-005, formation of antibodies against the administered substance was observed in some animals, whereas in the second rat study TKT-1U0-00-006, antibodies against the test substance were detectable in all dosing groups.

In study TKT-1U0-00-005, a decrease in the serum urea nitrogen concentration was observed in all male treatment groups. This was accompanied by an increase in serum albumin concentration in the low and mid dose group males and an increase in pH values in males in the high dose group. These effects may indicate a possible effect on the glomerular filtration rate and since no structural changes of the kidney histology were reported, no significant damage of the kidney is expected.
The observed signs of swelling and reddening appeared to be histamine-mediated antigen reactions. In blood samples on day 169 no increase of histamine values could be detected in the 6 month rat study. Contrary to this, in the additional non-GLP rat study SHGT-1U0-06-017 on histamine release and complement activation, a marked histamine release was observed 15 minutes post dose administration,

whereas complement activation did not occur. Therefore, the mechanism remains unclear; histamine release seems a likely cause but was not found in the repeat-dose toxicity study. Hypersensitivity and infusion related reactions are clearly stated in section 4.4 of the SmPC and the overall clinical relevance is minor.

In study TKT-1U-00-06, less frequent laboured breathing, reduced activity and/or lateral decumbency were observed in all groups including vehicle control. Convulsions were observed in 3 animals of the mid dose group only. In general, these effects were less frequent and less severe in the vehicle control and in the low dose groups. It remains unclear why these reactions are only apparent in this study, since the identical formulation was tested in the other rat repeated dose toxicity study but no such effects were reported. Nevertheless, the prediction of animal models for immunogenicity in humans is low and no such effects were reported in the repeated dose toxicity study in monkeys. Body weight, food consumption and ophthalmoscopic parameters appear to be unaffected. Statistical significant differences in haematology and clinical biochemistry parameters between treated and control groups were considered to be incidental and with no toxicological implication. A dose related reduction of total triglycerides was observed in the high dose group males. A statistically non significant increase in the other dosing groups seems to be apparent, but without a toxicological significance.

In the repeated dose toxicity study TKT-1U0-00-003 in monkeys, animals received slow (1 to 2 minutes) bolus IV injections of velaglucerase alfa every 2 weeks via a cephalic or saphenous vein (total of 13 doses). An antibody formation in the high dose group has been detected. Since velaglucerase alfa is a protein of human origin, this is an anticipated effect and considered to be not adverse. During the course of the study a reduction of AUC and C_{max} was observed, but no correlation to antibody formation could be established. Additional findings were elevations in LDH, AST, and, to a lesser extent, ALT, that occurred sporadically throughout the study. These findings are not judged severe enough to demand additional primate studies. Overall, the analytical methods and statistical analyses used in these trials are considered adequate. Nevertheless, a cell-based assay addressing the potential hindrance of cellular uptake by neutralising anti-drug antibodies will be developed and validated via a Follow-up measure as agreed with the CHMP.

In terms of the assessment of toxicokinetics, estimations of safety factors on a mg/kg b.w. basis and based on the surface area (mg/m^2) were provided. The high dose (17 mg/kg) in the repeated dose toxicity studies represents an 11-fold safety margin to the intended maximal human dose (60 U/kg).The safety margins with 1.8 to 3.7 calculated for the Human Equivalent Dose (HED) are considered rather low, however, since no relevant toxic effects could be detected within the toxicity studies, the low safety margin is considered acceptable. In addition, the AUCs were compared with the human value obtained in study TKT025 after multiple administration of the maximum clinical dose of 60 U/kg b.w. The animal to human factor was calculated to be between 0.45 to 0.18 times.

2.3.4.3. Genotoxicity

Studies on the genotoxicity of velagucerase alfa have not been performed in accordance with the Guideline ICH S6 stating that classical genotoxicity testing does not provide an appropriate testing model and these substances are not expected to interact directly with DNA or chromosomal material.

2.3.4.4. Carcinogenicity

Studies on the carcinogenic potential have not been performed. This is in line with the ICH S6 guideline stating that standard carcinogenicity studies are generally considered inappropriate for biotechnology-derived pharmaceuticals. The CHMP concluded that the rational for omitting carcinogenicity studies with velaglucerase alfa is acceptable.

2.3.4.5. Reproduction Toxicity

Reproductive toxicity studies have been performed in rats (fertility, embryo-foetal development and pre- and postnatal development) and rabbits (embryo-foetal development) in accordance to GLP and ICH recommendations. Embryo-foetal developmental studies were preceded by dose range studies in both species. The following table provides an overview on the studies conducted including major findings in the parent and F1-generation as well as the corresponding NOAELs:

Study type/ Study ID	Species; Number treated	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
Male fertility SHGT-1U0-06-010	rat CD [Crl:CD (SD)] 25	IV 0, 1.5, 5.0, 17.0 mg/kg	4 weeks before and throughout mating; twice weekly	MD + HD: swollen limbs/paws, swollen face/lips, red discolored ears/limbs → transient, not seen on treatment free days HD: ↓ in fertility and fecundity (84% vs 96% in control, LD and MD group)	F0: general toxicity: 1.5 mg/kg; F0: ♂ fertility + fecundity: 5 mg/kg F1: 17 mg/kg
Female fertility SHGT-1U0-06-011	rat CD [Crl:CD (SD)] 25	IV 0, 1.5, 5.0, 17.0 mg/kg	2 weeks before mating until gd 13; twice weekly before + during mating, gd 0, 3 + 7;	MD + HD: swollen limbs/paws, swollen face/lips, red discolored ears/limbs → transient, not seen on treatment free days	F0: general toxicity: 1.5 mg/kg; F0: ♀ fertility + fecundity: 17 mg/kg F1: 17 mg/kg
Embryo-fœtal development SHGT-1U0-06-013	rat CD [Crl:CD (SD)] 25	IV 0, 1.5, 5.0, 17.0 mg/kg	gd 6, 9, 12, 15, 17;	MD + HD: swollen limbs/paws, swollen face/lips; in MD only in few animals → in MD + HD transient, not seen on treatment free days	F0: general toxicity: 1.5 mg/kg; F1: 17 mg/kg
Embryo-fœtal development SHGT-1U0-06-013	rabbits NZW Hra: (NZW) SPF 23	IV 0, 1.5, 10.0, 20.0 mg/kg	gd 6, 9, 12, 15, 18;	1 HD impaired limb function during treatment, euthanized in extremis gd 13; 1 LD found dead on gd 23; HD: sign. lower food consumption but without any effect on body weight	F0: general toxicity: 17 mg/kg; F1: 20 mg/kg
Pre & postnatal development including maternal function SHGT-1U0-06-016	rat CD [Crl:CD (SD)] 25	IV 0, 1.5, 10.0, 17.0 mg/kg	gd 6, 9, 13, 16, 20 + ld 1, 5, 8, 12, 15, 19	MD + HD: swollen limbs/paws, swollen face/lips → transient, not seen on treatment free days	F0: general toxicity: 1.5 mg/kg F1: pre- and postnatal development including reproductive capacity: 17 mg/kg

A full reproductive and developmental toxicity program in rats and rabbits has been conducted. Treatment with velaglucerase alfa induced swelling in the face and/or paws in rats. As the swelling was transient and without any effect on body weights, not observed on treatment free days or in any other species tested, it was concluded that this histamine release was specific to the rat strain used and without any relevance to humans. Treatment with velaglucerase alfa twice weekly slightly reduced male fertility and fecundity at the highest dose tested (17 mg/kg, twice weekly) but had no effect on female reproductive capacity. Prenatal development was unaffected in rats and rabbits. In rats, postnatal development including morphological, behavioural and reproductive endpoints was unaffected. In addition to these studies, a literature search on available reports on the use of ERT in pregnant women with type 1 Gaucher disease. It appears that ERT in pregnant women is associated with marginal risks and an overall benefit regarding the outcome of pregnancy. There is no reason to believe that velaglucerase alfa should be different in this aspect.

2.3.4.6. Toxicokinetic data

Toxicokinetic analyses were conducted during the repeat-dose toxicity study with monkey and the results are discussed in the relevant section on repeat-dose toxicity.

2.3.4.7. Local Tolerance

Local tolerance was studies in conjunction with the repeat-dose toxicity studies and the absence of specific studies is acceptable. Mild to moderate reactions were seen at the injection sites, particularly in the monkeys (see section 3.3.4.2).

2.3.4.8. Other toxicity studies

Antibodies against velaglucerase alfa were detected in all groups dosed with the tested substance in the 3- and 6-month rat studies and in the monkey study, which was anticipated since velaglucerase alfa is a protein of human origin. The antibody response was not correlated with clinical observations.

No additional studies on immunotoxicity, dependence or metabolites were conducted and this is considered acceptable. However, the claim that impurity qualification studies were not relevant was not supported by the CHMP. Impurity might be relevant and in the need of qualification regardless of the type of product. Although no direct effects of a specific impurity derived from cell-culture medium are anticipated, the CHMP requested further information on this issue. It is agreed that the levels of this cell-culture medium derived impurity in velaglucerase alfa are low and not connected to any risks. However, the concern of immunogenicity was not covered sufficiently, since in some cases the amounts of velaglucerase alfa could trigger an immune reaction. Therefore, the CHMP requested a specific follow-up measure to examine the antibodies of this impurity in serum of patients treated with velaglucerase alfa for some time.

A specific non-GLP study SHGT-1U0-06-017 was conducted to investigate the potential differences in the response following IV bolus administration of velaglucerase alfa with and without antihistamine diphenhydramine (DPH) pre-treatment. Swollen limbs, paws and swollen faces were observed in all treatment groups. Mode of administration and substance concentration seems to have a small impact on this reaction. DPH treatment reduces the incidence of swelling partially. Velaglucerase alfa administration resulted in a marked histamine release after 15 min, which could be diminished by DPH treatment. Complement activation was unaffected in all groups. This study was performed with a slightly different formulation compared to the repeated dose toxicity studies (sorbitol was replaced by sucrose). However, apart from the fact that histamine concentration in the blood was increased and could not been reproduced in the repeated dose toxicity study TKT-1U-00-06, no further unexpected findings were reported.

2.3.5. Ecotoxicity/environmental risk assessment

Environmental Risk Assessment has not been performed. The CHMP agreed that an ERA is unnecessary for this type of product. Velaglucerase alfa is a glycoprotein expressed as a single polypeptide chain of amino acids and the excipients used to formulate the drug product are common pharmaceutical ingredients that pose no threat to the environment.

2.3.6. Discussion on non-clinical aspects

Velaglucerase alfa was shown in a relevant animal model to effectively counteract two pathognomonic characteristics of non-neuronopathic Gaucher disease, elevated glucocerebroside levels in the liver and spleen, and appearance of Gaucher cells in the liver. The effects of velaglucerase alfa observed in this model were overall indistinguishable from the effects of the medicinal product imiglucerase. Velagucerase differs from imiglucerase in the identity of the antepenultimate amino acid and in the identity of the glycosyl side chains only. No further pharmacodynamic or safety pharmacology studies were performed. In a 6-month toxicity study in monkeys no concerns in regard to cardiovascular, respiratory or CNS safety issues were identified. Due to the clinical and preclinical experience with imiglucerase no further pharmacodynamic or safety pharmacology studies are considered necessary.
After i.v. administration of a single dose of velaglucerase alfa to rats the serum elimination followed 1st order kinetics at all doses tested. In dogs, 1st order kinetics was observed at the low dose however, at the high dose, such kinetics was observed at 20 minutes post administration. After i.v. administration of repeated doses every other week to Rhesus monkeys, serum elimination followed 1st order kinetics at all doses tested. Whereas C_{max} was dose proportional, AUC increased more than dose-proportional in all three species.

Distribution studies in rats using radiolabelled velaglucerase alfa at a lower dose indicate that velaglucerase alfa is initially distributed to the liver with 70% of the total administered dose, but only 6% of the radioactivity is found in the blood. Other tissues with high initial ^{125}I-velaglucerase alfa concentrations at this dose are lungs, spleen bone marrow and kidneys. If a 10-times higher dose (10 mg/kg) is administered, the distribution to liver is reduced from 70% to 24 %, whereas that in blood is increased from 6% to 38%. This pharmacokinetic behaviour indicates a saturation of an uptake mechanism, which is in agreement with saturation of the assumed mannose-receptor mediated uptake mechanism. Serum half-life of velaglucerase alfa was determined to be in the range of minutes (based on determination of enzymatic activity); at higher doses reaching a maximum of 11 minutes. Plasma

pharmacokinetics appears to be comparable between velaglucerase alfa and imiglucerase. Due to the protein nature of velaglucerase alfa accumulation of the active substance in humans after an i.v. administration every other week is not expected to occur.

Toxicity studies were performed in rats, rabbits and monkeys. The choice of species was considered acceptable for this biotechnology derived product. All studies were GLP compliant with the exception of one additional study on histamine release and complement activation in rats (SHG-1U0-006-017). The single dose toxicity study in rats revealed no specific toxicity up to the highest dose tested 20 mg/kg bodyweight. In general, administration of up to 20 mg /kg b.w. velaglucerase alfa resulted in no treatment related effects with the exception of application traumata which are of no toxicological concern. The repeated dose toxicity studies were performed in rats and monkeys for up to 6 months duration and an additional recovery period. Transient swelling of paws/limbs and muzzle in the rat studies were considered to be rat specific and of no clinical relevance. Some animals formed antibody against the tested substance. The observed decrease in the serum urea nitrogen concentration and an increase in serum albumin concentration in male treatment groups may indicate a possible effect on the glomerular filtration rate, but no structural changes of the kidney histology were reported and thus, no significant kidney damage is expected. The differences in haematology and clinical biochemistry parameters between treated and control groups were considered to be incidental and with no toxicological implication.

In the repeated dose toxicity study in monkeys, no test substance related changes except antibody formation in the high dose group have been detected. Since velaglucerase alfa is a protein of human origin this is an anticipated effect and considered to be not adverse. Development of a cell-based assay to evaluate the potential hindrance of cellular uptake by neutralising anti-drug antibodies was agreed as a follow-up measure.

Estimations of safety factors on a mg/kg b.w. is provided basis as well as based on the surface area (mg/m^2). The safety margins calculated for the HED are with rather low, however, no relevant toxic effects could be detected within the toxicity studies and the low safety margin is considered acceptable. In the reproductive toxicity studies treatment with velaglucerase alfa induced swelling in the face and/or paws in rats, which was transient and without any clinical relevance for humans. Treatment with velaglucerase alfa twice weekly slightly reduced male fertility and fecundity at the highest dose tested but had no effect on female reproductive capacity. Prenatal development was unaffected in rats and rabbits. Although no additional studies on immunotoxicity studies were conducted, further evaluation of immunological response relating to the supplement to the cell culture medium was considered necessary by the CHMP and a specific Follow-up measure was agreed.

2.3.7. Conclusion on the non-clinical aspects

The toxicological program is considered adequate to support the marketing authorisation application for velaglucerase alfa and the concerns identified by the CHMP during its evaluation are considered resolved. Although no post-authorisation follow up measures related to non-clinical development were considered necessary, the CHMP requested several clinical follow-up measures for which the reason partially lies with the non-clinical findings.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for velaglucerase alfa in the frame of the centralised procedure according to Regulation (EC) No 726/2004. The application is submitted in accordance with Article 8(3) of the above mentioned regulation and with Article 3(1) of the Directive 2001/83/EC. A full dossier has been submitted.

Data from four finalised clinical trials (TKT025, TKT032, TKT034, HGT-GCB-039) and from an ongoing extension study TKT025EXT in patients with type 1 Gaucher disease have been provided. Patients with type 2 or type 3 Gaucher disease were excluded from the current clinical programme. For the ongoing extension study TKT025EXT a safety summary was submitted and for TKT034 only a preliminary CSR

was available at the time of submission. The Phase I/II study TKT025 and the Phase III studies TKT032 and HGT-GCB-039 were conducted in treatment-naïve patients. The Phase II/III study TKT034 enrolled patients who transitioned from treatment with imiglucerase.

There are two ongoing clinical trials for which no data have been provided (HGT-GCB-044, HGT-GCB-058).

Velaglucerase alfa was granted an orphan designation by the Committee for Orphan Medicinal Products in March 2010. The European Commission decision was received on 9 June 2010.

An application for the Paediatric Investigation Plan (PIP) was submitted to the EMA and the PDCO. The EMA issued a decision on the PIP agreement dated 27 November 2009 granting a deferral and a waiver for velaglucerase alfa (please see section 1.1.2 for further details).

An accelerated review according to Article 14 (9) of Regulation (EC) No 726/2004 has been accepted by CHMP on 22 October 2009 on the grounds of public health interest.

Scientific advice on aspects concerning the clinical development was received from the CHMP in July 2006. An active comparator clinical trial with imiglucerase was conducted. Analyses of response categories as requested in the CHMP scientific advice were included. However, these analyses are not included in the study protocol, or in the protocol amendments. The CHMP requested a clarification of this issue and although the opinion that these analyses by response categories did not require an amendment of the study protocol is not agreed, it is acknowledged that this omission did not have an influence on the validity of the data provided.

2.4.2. GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.
Studies have been conducted in Argentina, India, Israel, Paraguay, Russia, Serbia, South Korea, Tunisia, Poland, UK, and USA. 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

Study ID	Phase	Objective(s)	Design	Posology	N	Diagnosis	Duration	Status
HGT-GCB-039	III	Primary: Change in Hgb Secondary: Change in platelet counts, spleen volume, liver volume, chitotriosidase and CCL18 levels	Multicentre, Randomised, Double-blind, active comparator (imiglucerase), controlled	velaglucerase alfa 60 U/kg imiglucerase 60 U/kg Intravenous infusion EOW	34	Naïve patients ≥2 years of age with type 1 Gaucher disease	9 months	Full CSR
TKT032	III	Primary: Change in Hgb (60 U/kg) Secondary: Change in Hgb (45 U/kg), platelet count, spleen volume, liver volume, CCL18, chitotriosidase	Multicentre, Randomised, Double-blind, parallel group, controlled	velaglucerase alfa, 45 U/kg or 60 U/kg; intravenous infusion EOW	25	Naïve patients ≥2 years of age with type 1 Gaucher disease (Treatment naïve any previous treatment for Gaucher disease at least 30 months prior to entry)	12 months	Full CSR

Study ID	Phase	Objective(s)	Design	Posology	N	Diagnosis	Duration	Status
TKT025	I/II	Primary: Safety Secondary: Change in Hgb, platelet count, liver and spleen volumes	Single center, Open label	velaglucerase alfa; 15 U/kg to 60 U/kg[b]; intravenous infusion EOW	12	Naïve patients ≥18 years of age with type 1 Gaucher disease (Treatment-naïve any previous treatment for Gaucher disease at least 12 months prior to entry)	9 months	Full CSR
TKT025EXT	I/II	Primary: Long-term safety Secondary: Change in Hgb, platelet counts, liver and spleen volumes	Multicentre, Open label, extension	velaglucerase alfa; 60 U/kg-30 U/kg; intravenous infusion EOW	10	Patients ≥18 years of age with type 1 Gaucher disease who completed study TKT025 (Treatment-naïve any previous treatment for Gaucher disease at least 12 months prior to entry)	Ongoing; (data to be presented from 03 February 2005 to 01 June 2009)	Ongoing ; safety summary report
TKT034	II/III	Primary: Safety Secondary: Change in platelet counts, Hgb, spleen and liver volume, CCL18, chitotriosidase	Multicentre, Open label	velaglucerase alfa, 15 U/kg to 60 U/kg; intravenous infusion EOW	40	type 1 Gaucher disease patients ≥2 years of age previously treated with imiglucerase (same dose for the 6 months prior to entry)	12 months	Completed; Full CSR
HGT-GCB-044	III	Primary: Long-term Safety Secondary: Change in Hgb, platelet counts, spleen and liver volume	Multicentre, Open label	velaglucerase alfa, 15 U/kg to 60 U/kg; intravenous infusion EOW	Up to 102	Patients ≥2 years of age with type 1 Gaucher disease who completed TKT032, TKT034, or HGT-GCB-039	Until velaglucerase alfa is commercially available, patients participation is discontinued, or the study is discontinued	Ongoing
HGT-GCB-058	III	Primary: Safety	Multicentre, Open label Treatment Protocol	velaglucerase alfa, 15 U/kg to 60 U/kg; intravenous infusion EOW	Up to 500	Patients ≥2 years of age with type 1 Gaucher disease (naïve and patients previously treated with imiglucerase)	Until velaglucerase alfa is commercially available or for 1 year, whichever comes first	Ongoing

a Number represents number of patients dosed
b The first patient dosed with velaglucerase alfa in the dose-escalation phase received two 15- U/kg doses and then one 30- U/kg escalation dose. The next 2 patients enrolled received one 15 U/kg dose and then one 30- U/kg escalation dose. Based on acceptable safety evaluations, all 3 patients in the dose-escalation cohort had their doses increased to 60 U/kg All subsequent patients in this study received 60 U/kg EOW for the entire study.

2.4.3. Pharmacokinetics

Pharmacokinetics data are derived from studies TKT025, TKT032, and TKT025EXT.

In study TKT025 twelve patients with type 1 Gaucher disease aged 19-70 years were enrolled into two cohorts. In the initial dose-escalating cohort 3 patients received 1-hour infusions of velaglucerase alfa 15 U/kg at week 1, 30 U/kg at week 3, and 60 U/kg EOW for weeks 5-39 (end of study). Nine additional patients in the second cohort received 60 U/kg EOW for weeks 1-39. In study TKT032, paediatric (≥ 2 years old) and adult patients (age range 4-62 years) were randomised to receive either 45 or 60 U/kg velaglucerase alfa EOW for 51 weeks.

Clinical Studies with Pharmacokinetics components

Study No.	Objective of the Study	Treatment (Duration)	No. of Patients
TKT025	Phase I/II dose-finding, safety, efficacy, and PK	15 U/kg (Week 1) 30 U/kg (Week 3) 60 U/kg (Weeks 5 to 39)	3
		60 U/kg (Weeks 1 to 39)	9
TKT025EXT	Long-term, 5-year, safety, efficacy, and PK	60 U/kg (up to 367 weeks)	10
TKT032	Phase III, safety, efficacy, and PK	45 U/kg (51 Weeks)	13
		60 U/kg (51 Weeks)	12

Overall, the analytical methods and statistical analyses used in these trials are considered adequate. The information provided on the request of CHMP in order to clarify calculation of LOQ determined by velaglucerase alfa enzymatic activity assay, data on immunogenicity testing methods or immunoassays supplemental information was considered satisfactory. In addition, a follow up measure to develop a new assay for the potential neutralising activity of antibodies in terms of velaglucerase alfa or imiglucerase cellular uptake was agreed.

2.4.3.1. Absorption

Velaglucerase alfa is intended for intravenous administration.

2.4.3.2. Distribution

Velaglucerase alfa serum concentrations rose rapidly for the first 20 min of the 1 h infusion before levelling off at all dose levels. C_{max} was typically attained between 40 to 60 min. At end of infusion serum concentrations fell rapidly in a mono- or biphasic fashion, with mean $t_{1/2}$ from 5 to 12 min for the 15, 30, 45 and 60 U/kg doses.

2.4.3.3. Elimination

For subjects in the 60 U/kg cohort in study TKT025 mean serum CL changed from 12.6 mL/min/kg at week 1 to 5.6 mL/min/kg at Week 37/39, and 6.5 mL/min/kg at week 65 in TKT025EXT. Mean Vss changed from 17.5% at Week 1 to 5.4% at Week 37/39 and 8.3% at week 65. In study TKT032 mean CL and Vss were similar for 45 and 60 U/kg between week 1 and week 37 (mean CL 6.7 to 7.6 mL/min/kg, mean Vss 8.2% to 10.8%). Mean disposition t1/2 ranged from 6.8 to 9.8 min in TKT025 and TKT025EXT compared to 11.4 to 12.4 min in TKT032.

Pharmacokinetic Parameters Following Infusion of Velaglucerase alfa 45 or 60 U/kg (Week 1 and Week 37) in Study TKT032

	C_{max} (ng/mL)	T_{max} (min)	AUC_{inf} (ng·min/mL)	CL (mL/min/kg)	$T_{1/2}$ (min)	V_{ss} (mL/kg)
45 U/kg Velaglucerase alfa (Week 1)						
Mean	3437	40	178318	7.02	12.4	104
± SD	± 1283	± 19	± 62162	± 2.59	± 3.1	± 66
N	13	13	10	10	10	10
45 U/kg Velaglucerase alfa (Week 37)						
Mean	4033	37	181056	7.56	11.9	108
± SD	± 2939	± 20	± 91591	± 3.56	± 5.5	± 59
N	12	12	10	10	10	9
60 U/kg Velaglucerase alfa (Week 1)						
Mean	5256	45	254148	7.16	11.5	106
± SD	± 2323	± 16	± 111749	± 3.54	± 3.5	± 60
N	12	12	12	12	12	12

	C_{max} (ng/mL)	T_{max} (min)	AUC_{inf} (ng·min/mL)	CL (mL/min/kg)	$T_{1/2}$ (min)	V_{ss} (mL/kg)
60 U/kg Velaglucerase alfa (Week 37)						
Mean	5712	44	268085	6.72	11.4	82
± SD	± 2795	± 15	± 125438	± 2.91	± 3.2	± 39
N	12	12	12	12	12	12

The rapid clearance from serum is consistent with uptake of velaglucerase alfa into macrophages *via* mannose receptors. Velaglucerase alfa is similar to naturally occurring β-glucocerebrosidase and thus it is unlikely that plasma protein binding and blood cell distribution patterns would differ from subjects with normal β-glucocerebrosidase levels. Studies in animals have demonstrated that the vast majority of velaglucerase alfa is eliminated from the systemic circulation independent of species within 2 to 3 h of dosing. Studies examining plasma protein binding and blood cell distribution have thus not been performed.

2.4.3.4. Dose proportionality and time dependencies

In the dose escalating cohort in study TKT025, velaglucerase alfa Cmax and AUC increased approximately in a linear manner for 2 patients with pharmacokinetic evaluation at 15, 30, and 60 U/kg compared to study TKT032 where C_{max} and AUC increased slightly more than proportional to dose between 45 U/kg and 60 U/kg groups. Overall, velaglucerase alfa exhibited approximately linear dose proportionality over the dose range of 15 to 60 U/kg. Since mean velaglucerase alfa pharmacokinetics parameters were similar between Week 1 and Week 37 and $t_{1/2}$ is considerably shorter than the dosing interval, velaglucerase alfa is not expected to accumulate.

2.4.3.5. Special populations

Pharmacokinetics in special populations impaired renal or hepatic function, race, weight and elderly have not been investigated. Pharmacokinetic data are available in the age range 6 to 62 years old in subjects receiving 45 U/kg and 4 to 42 years old in subjects receiving 60 U/kg in study TKT032. No apparent pharmacokinetic differences between male and female patients have been identified. While there was no trend for AUC or clearance changes with increasing age with 45 U/kg, in the 60 U/kg group a trend for lower AUC and higher clearance in patients below 10 years compared to adults was seen. However, the range of clearance values in children is contained within the range of values in adults and it is considered unlikely that a difference in systemic clearance between children and adults would significantly alter overall tissue bio-distribution. Thus data do not indicate a need for differences in the weight-normalised dose based on age. The influence of weight on velaglucerase alfa pharmacokinetics has not been evaluated. However, as velaglucerase alfa is an enzyme administered intravenously and with a low volume of distribution, dosing by weight is appropriate.

2.4.3.6. Pharmacokinetic interaction studies

No specific drug-interaction studies have been performed. As with other enzyme replacement therapies, drug-drug interactions are not expected.

2.4.3.7. Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials have been conducted.

2.4.4. Pharmacodynamics

Pharmacodynamics of velaglucerase alfa has been evaluated in animals and no separate studies of pharmacodynamics in man have been provided. However, assessment of efficacy is based on pharmacodynamic parameters: all clinical studies evaluated effects of velaglucerase alfa on surrogate endpoints platelet count and haemoglobin, as well as spleen and liver organ volumes. No clinical pharmacodynamic studies have been conducted in healthy volunteers.

2.4.4.1. Mechanism of action

The mechanism of action is well established. Velaglucerase alfa is a human glucocerebrosidase intended as long-term ERT for patients with type 1 Gaucher disease to supplement or replace deficient beta-glucocerebrosidase in lysosomes and thus, to reduce the amount of accumulated glucocerebroside. To facilitate uptake by phagocytic cells *via* mannose receptors, velaglucerase alfa contains mannose-type-linked glycans. Binding of velaglucerase alfa to isolated recombinant human mannose receptor has been investigated in preclinical studies and the available preclinical data as well as experience with alglucerase and imiglucerase provide an adequate rational for the clinical development.

2.4.4.2. Primary and Secondary pharmacology

Primary pharmacology has been investigated in a series of nonclinical studies comparing biological and biochemical effects of velaglucerase alfa and imiglucerase in a mouse model of Gaucher disease. Results show that both velaglucerase alfa and imiglucerase comparably reduce the number of Gaucher cells. No clinical pharmacodynamic studies have been performed, which is considered acceptable for this type of product.

2.4.5. Discussion on clinical pharmacology

Pharmacokinetic data have been derived from evaluations of clinical trials with type 1 Gaucher disease patients and this is considered acceptable. Velaglucerase alfa demonstrated a rapid increase in serum concentration during infusion with C_{max} of about 45 min and fast clearance with $t_{1/2}$ of about 12 min. Pharmacokinetic characteristics are in agreement with a mannose receptor mediated uptake mechanism. In study TKT032 the mean clearance and V_{ss} were similar for 45 and 60 U/kg dose between Week 1 and Week 37. These results indicate that pharmacokinetics is not time dependent. Clinical trials examining plasma protein binding and blood cell distribution patterns have not been performed which is considered acceptable. No drug-drug interaction studies have been performed.

Data in special populations are limited to age, excluding elderly, and gender. Data do not indicate a need for differences in the weight-normalised dose based on either gender or age.

Velaglucerase alfa appears to induce antibodies including neutralising antibodies. This is adequately reflected in the SmPC. Since the influence of anti-velaglucerase alfa antibodies on pharmacokinetics has not been assessed, adequate surveillance of antibody formation *via* monitoring the pharmacokinetic profile of antibody positive patients has been agreed.

Velaglucerase alfa was shown to effectively counteract elevated glucocerebroside levels in liver and spleen, and appearance of Gaucher cells in the liver assessment of efficacy is based on pharmacodynamic parameters of platelet count and haemoglobin, as well as spleen and liver organ volumes. No 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.

2.4.6. Conclusions on clinical pharmacology

The non-clinical and clinical data submitted together with the experience with alglucerase and imiglucerase are considered adequate to support the marketing authorisation and use of velaglucerase alfa.

2.4.7. Clinical efficacy

2.4.7.1. Dose response study

Dose selection was based on results from preclinical studies in animals. Clinical and laboratory assessments of safety and tolerability, as well as of the clinical activity of velaglucerase alfa were performed. The obtained results support doses 15, 30, and 60 U/kg used in the Phase I/II study TKT025.
The NOAEL from the animal toxicology studies were ≥23 mg/kg (single acute dose study) and ≥17 mg/kg (repeat dose study) with the highest doses evaluated. Repeat dose NOAEL provided a

safety margin of approximately 45-fold and 11-fold for the 15 U/kg and 60 U/kg doses, respectively. The 60 U/kg dose for study TKT032 was selected based on the safety and clinical activity experience in TKT025 and during the first 3 months of the ongoing open-label extension study TKT025EXT.

No further specific dose-response studies have been conducted. Although TKT032 included two doses of velaglucerase alfa, these have not been formally compared within this trial; no direct statistical comparison of the 45 and 60 U/kg dose groups was conducted. Furthermore, no dose comparisons of the 4 nominal dosage groups of 15, 30, 45, and 60 U/kg in study TKT034 were presented in the dossier. However, data from study TKT025 clearly indicate that 60 U/kg dose is effective, and the results are consistent across both primary and secondary endpoints. In study TKT032 both doses, 45 and 60 U/kg appear to be effective with an improved efficacy for the 60 U/kg dose. Results were consistent for all endpoints and in line with the findings in study TKT025. Further information on the appropriate maintenance dose is expected to be derived from the ongoing open-label extension study TKT025EXT. Overall, although information from clinical trials is limited, the rational and data provided for dose selection are considered acceptable.

2.4.7.2. Main study(ies)

In the clinical development programme for velaglucerase alfa, four studies have been completed: TKT025, TKT032, HGT-GCB-039, and TKT034.
Phase I/II study TKT025 and Phase III studies TKT032 and HGT-GCB-039 were conducted in treatment-naïve patients. The Phase II/III study TKT034 enrolled patients who transitioned from treatment with imiglucerase. Two extension studies are ongoing: TKT025EXT (patients rolled over from TKT025), and HGT-GCB-044 (patients rolled over from TKT032, TKT034, and HGT-GCB-039).

Trial HGT-GCB-039 is considered the pivotal since it is the only study comparing velaglucerase alfa with a comparator, imiglucerase. No placebo controlled data have been provided, which is acceptable for the patient population investigated. Study TKT032, although testing two doses of velaglucerase alfa, 45 U/kg and 60 U/kg and labelled as a controlled trial, was not designed to formally compare these two doses and thus, is assessed as an uncontrolled trial.

Pivotal study HGT-GCB-039 title: A Multicenter, Randomized, Double-Blind, Parallel-Group Study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy Compared With Imiglucerase in Patients With Type I Gaucher Disease. This was a multi-centre, Phase III, non-inferiority, randomised, double-blind, parallel-group study comparing efficacy and safety of velaglucerase alfa to imiglucerase (Cerezyme), for duration of 9 months.

The majority of the clinical efficacy chapter refers to the conduct and results of the pivotal study HGT-GCB-039 and data from other studies are quoted as appropriate. Further details of the supportive studies are given in section 3.4.7.5.

2.4.7.2.1. Methods

2.4.7.2.1.1. Study Participants

In study HGT-GCB-039, patients were to be treatment-naïve (no therapy ≥12 months prior to study entry) with a documented diagnosis of type 1 Gaucher disease and ≥2 years of age. They had to have Hgb below LLN for age and gender and at least one of the following criteria: at least moderate splenomegaly by palpation (2 to 3 cm below left costal margin), thrombocytopenia (platelet count ≤120 x 10^3/mm^3), or a palpable enlarged liver.
Main exclusion criteria were presence of imiglucerase or velaglucerase alfa antibodies at screening, history of anaphylactic or anaphylactoid reaction to imiglucerase or velaglucerase alfa, requirement for routine pre-medication to manage infusion related reactions to imiglucerase or velaglucerase alfa, receiving red blood cell growth factor (e.g. erythropoietin), receiving chronic systemic corticosteroids within last 6 months, or HIV or active hepatitis B or C infection. Inclusion and exclusion criteria were acceptable to the CHMP.

Forty-two patients were screened, 7 (17%) were not eligible, 35 were randomised, and 34 received at least one dose; 17 velaglucerase alfa and 17 imiglucerase. One patient in the velaglucerase alfa group discontinued after 17 weeks of treatment as she was lost to follow-up following an SAE, unrelated to treatment. One patient in the imiglucerase treatment group withdrew consent after 23 weeks of treatment due to multiple infusion-related reactions. A second patient randomized to imiglucerase was

also considered discontinued. This patient was in fact randomized in error before the confirmation of all eligibility criteria.

2.4.7.2.1.2. Treatments

In study HGT-GCB-039, treatment of 60 U/kg was administered in double-blind fashion as continuous i.v. infusion over 60 min every other week (EOW) (±3 d) for 39 weeks (20 infusions). Dose was based on patient body weight at baseline; a change of ≥5% from baseline or the most recent recorded measurement (weeks 13 or 25) required re-calculation.

Dosing information for all reported studies

Description	Treatment Naïve Patients				Transition from ERT Patients
	TKT025	TKT025EXT	TKT032	HGT-GCB-039	TKT034
Clinical Trial Phase	I/II	I/II	III	III	II/III
Randomization	No	No	Yes	Yes	No
Dose of velaglucerase alfa	15-60 U/kg	30-60 U/kg[b]	45 U/kg; 60 U/kg	60 U/kg	15-60 U/kg[c]
Dose of imiglucerase	-	-	-	60 U/kg	-
Previously Treated	Not within 12 months prior to study entry	Already on velaglucerase alfa from TKT025	Not within 30 months prior to study entry	Not within 12 months prior to study entry	Yes, for a minimum of 30 months with imiglucerase, with the same dose for the 6 months prior to study entry
Home therapy	No	Yes[d]	No	No	Yes

All doses were administered by a 60-minute IV infusion.

The first patient dosed with velaglucerase alfa in the dose-escalation phase received two 15- U/kg doses and then one 30- U/kg escalation dose. The next 2 patients enrolled received one 15 U/kg dose and then one 30- U/kg escalation dose. Based on acceptable safety evaluations, all 3 patients in the dose-escalation cohort had their doses increased to 60 U/kg. The remaining 9 patients were infused at 60 U/kg of velaglucerase alfa EOW throughout the 9-month study.

Patients were treated with 60 U/kg until they had completed at least 12 months of dosing at 60 U/kg inclusive of TKT025. All patients were subsequently titrated down to a maintenance dose of 30 U/kg.

Patient's velaglucerase alfa dose was matched to their dose of imiglucerase for the 6 months prior to study entry.

Seven patients have received one or more infusions in the home.

2.4.7.2.1.3. Objectives

The primary objective in study HGT-GCB-039 was to compare the effects of velaglucerase alfa and imiglucerase on haemoglobin. Secondary objectives included effect comparison of platelet count, liver and spleen volume, and plasma chitotriosidase and CCL18 levels. Safety evaluations included rates of antibody formation and neutralising antibody activity, rates of infusion-related adverse events (AEs), and proportion of patients requiring premedication to manage infusion-related AEs.

2.4.7.2.1.4. Outcomes/endpoints

The primary efficacy endpoint in study HGT-GCB-039 was the difference in Hgb mean change from baseline to week 41 between groups. Secondary endpoints in this study included differences in mean and percent changes from baseline in platelet count, liver and spleen volumes measured by MRI, plasma chitotriosidase activity, plasma CCL18 levels, and in time to response for Hgb ≥1 g/dL from baseline.

There were several efficacy measures common to all studies in the velaglucerase alfa clinical programme: changes in haemoglobin concentration, changes in platelet count, and changes in normalized liver volume measured by magnetic resonance imaging (MRI), changes in normalized spleen volume measured by MRI, changes in plasma chitotriosidase level, and changes in plasma chemokine (C-C motif) ligand 18 (CCL18) level. Only changes in haemoglobin concentration and platelet count are reported for the TKT034 study. Other secondary or tertiary efficacy measures used at least in one study were: pulmonary function, bone abnormalities, bone density, bone marrow, growth velocity, skeletal growth, Tanner staging, bone disease, and overall quality of life (QoL), as measured by the Short Form-36 (SF-36) for patients ≥18 years-old and the Childhood Health Questionnaire (CHQ, PF50) for patients 5 to 17 years-old. The primary and secondary endpoints are adequate and in line with the scientific advice given by the CHMP.

Summary of endpoints for all reported studies

Description	Treatment Naïve Patients				Transition from ERT Patients
	TKT025 n = 12	TKT025EXT n = 10	TKT032 n = 25	HGT-GCB-039 n = 35	TKT034 n = 40
Clinical Trial Phase	I/II	I/II	III	III	II/III
Primary Endpoint	Safety	Long-term safety	Change in hemoglobin concentration from Baseline to end of study (60 U/kg)	Non inferiority, comparison between the groups of change in hemoglobin concentration	Safety
Secondary Endpoints	Change in hemoglobin concentration, platelet count, and liver and spleen volumes	Change in hemoglobin concentration, platelet count, and liver and spleen volumes	Change in hemoglobin concentration (45 U/kg), platelet count, and spleen and liver volume, biomarkers	Change in platelet count, spleen and liver volume, chitotriosidase and CCL18 (Confidence interval of mean treatment difference)	Change in hemoglobin concentration, platelet count, and spleen and liver volume

2.4.7.2.1.5. Sample size

With a sample size in each treatment group of 14 (for a total of 28 patients overall) in study HGT-GCB-039, a two-group, 0.025 one-sided *t* test would have an 80% power to reject the null hypothesis that the difference in means for haemoglobin is less than −1 g/dL in favour of the alternative hypothesis that the difference in means is greater than −1 g/dL, assuming that the expected difference in means is 0, and the common standard deviation is 0.90. A 15% dropout was assumed, therefore a total of 32 patients (16 patients per treatment arm) were to be enrolled into the study. The CHMP concluded that the sample size calculation is adequate considering the rarity of the disease investigated.

2.4.7.2.1.6. Randomisation

Eligible patients were enrolled and randomly allocated according to a 1:1 ratio to receive either velaglucerase alfa 60 U/kg every other week or imiglucerase 60 U/kg every other week. A covariate adaptive randomization algorithm was used to balance age at randomization (2 to 17 years vs ≥18 years), haemoglobin concentration (<8 g/dL vs ≥8 g/dL), and splenectomy status between the two treatment groups. Randomization was performed centrally by a contract research organization and this strategy was considered adequate.

2.4.7.2.1.7. Blinding (masking)

Patients, investigators, site personnel (except the clinical site's pharmacist and one clinical research associate at each site) and the sponsor's personnel who had direct responsibility for monitoring the sites were blinded throughout the study. All images were read by a single independent reviewer who remained blinded to the study medication and the order in which the images were taken. Unblinding of a patient's treatment was restricted to emergency situations and was only done to facilitate care of a patient. Further details on the procedures for breaking the blind were described in the study protocol.

2.4.7.2.1.8. Statistical methods

For the primary endpoint a one-sided 97.5% CI was used to test the null hypothesis that the treatment difference is less than or equal to the lower equivalence margin in haemoglobin (-1 g/dL). The ITT population was used for primary analysis, followed by the PP population. For secondary efficacy parameters, a linear mixed model was used to evaluate mean changes from baseline to week 41 and a 95% CI was computed for the difference in mean changes. Estimates of mean treatment difference and corresponding 95% CI were adjusted for baseline age, splenectomy status except for normalised spleen volume, and the corresponding parameter's baseline value. For time to first Hgb response, Kaplan-Meier survival curves were presented and a log-rank test was used to compare treatments. To minimise potential for inter-site bias Hgb, platelet count, chitotriosidase levels, and CCL18 levels were analysed at a central laboratory, and liver and spleen volumes were analysed at a central imaging centre. The number of patients per country was not considered sufficient for assessing efficacy parameters and no formal statistical tests were performed on safety parameters. Statistical methods are considered acceptable. The non-inferiority margin of 1 g/dL is considered adequate.

2.4.7.2.2. Results

In study HGT-GCB-039, 42 patients were screened, 35 were randomised, and 34 received at least one dose. The majority of patients completed the study. Discontinuations were evenly distributed between the groups. Details on participant flow are given in the following table.

Summary of Patient Disposition (HGT-GCB-039)

Disposition	velaglucerase alfa 60 U/kg n (%)	imiglucerase 60 U/kg n (%)	Total n (%)
Signed informed consent			42
Patients randomized	17 (100.0)	18 (100.0)	35 (100.0)
Patients treated	17 (100.0)	17 (94.4)	34 (97.1)
Patient status			
Completed	16 (94.1)	16 (88.9)	32 (91.4)
Discontinued	1 (5.9)	2 (11.1)	3 (8.6)
Reason for discontinuation			
Adverse experience including serious adverse event	0	0	0
Adverse laboratory experience	0	0	0
Intercurrent illness	0	0	0
Refusal of required diagnostic evaluation or investigational product	0	0	0
Withdrawal of consent	0	1 (5.6)	1 (2.9)
Termination of study by Investigator	0	1 (5.6)	1 (2.9)
Termination of study by Sponsor	0	0	0
Patient lost to follow-up	1 (5.9)	0	1 (2.9)
Death	0	0	0
Other	0	0	0

Abbreviations: ITT = Intent-to-treat; all randomized patients who received at least 1 study drug infusion (full or partial); PP = the randomized patients who received ≥80% of the scheduled full infusions (≥16 out of 20 infusions; not including partial infusions), and who have non-missing primary efficacy assessments at Baseline or Screening, and Week 41; protocol violators are excluded.
Note: Percentages are based on all randomized patients within each randomized treatment group or overall.

2.4.7.2.2.1. Recruitment

The study was conducted at a total of 11 sites in 9 countries: Paraguay, Argentina, Israel, Tunisia, Russia, US, Spain, and UK with 1 site each, and India with 3 sites. First patient was recruited on Jan 29th 2008 and the last patient completed this study on May 5th 2009.

2.4.7.2.2.2. Conduct of the study

The original protocol HGT-GCB-039 was issued on 25 January 2007. There were 2 protocol amendments. The first amendment was done before recruitment started. The second amendment,

dated June 10th 2008, included a change in the inclusion criteria defining Gaucher-disease-related anaemia, which was altered by removing the definition of "being at least 0.5 g/dL" below the lower limit of normal for age and gender. These protocol amendments would not affect the outcome of the study in a negative way. The change in the haemoglobin inclusion criterion would equally affect both treatment arms and this would only attenuate the effect of treatment.

Protocol violations/deviations
No patient in the study had a protocol deviation that met the definition of a protocol violation, which was defined as a violation of admission (inclusion/exclusion) criteria (ie, eligibility violation), occurrence of a treatment dispensing error or a prohibited medication during study. Seven patients were allowed to enrol into the study with waivers to deviations from the inclusion/exclusion criteria. All seven exemptions were for haemoglobin concentrations at baseline that were above the threshold (0.5 g/dL below the lower limit of normal for age and gender) for study entry. These patients were allowed into the study with the knowledge that protocol amendment 2 would change the relevant inclusion criterion. The seven waivered patients are balanced between the 2 treatment groups; 4 patients were randomized to the velaglucerase alfa group and 3 to the imiglucerase group. These patients were not appreciably different from the other patients, participating in the study, 6 of 7 (85.7%) patients completed the study. It is reasonable to conclude that the inclusion of these patients in the study did not bias the study results or conclusions.

2.4.7.2.2.3. Baseline data

In study HGT-GCB-039, 73.5% of patients were adults. Number of paediatric patients was similar in both groups (4 children - velaglucerase alfa, 5 children - imiglucerase) as was the splenectomy status (58.8% each). No patient had a screening Hgb <8 g/dL. Median modified platelet count at baseline was within normal range (172.0 x 10^3 velaglucerase alfa, 188 x 10^3 imiglucerase). Groups were balanced with respect to gender, medical history and concomitant medications and therapy. 16/17 (94.1%) of patients on velaglucerase alfa and 15/17 (88.2%) on imiglucerase had not been previously treated. Time from diagnosis to first treatment ranged from 0.1 years to 18.7 years on velaglucerase alfa and 0.1 to 51.2 years on imiglucerase. Baseline demographic data, medical history and concomitant medication did not differ significantly between groups.

Baseline Demographic Profile of Patients, study HGT-GCB-039

	Velaglucerase alfa 60 U/kg	Imiglucerase 60 U/kg
Age (years)		
Mean (±SD)	31.5 (±16.67)	27.8 (±20.42)
Median	36.0	27.0
Range	7 – 60	3 – 73
Age Range		
2 to 4 years	0	4 (23.5)
5 to 17 years	4 (23.5)	1 (5.9)
≥18 years	13 (76.5)	12 (70.6)
Sex (n; %)		
Male	8 (47.1)	8 (47.1)
Female	9 (52.9)	9 (52.9)
Race (n; %)		
Asian	4 (23.5)	4 (23.5)
Black	0	1 (5.9)
Caucasian	12 (70.6)	10 (58.8)
Other	1 (5.9)	2 (11.8)
Gaucher disease genotype (n; %)		
N370S/N370S	6 (35.3)	3 (17.6)
Other	11 (64.7)	14 (82.3)
Splenectomy	10 (58.8)	10 (58.8)
Positive for anti-imiglucerase antibodies	0	0
Patients Completed	16	16
Patients Dosed (ITT and Safety Pop.)	17	17
Study Duration (months)	9	9
Total Patients enrolled	17	18

Although groups were balanced for age groups of paediatric and adult patients, there was a considerable imbalance within the paediatric group with none of the 4 children in the 2-4 years subgroup for velaglucerase alfa, compared to 4 of 5 on imiglucerase.

2.4.7.2.2.4. Numbers analysed

Forty-two patients were screened, 7 (17%) were not eligible, 35 were randomised, and 34 received at least one dose. One patient on velaglucerase alfa discontinued after 17 weeks of treatment due to a SAE of convulsion, unrelated to treatment. One patient in the imiglucerase group withdrew consent after 23 weeks of treatment due to multiple infusion-related reactions; the patient had developed antibodies to both imiglucerase and velaglucerase alfa after 13 weeks. A second patient on imiglucerase was considered discontinued since he was found to have antibodies to imiglucerase and was terminated from the study by the investigator prior to first infusion and thus not included in the safety population. The ITT population included 17 patients per group. 2 patients in each group were excluded for the PP analysis; 2 patients, 1 per group, had discontinued without Week 41 assessment, 2 patients, 1 per group, had not received ≥80% of scheduled infusions, and 1 patient on imiglucerase did not receive at least one dose.

Data sets analysed - all patients, study HGT-GCB-039

Disposition	velaglucerase alfa 60 U/kg n (%)	imiglucerase 60 U/kg n (%)	Total n (%)
Patients randomized	17 (100.0)	18 (100.0)	35 (100.0)
Efficacy populations			
ITT	17 (100.0)	17 (94.4)	34 (97.1)
Per protocol	15 (88.2)	15 (83.3)	30 (85.7)
Safety population	17 (100.0)	17 (94.4)	34 (97.1)

Abbreviations: ITT = Intent-to-treat; all randomized patients who received at least 1 study drug infusion (full or partial); PP = the randomized patients who received ≥80% of the scheduled full infusions (≥16 out of 20 infusions; not including partial infusions), and who have non-missing primary efficacy assessments at Baseline or Screening, and Week 41; protocol violators are excluded.
Note: Percentages are based on all randomized patients within each randomized treatment group or overall.

2.4.7.2.2.5. Outcomes and estimation

Primary endpoint

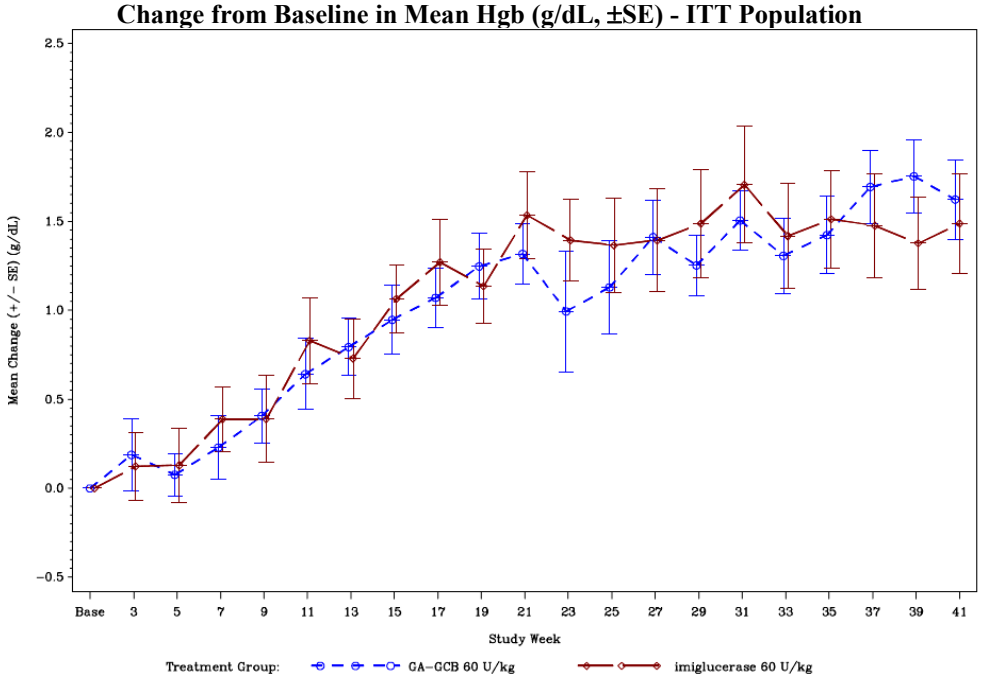
Haemoglobin
For the ITT population mean absolute changes were 1.624 g/dL for velaglucerase alfa and 1.488 g/dL for imiglucerase. The estimated mean treatment difference was 0.135 g/dL with the lower bound of the one-sided 97.5% CI of -0.596 g/dL. Results were consistent with the PP population. Thus, results met the predefined non-inferiority criteria. Response was similar between treatment groups for subgroups paediatric (age 2 to 17 years), adult (age ≥18 years), gender, and splenectomy status. The median baseline Hgb was 11.4 g/dL in the velaglucerase alfa and 10.6 g/dL in the imiglucerase group. This difference between groups remained during the entire study.

Change from Baseline in Mean Hgb (g/dL, ±SE) – ITT and PP Populations

	Baseline		Change from Baseline Week 41		Difference in Mean Change between Treatment Groups	
Hgb Concentration	velaglucerase alfa 60 U/kg	imiglucerase 60 U/kg	velaglucerase alfa 60 U/kg	imiglucerase 60 U/kg	Mean Treatment Difference	97.5% One-sided CI (L, U)
ITT Population						
n	17	17	17	17	34	
Mean	11.512	10.459	1.624	1.488	0.135	-0.596, inf
Std. Err.	0.299	0.329	0.223	0.281		
Median	11.400	10.600	1.550	1.450		

Hgb Concentration	Baseline velaglucerase alfa 60 U/kg	Baseline imiglucerase 60 U/kg	Change from Baseline Week 41 velaglucerase alfa 60 U/kg	Change from Baseline Week 41 imiglucerase 60 U/kg	Difference in Mean Change between Treatment Groups Mean Treatment Difference	Difference in Mean Change between Treatment Groups 97.5% One-sided CI (L, U)
Minimum	9.65	8.10	-0.15	-0.55		
Maximum	14.35	13.05	3.60	3.50		
PP Population						
n	15	15	15	15	30	
Mean	11.343	10.387	1.677	1.520	0.157	-0.599, inf
Std. Err.	0.274	0.311	0.249	0.273		
Median	11.400	10.600	1.750	1.450		
Minimum	9.65	8.10	-0.15	-0.55		
Maximum	13.20	11.95	3.60	3.50		

Change from Baseline in Mean Hgb (g/dL, ±SE) - ITT Population



Mean changes from baseline in Hgb were comparable between velaglucerase alfa and imiglucerase treatment groups and the predefined primary endpoint was met. However, there was a 0.8 g/dL difference in median Hgb between groups at baseline, which was maintained throughout the study. The CHMP requested a discussion on whether the difference in baseline Hgb indicates clinically relevant differences in disease severity between groups and whether this difference might have masked a difference in Hgb response to therapy. An adequate discussion on these findings has been provided. Analysis adjusting for the baseline haemoglobin concentration values confirmed the primary efficacy analysis. The baseline difference is also considered to be to the disadvantage of the efficacy of velaglucerase alfa rather than imiglucerase and thus, adding re-assurance to the assessment of the efficacy of velaglucerase alfa.

Secondary endpoints

Platelet Count

Mean platelet counts increased with both treatments. Baseline values were higher in the imiglucerase compared to the velaglucerase alfa group (181.2 vs. 161.1 x 10^9/L); the difference was not considered clinically meaningful. The difference persisted at each assessment and appeared to increase in the latter half of the study. At Week 41 the unadjusted mean change was 110.4 x 10^9/L in the velaglucerase alfa and 144.4 x 10^9/L in the imiglucerase group. The model-based estimated treatment difference in mean change at Week 41 was 38.71 x 10^9 cells/L, with a 95% CI of -88.42 to 10.99, and thus not statistically significant. The difference might partially be explained by the fact that all four children under the age of 5 years, 3 with spleen and 1 splenectomised, were randomised to imiglucerase indicating a more severe course of disease; children with more severe disease are expected to have a better response to treatment. Post hoc analyses suggest that patients in the 2 - 4 years age group have skewed the data; those three not splenectomised had large spleens and low

platelet counts at baseline and appeared to have worse disease at the start of the study. Results of the post-hoc analysis suggest that there is no relevant difference in changes in platelet count between velaglucerase alfa and imiglucerase.

Platelet Counts observed Values at Baseline and Change from Baseline – ITT Population

	Baseline		Change from Baseline Week 41		Difference in Mean Change between Treatment Groups	
Platelet Count	velaglucerase alfa 60 U/kg	imiglucerase 60 U/kg	velaglucerase alfa 60 U/kg	imiglucerase 60 U/kg	Mean Treatment Difference	97.5% One-sided CI (L, U)
n	17	17	17	17		34
Mean	161.12	181.21	110.41	144.38	-38.71	(-88.42, 10.99)
Std. Err.	22.068	24.580	17.159	22.760		
Median	172.00	188.00	98.00	119.00		
Minimum	44.0	63.0	20.0	32.0		
Maximum	310.5	430.5	271.0	314.5		

Liver Volume
Mean normalised liver volumes were 4.44% and 4.16% of body weight at baseline and 3.13% and 3.06% at Week 41 on velaglucerase alfa and imiglucerase, respectively. Corresponding median normalised liver volumes were 3.90% and 4.00% at baseline and 2.6% and 3.0% at week 41, respectively. Model-based estimated mean treatment difference was -0.07% of body weight with a 95% CI of -0.43 to 0.29. Thus, the mean change was comparable between groups and not statistically significant different. Change in liver volume is considered comparable between groups.

Spleen Volume
Twenty splenectomised patients, 10 per group, were excluded and thus results are based on 7 patients per group. Mean normalised spleen volumes were 2.53% and 4.24% of body weight at baseline and 1.19% and 1.79% of body weight at week 41 on velaglucerase alfa and imiglucerase, respectively. Corresponding median normalised values were 1.90% and 1.40% of body weight at Baseline and 1.00% and 0.90% of body weight at Week 41. Results indicate a substantial reduction in spleen volume during treatment. The model-based estimated mean treatment difference for the mean change was 0.08% of body weight with a 95% CI of -0.52 to 0.68. Although there is a considerable imbalance in mean spleen volume at baseline results indicate a comparable response on change in spleen volume between groups (see also section on platelet count).

Plasma Chitotriosidase
Chitotriosidase levels were measured in 21 patients, 11 on velaglucerase alfa and 10 on imiglucerase. Twelve of 13 patients in whom chitotriosidase was not detected had a 24bp duplication. Baseline median chitotriosidase levels were 45,534.2 nmol/mL/h in the velaglucerase alfa and 50,076.9 nmol/mL/h in the imiglucerase group; levels decreased during treatment. At Week 41, unadjusted mean decrease was 34,711.9 nmol/mL/h on velaglucerase alfa and 35,109.5 nmol/mL/h on imiglucerase. Using a linear mixed model adjusting for Baseline chitotriosidase values, splenectomy status and age at informed consent (2 to 17 vs. ≥18), the estimated mean treatment difference was -703.6 nmol/mL/h with a 95% CI of -11,762.3 to 10,355.1. The CHMP concluded that the effects on plasma chitotriosidase values are comparable between groups.

Plasma CCL18
Median Baseline CCL18 levels were 1,637.0 ng/mL and 1,849.0 ng/mL for the velaglucerase alfa and imiglucerase groups, respectively. Levels decreased over treatment; Week 41 unadjusted mean changes were -926.2 ng/mL (-55.12%) and -1153.4 ng/mL (-48.82%) for the velaglucerase alfa and imiglucerase groups, respectively. Using a linear mixed model adjusting for Baseline chitotriosidase values, splenectomy status and age at informed consent (2 to 17 vs. ≥ 18), the estimated mean treatment difference was 145.7 ng/mL with a 95% CI of -186.6 to 480.0. Effects on plasma CCL18 values are comparable between groups.

Time to first Hgb response
Time to first Hgb response, defined as an increase of ≥1 g/dL from Baseline, was similar between groups (log-rank p-value = 0.8965). 2 patients, 1 per group, were censored due to study discontinuation prior to reaching a first Hgb response and 1 patient on velaglucerase alfa completed

the study without achieving a ≥1 g/dL change from Baseline in Hgb. Time to first Hgb response was comparable between groups.

Tertiary endpoints

Annualised growth velocity, difference in skeletal from chronological age, and Tanner stage in patients 2 to 17 years
Medians for annualised growth velocity at study endpoint were 7.7 cm/year and 8.3 cm/year for velaglucerase alfa (n=3) and imiglucerase (n=5), respectively. Median differences between chronological age and calculated skeletal age at Baseline were -2.00 (n=4) and -1.15 (n=4) for velaglucerase alfa and imiglucerase, respectively. Medians at study endpoint were -0.90 (n=3) and -2.10 (n=5), respectively. Of the four paediatric patients in the velaglucerase alfa group, 2 patients were Tanner stage 1 at Baseline, 1 of these remained Stage 1 at study endpoint and the other had missing data; 1 patient was stage 3 at Baseline and stage 4 at study endpoint; 1 patient was at stage 4 at both time points. All five paediatric patients in the imiglucerase group were Tanner stage 1 at both Baseline and Week 41. Mean and median annualised growth velocity was slightly higher in patients on imiglucerase. However, maximum results observed with imiglucerase are considerably higher compared to velaglucerase alfa and the low number of patients per group does not allow for any definite conclusion. The limited data on difference in skeletal from chronological age and the development of Tanner stage do not allow for a meaningful conclusion on the comparison between groups. Analyses of annualised growth velocity and Tanner stage are hampered not only by the low absolute numbers, but also by the significant imbalance in age.

Quality of life
In the adult group results of the analyses of the SF36 questionnaire showed improvements for both groups in most categories investigated. 6 of 10 (60%) patients in the velaglucerase alfa and 7 of 9 (78%) patients in the imiglucerase group reported an either "much better now than 1 year ago" or "somewhat better now than 1 year ago" health. In the group of children 5 to 17 years old only 1 patient per group completed the CHQ-PF50 questionnaire at Week 41; both reported a "somewhat better now than 1 year ago" health. For adults changes in QoL measurements appear to be comparable between groups. For younger patients data do not allow for any conclusion (1 patient per group only).

Cytokines
TNF-α, IL-6, IL1-β, IL-8, IL-13, CD14, and GM-CSF were measured at Baseline, Week 13, Week 25, and at study endpoint. No consistent patterns were observed for these data.

Other exploratory endpoints included measurements of bone biomarkers by DXA and MRI of lumbar spine and femoral neck for adult and paediatric patients, respectively, as well as alkaline phosphatase, NTx and CTx in adult patients. As it was not expected to see changes after 40 weeks of treatment, only baseline measures were collected and these were not summarised but intended to serve as a reference for patients continuing in the long-term open-label study.

Responder analysis
As requested in the CHMP scientific advice analyses of response categories for Hgb, platelet count, and liver and spleen volumes were performed. For Hgb response categories on velaglucerase alfa, 52.9% (9/17) had a good response (increase from baseline ≥1.5 g/dL), 35.3% (6/17) had a moderate response (>0.5 g/dL, <1.5 g/dL), and 11.8% (2/17) had no response (≤0.5 g/dL). Corresponding figures on imiglucerase were 41.2% (7/17), 41.2% (7/17), and 17.6% (3/17), respectively. For platelet count response categories, 15 patients with platelet counts below normal (150×10^9/L) at baseline were evaluated, 8 on velaglucerase alfa and 7 on imiglucerase. Categories were *good response* (>30×10^9/L), *moderate response* (>15×10^9/L and ≤30×10^9/L), and *no response* (≤15×10^9/L). In the velaglucerase alfa group, 7 patients had a good and 1 a moderate response; all 7 patients on imiglucerase had a good response. For liver volume response categories 16 patients on velaglucerase alfa and 15 on imiglucerase were included, categorised as good response (≥30% reduction from baseline), moderate response (≥10% and <30%), or no response (<10%). Distribution of patients across response categories for each treatment group was similar. For spleen volume response categories 7 patients on velaglucerase alfa and 6 on imiglucerase were included. They were categorised as good response (≥30% reduction from baseline), moderate response (≥10% and <30%), or no response (<10%). All patients achieved a good response. In conclusion, exploratory endpoints Hgb, platelet count, liver and spleen volume response categories showed comparable results

between velaglucerase alfa and imiglucerase groups. Response categories as proposed in the CHMP scientific advice (July 2006) were used.

2.4.7.2.2.6. Ancillary analyses

Prospectively defined subgroup analyses were planned for exploratory purposes only. The effect of velaglucerase alfa and imiglucerase on haemoglobin concentration were compared at Week 41 within the following subgroups: age (2 to 17 years old; ≥18 years old); gender (male; female);and splenectomy status. The 95% confidence intervals for each estimated treatment difference included 0, demonstrating that there were no statistically significant treatment differences between the two groups in change in haemoglobin concentration for the subgroups examined. The differences are summarized in the below table.

Haemoglobin Concentration (g/dL): Difference in Mean Change from baseline to week 41 between randomized Treatment Group (velaglucerase alfa vs imiglucerase) according to age, gender, and splenectomy status–ITT Patient population

	Treatment Difference[a] in the Change from Baseline[b] to Week 41		
Subgroup	n	Mean Treatment Difference	95% Two-Sided CI
Age			
2 to 17 years old	9	-0.355	(-1.909, 1.199)
≥18 years old	25	0.378	(-0.444, 1.200)
Gender			
Males	16	-0.031	(-1.310, 1.248)
Females	18	0.283	(-0.424, 0.991)
Splenectomy status			
Yes	20	0.525	(-0.385, 1.435)
No	14	-0.421	(-1.593, 0.750)

Note: Imputation was applied to missing data.
[a] The treatment difference reflects velaglucerase alfa compared to imiglucerase
[b] Baseline is the modified baseline hemoglobin concentration.

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

Analysis of results across trials has not been provided. However, assessment of data from single trials indicates comparable effects of velaglucerase alfa on Hgb, platelet count and organ volumes across the trials.

2.4.7.4. Clinical studies in special populations

No clinical studies in special populations have been performed. However, in study TKT032 exploratory subgroup analyses were pre-specified for age groups 2 to 17 years versus ≥18 years, gender and anti-velaglucerase alfa antibody status (positive; negative). Since only one patient developed anti-velaglucerase alfa antibodies, no subgroup analysis of anti-velaglucerase alfa antibody status has been performed. No subgroup analyses have been provided for studies HGT-GCB-039 and TKT034. Analyses of Hgb for subgroups age and gender in trial TKT032 do not indicate differences in the response to treatment for either age or gender.

2.4.7.5. Supportive study(ies)

Study HGT-GCB-039 is the only trial providing controlled data. The statistical analyses provided in the study reports of the supportive trials TKT025, TKT025EXT, TKT032 and TKT034 are not considered relevant, since none of these had a comparator. Details of baseline characteristics for the supportive trials are listed in the following table.

Baseline Demographic Profile of Patients in Velaglucerase alfa Supportive Studies

	ERT-naïve				Transitioned
	TKT025	**TKT025EXT**	**TKT032**		**TKT034**
	N=12	**N=10**	**N=25**		**N=40**
	60 U/kg	**60 U/kg**	**45 U/kg**	**60 U/kg**	**15 to 60 U/kg**
Age (years)					
Mean	41.68	38.8	31.2	20.5	35.6
±SD	±17.31	±16.36	±16.75	±11.77	±18.37
Median	39.30	35.0	30.0	23.5	36.5
Range	18.8 – 69.8	18 – 62	6 – 62	4 - 42	9 - 71
Groups					
Age Range					
2 to 4 years	0	0	0	1 (8.3)	0
5 to 17 years	0	0	3 (23.1)	3 (25.0)	9 (22.5)
≥18 years	12 (100)	10 (100)	10 (76.9)	8 (67.7)	31 (77.5)
Sex (n; %)					
Male	5 (41.7)	4 (40.0)	8 (61.5)	7 (58.3)	18 (45.0)
Female	7 (58.3)	6 (60.0)	5 (38.5)	5 (41.7)	22 (55.0)
Race (n; %)					
Asian					1 (2.5)
Black					
Caucasian	12 (100)	10 (100)	13 (100)	12 (100)	37 (92.5)
Other					2 (5.0)
Gaucher disease genotype (n; %)					
N370S/N370S		4 (40.0)	3 (23.1)	4 (33.3)	14 (35.0)
Other		6 (60.0)	10 (76.9)	8 (67.7)	26 (65.0)
Splenectomy	0	0	0	0	4 (10.0)
Positive for anti-imiglucerase antibodies	0	0	0	0	3
Patients Completed	11[a]		13	12	38[b]
Patients Dosed (ITT and Safety Population)	12		13	12	40
Study Duration (months)	9	60	12	12	12
Total Patients enrolled	12	10	13	12	41
Transitioned to TKT025EXT	10	n/a	n/a	n/a	n/a

Abbreviations: Vela = velaglucerase alfa; imi = imiglucerase; n/a = not applicable

[a] 1 patient withdrew consent

[b] 2 patients withdrew consent and 1 patient withdrew due to an SAE. 41 patients were randomised but only 40 were dosed.

Study TKT025

Study TKT025 was a Phase I/II open-label study conducted April 2004 to April 2005 and the initial clinical trial. It was conducted at a single study centre in Israel. Twelve treatment-naïve (≥12 months) patients were included. Phase I consisted of a dose-escalation design; the first patient received two 15 U/kg doses and then one 30 U/kg dose. The next two patients received one 15 U/kg and then one 30 U/kg dose. Based on acceptable safety evaluations, all three patients had their doses increased to 60 U/kg. Further nine patients in the second phase were dosed at 60 U/kg throughout the study. Patients were treated every other week (EOW) for total of 20 doses. In the pooled analyses all twelve patients were included in an "As Received" 60 U/kg treatment group since 60 U/kg was the dosage predominantly received.

Clinically relevant and statistically significant mean increases from baseline in Hgb and statistically significant mean increases in platelet counts were observed after 3 months of therapy, as well as statistically significant reductions from baseline in mean liver and spleen volumes after 6 month (first scheduled liver and spleen evaluation). Reductions in biomarker values of serum chitotriosidase and CCL18 were observed after 3 months. Changes in these parameters were continuous during the course of the study. Each patient experienced improvements in at least 2 of the 4 therapeutic parameters Hgb, platelet counts, spleen volume, or liver volume. Key results are given in the following table.

Summary of key results for study TKT025

	Baseline n=12	Week 13 (month 3) n=11	Week 25 (month 6) n=11	Week 37 (month 9) n=11
Haemoglobin (g/dL)				
Observed value (mean)	11.59	12.89	13.57	13.89
% change from baseline (mean)	-	10.51	16.49	19.22
p-value		p<0.001	p<0.001	p<0.001
Platelet count (x 10^3/mm^3)				
Observed value (mean)	57.3	66.4	80.8	98.1
% change from baseline (mean)	-	14.6	37.8	67.6
p-value		p=0.028	p=0.013	p=0.002
Liver volume (% of body weight)				
Observed value (mean)	4.19	-	3.43	3.31
% change from baseline (mean)	-	-	-14.71	-18.20
p-value			p=0.002	p<0.001
Spleen volume (% of body weight)				
Observed value (mean)	3.81	-	2.25	1.98
% change from baseline (mean)	-	-	-41.43	-49.47
p-value			p<0.001	p<0.001

No clinically significant changes or trends were observed in pulmonary function, bone density, bone marrow as evaluated by MRI, or cardiac function as evaluated by ECG. The efficacy data from study TKT025 are consistent with a clinically significant positive effect of velaglucerase alfa dosed as 60 U/kg EOW on relevant markers of type 1 Gaucher disease. Effects were maintained throughout nine month duration of the trial. The pharmacokinetics is described in section 3.4.3.

Study TKT025EXT

Study TKT025EXT is an ongoing, open-label extension study of velaglucerase alfa therapy in patients who completed study TKT025. Patients continued with 60 U/kg EOW for at least 3 months. At 12 months of cumulative therapy, patients were evaluated for a reduction in dose, a transitional dose of 45 U/kg administered EOW for 3 months and 30 U/kg thereafter. To be eligible, patients must have met at least 2 of the 4 pre-defined therapeutic goals for year-one (i.e. Hgb ≥11.0 g/dL females, children, ≥12.0 g/dL males within 12 to 24 months of treatment in the absence of iron deficiency; 1.5-fold increase in platelet count in patients with intact spleen, avoiding splenectomy and preventing surgical, obstetrical or spontaneous bleeding; reduction of liver volume by 20% to 30% within one year of treatment, maintenance of liver volume to 1 to 1.5-times normal volume; reduction of spleen volume by 30% to 50% within one year of treatment, maintenance of spleen volume to ≤2 to 8-times normal volume while alleviating symptoms due to splenomegaly. The primary objective was the evaluation of the long-term safety of velaglucerase alfa when administered IV at a dose of 30 or 60 U/kg. The secondary objective was the assessment of the effects of velaglucerase alfa on clinical activity in these patients as measured by haematological parameters and reduction in liver and spleen volumes.

Of the eleven patients who completed Study TKT025, ten elected to enrol in TKT025EXT. As of 1 June 2009, the data cut-off, 8 of 10 patients were still participating and had been receiving velaglucerase alfa EOW for 60 months. The predominant dose of velaglucerase alfa received in this extension was 30 U/kg. The preliminary data indicate that mean Hgb remained within the normal range. At 60 months, there was a mean increase in Hgb concentration from baseline of +2.38 g/dL (95% CI: 1.60, 3.16; 21.26% change). The improvement in the Hgb concentration continues to be maintained in the 8 remaining patients. Mean increase in platelet count from baseline at 60 months was +85.1 x 10^9/L (95% CI: 59.8, 110.4; 157.18% change). The improvement in platelet count is robust at 60 months and not only is velaglucerase alfa treatment maintaining the effect achieved so far, but continues to improve the platelet count even after 5 years of therapy. Mean decrease in normalised liver volume following 57 months of treatment revealed a mean percent reduction from baseline of -38.80% (95% CI: -49.10, -28.50). The reduction in mean normalised liver volume continues to be maintained in the remaining 8 patients who are still on the study. Spleen volume following 57 months treatment revealed a mean percent reduction in normalised spleen volume from baseline of -73.97% (95% CI: -89.33, -58.60) and the improvement in spleen volume continues to be maintained in the remaining 8 patients.
Study TKT025EXT shows that the treatment effect is maintained over an extended period of five years in spite of lowering of the dose by 50%. Since this study might contribute relevant information for dosing in maintenance therapy, the a commitment to provide the final study report 6 months after finalisation of this trial in form of a follow-up measure has been agreed.

Study TKT032
Study TKT032 is a completed, randomised, Phase III, double-blind, parallel group, 2-dose, multi-centre, multinational, 12-month clinical study designed to evaluate the efficacy and safety of velaglucerase alfa in patients with type 1 Gaucher disease. It was conducted between February 2007 and April 2009, the study report is dated July 2009. To be eligible patients were to be treatment-naïve, defined as no Gaucher disease therapy ≤30 months prior to study entry. Eligible patients were randomly allocated 1:1 to either a fixed dose of 60 or 45 U/kg of velaglucerase alfa EOW. Splenectomised patients were excluded. Twenty-five patients were randomised, 13 to 45 U/kg and 12 to 60 U/kg; all 25 patients completed the study. The primary endpoint was the change in Hgb from baseline to month 12 in patients treated with 60 U/kg velaglucerase alfa EOW (ITT population). Velaglucerase alfa 60 U/kg led to a clinically meaningful and statistically significant ($p<0.0001$) increase in mean Hgb from baseline of 2.43 g/dL (23.25%). Median Hgb was 10.825 g/dL and 12.550 g/dL at baseline and study endpoint, respectively.

Regarding the secondary endpoints, velaglucerase alfa at 45 U/kg EOW led to a clinically and statistically significant increases in mean Hgb of 2.438 g/dL ($p=0.0001$, adjusted for multiple testing), a 23.81% increase. In both dose groups statistically significant mean increases from Baseline in platelet counts were observed, 50.88 x 10^9/L (65.93%, $p=0.0016$) and 40.92 x 10^9/L (66.38%, $p=0.0111$) in the 60 U/kg and 45 U/kg dose groups, respectively. Mean normalised spleen volume decreased statistically significant by 1.92% ($p=0.0032$) and 1.87% ($p=0.0085$) of body weight in the 60 U/kg and 45 U/kg dose groups, respectively, corresponding to -50.35% and -39.88% changes from baseline. Decreases from baseline in mean normalised liver volume were less pronounced. Results were not statistically significant after adjusting for multiple testing. Mean values of CCL18 and chitotriosidase levels decreased throughout the study in both dose groups. Regarding the secondary endpoint QoL (SF-36 or CHQ-PF50) no conclusions could be drawn due to small sample sizes for each item evaluated. Regarding tertiary endpoints, time to first response of at least +1 g/dL was reached for all patients at Week 27 and at Week 37 in the 60 U/kg and 45 U/kg groups, respectively. Analyses of the modified ITT population confirmed results of the ITT population.

Summary of key results for study TKT032

	Baseline			Week 53		
	GA-GCB Overall n=25	**GA-GCB 45 U/kg n=13**	**GA-GCB 60 U/kg n=12**	**GA-GCB Overall n=25**	**GA-GCB 45 U/kg n=13**	**GA-GCB 60 U/kg n=12**
Haemoglobin (g/dL)						
Observed value (mean)	10.706	10.723	10.688	13.140	13.162	13.117
Platelet count (x 10^3/mm^3)						
Observed value (mean)	95.70	84.38	107.96	141.40	125.31	158.83
Liver volume (% of body weight)						
Observed value (median)	-	3.50	3.65	-	3.10	3.05
% change from baseline (mean)	-	-	-	-11.40	-6.22	-17.02
Spleen volume (% of body weight)						
Observed value (median)	-	2.90	2.80	-	1.90	1.15
% change from baseline (mean)	-	-	-	-44.90	-39.88	-50.35

The assumption of a difference in efficacy between the velaglucerase alfa dose groups in this study was based on the observation of differences in Hgb first response, platelet response categories, and the reduction of liver volumes. No other comparisons of dose related effects have been provided. In the group receiving 60 U/kg, 100% of patients had a Hgb first response (increase >1.0 g/dL) 10 weeks earlier, i.e. by Week 27, than patients on 45 U/kg, i.e. on Week 37. A comparison of platelet response categories between dose groups showed fewer non-responders on velaglucerase alfa 60 U/kg compared to 45 U/kg. A moderate to good response was defined as an increase in platelet count of at least 15 x 10^9/L in patients with below normal values at baseline (<150 x 10^9/L). Regarding liver volumes, although both doses resulted in a marked reduction by month 12, results achieved a nominal significance level of 0.05 within the velaglucerase alfa 60 U/kg group but not the 45 U/kg group, suggesting a dose-related effect in favour of velaglucerase alfa 60 U/kg. However, according to the clinical study report and the statistical analysis plan no direct statistical comparisons of the 45 and 60 U/kg dose groups were planned or conducted. Comparison of Hgb results by age groups for adults and paediatric (<17 years) and by gender did not indicate a difference between groups independent of dose. Regarding skeletal age, annualised growth velocity, changes in Tanner stage, and pulmonary function, no conclusions could be drawn due to insufficient data.

In conclusion no formal comparisons of the different dose groups in this trial have been pre-specified or provided. It appears that effects on Hgb and platelet count were equal or greater in the 45 U/kg group while the opposite was seen for effects on liver and spleen volume and time to first response, indicating an earlier response in the 60 U/kg group.

Study TKT034
Study TKT034 is a completed, multi-centre, Phase II/III, open-label, 12-month study designed to evaluate safety of velaglucerase alfa therapy for patients who had received imiglucerase therapy for at least 30 consecutive months. The study was conducted between July 2007 and June 2009. Patients splenectomised or positive for imiglucerase antibodies were not excluded. Patients were required to have received imiglucerase at a constant dose during 6 months prior to study enrolment. Patients received the same dose in U/kg of velaglucerase alfa as prior imiglucerase. Prior imiglucerase dose ranged from 15 to 60 U/kg. Administration of velaglucerase alfa at home was available to patients who met the necessary requirements. Patients were monitored for changes in clinical parameters such as Hgb, platelet count, and liver and spleen volume. Forty-one patients were enrolled and 40 received at least one full or partial dose. One patient withdrew consent prior to receiving study drug. For analysis data were summarised based on mean dose in 1 of 4 nominal dose groups presented in the following table.

Assignment to "As Received" Dose Groups Based on Mean Dose

	Dosage (U/kg)			
Nominal 'As-Received' Dosage	**15**	**30**	**45**	**60**
Observed Dosage	≤ 22.5	> 22.5 to ≤ 37.5	> 37.5 to ≤ 52.5	> 52.5
Patients n (%)	15 (37.5%)	12 (30.0%)	6 (15.0%)	7 (17.5%)

The main focus of this trial was on the safety assessment of switching patients from imiglucerase to velaglucerase alfa. In terms of efficacy, the mean baseline Hgb was sustained throughout the study. Median Hgb at baseline was 13.775 g/dL. Mean change from baseline was -0.101 g/dL and the corresponding 90% CI was -0.272 to 0.070, within the efficacy criterion of ±1 g/dL. Mean baseline platelet count was also sustained during the study; median platelet count was 162,000 × 10^9/L and the % change from baseline was 7.04% with a 90% CI of 0.54 to 13.53, within the efficacy criterion of ±20%. The mean baseline normalised liver volume was sustained from baseline over the course of the study. At baseline the mean normalised liver volume was 2.1%; after 51 weeks the mean percent change from baseline in normalised liver volume was -0.03% with a 90% CI of -2.62% to 2.56%, within the predefined efficacy criterion of 15%. The mean baseline normalised spleen volume was sustained throughout the trial. Baseline mean normalised spleen volume was 0.84%; mean percent change from Baseline was -5.56% with a 90% CI of -10.77% to -0.35%, within the predefined efficacy criterion of 15%.

2.4.8. Discussion on clinical efficacy

The proposed indication for velaglucerase alfa was the long-term ERT for patients with type 1 Gaucher disease. Currently, only imiglucerase is authorised for the treatment of this condition. Data from 4 finalised clinical trials, one which was designed as a non-inferiority trial to imiglucerase, were provided. Other trials were uncontrolled. Trial HGT-GCB-039 is considered to be the pivotal study. No placebo controlled data have been provided, which is acceptable for the patient population investigated.

In trial HGT-GCB-039, treatment with 60 U/kg velaglucerase alfa over 9 months was comparable to treatment with 60 U/kg imiglucerase in treatment-naïve patients. Mean changes from baseline in Hgb were comparable between velaglucerase alfa and imiglucerase treatment groups and the pre-defined primary endpoint was met. However, there was a 0.8 g/dL difference in median Hgb between groups at baseline, which was maintained throughout the study. An analysis adjusting for the baseline Hgb concentration values confirmed the primary efficacy analysis. Furthermore, the baseline difference is considered to be to the disadvantage of the efficacy of velaglucerase alfa rather than imiglucerase and thus, adding more reassurance for the assessment of velaglucerase alfa efficacy. Regarding the secondary endpoint platelet count, study results in the post-hoc analysis suggest that there is no relevant difference in changes between velaglucerase alfa and imiglucerase. Although there was a considerable imbalance in mean spleen volume at baseline, the obtained results indicate a comparable response in change of spleen volume between the groups. Change in liver volume, effects on plasma chitotriosidase and CCL18 values, and time to first Hgb response were comparable between the groups.

Mean and median annualised growth velocity were slightly higher in patients on imiglucerase, but the low number of patients per group does not allow for any definite conclusion. The limited data on difference in skeletal from chronological age and the development of Tanner stage do not allow for a meaningful conclusion on the comparison between groups. Analyses of annualised growth velocity and Tanner stage are hampered not only by the low absolute numbers, but also by the significant imbalance in age subgroups in the paediatric population.

For adults changes in QoL measurements appear to be comparable between groups. Data do not allow any conclusion for paediatric patients (only one patient per group). The exploratory endpoints of Hgb levels, platelet count, liver and spleen volume response categories showed comparable results between velaglucerase alfa and imiglucerase groups; response categories as proposed in the CHMP scientific advice from July 2006 were used.

Data from 4 supportive studies were provided:

- Efficacy data from study TKT025 are consistent with a clinically significant positive effect of velaglucerase alfa dosed as 60 U/kg EOW on relevant markers of type 1 Gaucher disease. Effects were maintained throughout the 9 month duration of the trial.
- Study TKT032 provided results from two dose groups of velaglucerase alfa patients, 45 and 60 U/kg. No formal comparisons of these dose groups have been pre-specified or provided and thus, this trial is considered uncontrolled. It appears that effects on Hgb and platelet count were equal or greater in the 45 U/kg dose group, while the opposite was seen for effects on liver, spleen volume and time to first Hgb response, indicating an earlier response in the 60 U/kg group.
- The main focus of study TKT034 was on the safety assessment of transitioning patients from imiglucerase to velaglucerase alfa. Regarding efficacy mean baseline Hgb, platelet count, and normalised liver and spleen volumes were sustained throughout this study.
- There are currently no final data from study TKT025EXT contributing to the efficacy evaluation of velaglucerase alfa. The preliminary data indicate that the treatment effect is maintained over an extended period of five years in spite of lowering of the dose by 50%. Further information on the appropriate maintenance dose is expected to be derived from the final study results. Final study report will be provided within 6 months after finalisation of this trial.

Overall, data from these trials support the assumption that velaglucerase alfa is effective in type 1 Gaucher disease patients.

No clinical studies in special populations have been performed. Exploratory subgroup analyses of data from study TKT032 do not indicate differences in the response to treatment for either age or gender. Data from children are scarce and relevant information has been included in the SmPC. Although no analyses of efficacy data across the clinical trials have been conducted, assessment of data from single trials indicates comparable effects of velaglucerase alfa on Hgb, platelet count and liver and spleen organ volumes across all trials.

2.4.9. Conclusions on the clinical efficacy

Efficacy data from trial HGT-GCB-039 indicate that velaglucerase alfa 60 U/kg EOW in treatment naïve patients is not inferior to imiglucerase as assessed by increases in Hgb and platelet count. Results from supportive studies are in line with the findings in the pivotal trial. Long term data do not indicate any inconsistent effects in increases in Hgb and platelet count, or decreases in liver and spleen volumes. Efficacy results were consistent between the limited paediatric and adult patient population and no gender related differences were observed.

2.4.10. Clinical safety

Safety data are derived from the Phase I/II study TKT025, the Phase II/III or III studies TKT032, TKT034, and HGT-GCB-039, and the extension study TKT025EXT. Study TKT025EXT is ongoing, but safety data report with data cut-off 01 June 2009 has been provided. Velaglucerase alfa clinical programme does not compare velaglucerase alfa to placebo. The only available controlled safety data are from trial HGT-GCB-039 comparing velaglucerase alfa to ERT imiglucerase, the current standard of treatment in type 1 Gaucher disease. Discussion of the safety of velaglucerase alfa in comparison to imiglucerase has not been provided but reference is made to the HGT-GCB-039 clinical study report.

2.4.10.1. Patient exposure

Exposure to velaglucerase alfa in the clinical programme is limited. However, in light of the low prevalence of type 1 Gaucher disease, exposure is considered adequate to assess safety, especially since a large proportion of patients have been treated for at least one year. There are safety data available for as long as 60 months of treatment.

Different pools for the integrated safety analysis have been compiled and evaluated:

- Treatment naïve patients from TKT025, TKT032, and HGT-GCB-039 pooled for 0 to 9 months exposure;
- Treatment naïve patients from TKT025, TKT025EXT, and TKT032 pooled for 0 to 12 months exposure;
- Treatment naïve patients from TKT025EXT for >9 months exposure;
- Patients transitioning from imiglucerase (TKT034).
-

Overall 94 patients have been treated with velaglucerase alfa 15 to 60 U/kg. Of these, 54 patients were treatment-naïve as pre-defined, 41 on 60 U/kg. Ten out of eleven patients who completed study TKT025 continued in extension study TKT025EXT, eight of these have received 51 months of treatment (cumulative exposure 60 months). Forty patients transitioning from imiglucerase were included in TKT034, with doses of 15 to 60 U/kg; equivalent to their previous dose of imiglucerase. Twenty-five (22.5%) patients were in the paediatric age group (2-17 years); the majority of all patients were white. Gender was balanced between treatment groups in all populations.

Number of Patients Exposed to Velaglucerase alfa

Study Number/Dose	Safety Population (N)	Duration of Exposure 0 to 9 months	0 to 12 months	> 9 months
Treatment-naïve patients				
TKT032				
60 U/kg	12	12	12	NA[a]
45 U/kg	13	13	13	
HGT-GCB-039				
60 U/kg	17	17	NA	NA[a,b]
TKT025				
60 U/kg	12	12	NA	NA
TKT025EXT				
30 to 60 U/kg	10	NA	10	10
Total Treatment-Naïve patients	54	52	35	10
Patients transitioning from imiglucerase				
TKT034		NA		NA
60 U/kg	7		7	
45 U/kg	6		6	
30 U/kg	12		12	
15 U/kg	15		15	
Total TKT034	40		40	
All patients				
Overall total	94	52	75	10

[a] Patients in TKT032 were exposed to velaglucerase alfa for 12 months in TKT032 and beyond 12 months in HGT-GCB-044, however, their data are not included in the >9 months exposure group for this document.

[b] Patients randomised to velaglucerase alfa in Study HGT-GCB-039 were exposed to velaglucerase alfa for 9 months in that study and >9 months in HGT-GCB-044 however, their data are not included in the >9 month exposure group in this document

Patient exposure in the pivotal study HGT-GCB-039 is shown in the following table. Seventeen patients per group were included in the study. Duration of exposure and mean actual dose administered at each infusion were comparable between groups.

Patient Exposure – Safety Population HGT-GCB-039

	velaglucerase alfa 60 U/kg N = 17	imiglucerase 60 U/kg N = 17
Duration of velaglucerase alfa (days)		
n	17	17
Mean	256.7	260.2
Std. Dev.	36.12	27.17
Median	267.0	267.0
Minimum	118	155
Maximum	274	270
Duration of velaglucerase alfa (weeks)		
n	17	17
Mean	36.66	37.16
Std. Dev.	5.145	3.890
Median	38.10	38.10
Minimum	16.9	22.1
Maximum	39.1	38.6
Actual average dose (U/kg)		
n	17	17
Mean	59.86	59.89
Std. Dev.	0.376	0.286
Median	60.00	60.00
Minimum	58.9	59.1
Maximum	60.3	60.3
Actual average duration of infusions (minutes)		
n	17	17
Mean	60.05	60.39
Std. Dev.	0.212	0.658
Median	60.00	60.00
Minimum	59.7	59.9
Maximum	60.5	62.0

2.4.10.2. Adverse events

Treatment-Naïve Patients 0 to 9 Months Exposure
Fifty-one of 54 patients (94.4%) treated with velaglucerase alfa and 16 of 17 (94.1%) patients on imiglucerase experienced a treatment emergent adverse event (TEAE). The most common events on velaglucerase alfa were headache, nasopharyngitis, bone pain, arthralgia, pyrexia, and dizziness; on imiglucerase these were influenza, headache, nasopharyngitis, bone pain, arthralgia, and abdominal pain, upper.

Thirty-three patients (61.1%) on velaglucerase alfa experienced AEs considered possibly or probably related to study drug, 9 (69.2%) on 45 U/kg and 24 (58.5%) on 60 U/kg. On imiglucerase 6 patients (35.3%) experienced AEs considered study drug related. The majority of events were infusion-related; 1 patient on imiglucerase withdrew consent due to such an event. Five patients (9.3%) on velaglucerase alfa experienced severe AEs. Two patients treated with 45 U/kg had a single AE of Grade 3 severity. One patient had severe thrombocytopenia, reported 1 day prior to Week 9 infusion, considered not related, and resolved without sequelae and without intervention. The other patient experienced severe syncope (fainting) 1 day prior to Week 31 infusion, considered not related, and resolved without sequelae. Two patients on 60 U/kg velaglucerase alfa had severe AEs and 1 patient had a life-threatening AE. One patient had a severe prolongation of activated partial thromboplastin time (probably related). A second patient had severe worsening back pain (not related) not resolved by end of study, and severe allergic dermatitis (probably related). The third patient experienced life-threatening convulsion (not related) that was resolved by end of study. Two patients (11.8%) on 60 U/kg imiglucerase experienced 1 severe AE each; 1 patient experienced severe arthralgia (not related) and 1 patient experienced severe chills (probably related).

Summary of TEAEs 0 to 9 Months Exposure

	Patients n (%)			
	Velaglucerase alfa			Imiglucerase
Description	**Overall N = 54**	**45 U/kg N = 13**	**60 U/kg N = 41**	**60 U/kg N = 17**
Experienced No AEs	3 (5.6)	2 (15.4)	1 (2.4)	1 (5.9)
Experienced At Least 1 AE	51 (94.4)	11 (84.6)	40 (97.6)	16 (94.1)
Experienced At Least 1 Drug-Related AE	33 (61.1)	9 (69.2)	24 (58.5)	6 (35.3)
Experienced At Least 1 Infusion-Related AE	28 (51.9)	8 (61.5)	20 (48.8)	4 (23.5)
Experienced At Least 1 Severe Or Life-Threatening AE	5 (9.3)	2 (15.4)	3 (7.3)	2 (11.8)
Experienced At Least 1 SAE	4 (7.4)	0	4 (9.8)	0
Discontinued Due To An AE	0	0	0	0
Deaths	0	0	0	0

Treatment-Naïve Patients 0 to 12 Months Exposure
This group only includes patients treated with velaglucerase alfa. Data are comparable to safety findings in the 0 to 9 months group.

Treatment-Naïve Patients Long-term Exposure (>9 Months)
This group only includes patients treated with velaglucerase alfa. Safety results are comparable to findings in the 0 to 9 months group and the pattern of adverse event does not appear to change over time. However the small numbers make it impossible to draw any conclusions.

Patients transitioned from Imiglucerase
The following table summarises AEs in patients transitioned from imiglucerase. Thirty-four of 40 patients (85.0%) experienced at least 1 TEAE. The most frequent AEs were headache, arthralgia, nasopharyngitis, back pain cough, pharyngolaryngeal pain, and myalgia. Eleven patients (27.5%) experienced AEs considered possibly or probably related to study drug. The majority of those events were infusion related.

Summary of AEs in Patients Transitioned from Imiglucerase

	Patients n (%)				
	Velaglucerase alfa				
	Total N = 40	**15 U/kg N = 15**	**30 U/kg N = 12**	**45 U/kg N = 6**	**60 U/kg N = 7**
Experienced No AEs	6 (15.0)	3 (20.0)	1 (8.3)	1 (16.7)	1 (14.3)
Experienced At Least 1 AE	34 (85.0)	12 (80.0)	11 (91.7)	5 (83.3)	6 (85.7)
Experienced At Least 1 Drug-Related AE	11 (27.5)	6 (40.0)	3 (25.0)	1 (16.7)	1 (14.3)
Experienced At Least 1 Infusion-Related AE	9 (22.5)	6 (40.0)	2 (16.7)	0	1 (14.3)
Experienced At Least 1 Severe Or Life-Threatening AE	5 (12.5)	0	2 (16.7)	1 (16.7)	2 (28.6)
Experienced At Least 1 SAE	4 (10.0)	1 (6.7)	1 (8.3)	2 (33.3)	0
Discontinued Due To An AE	1 (2.5)	1 (6.7)	0	0	0
Deaths	0	0	0	0	0

Study HGT-GCB-039
Adverse events were summarised by SOC and MedDRA preferred term. The following table presents an overview of these AEs.

Overall Summary of AEs HGT-GCB-039

DESCRIPTION	Patients n(%)	
	velaglucerase alfa 60 U/kg N = 17	imiglucerase 60 U/kg N = 17
Experienced No Adverse Events	1 (5.9)	1 (5.9)
Experienced At Least 1 Adverse Event	16 (94.1)	16 (94.1)
Experienced At Least 1 Drug-Related Adverse Event	8 (47.1)	6 (35.3)
Experienced At Least 1 Infusion-Related Adverse Event	5 (29.4)	4 (23.5)
Experienced At Least 1 Severe Or Life-Threatening Adverse Event	3 (17.6)	2 (11.8)
Experienced At Least 1 Serious Adverse Event	3 (17.6)	0
Discontinued Due To An Adverse Event	0	0
Deaths	0	0

Regarding the AEs occurring in ≥10% of patients in both groups, 94.1% reported at least one AE. AEs were most commonly reported within the SOCs infections and infestations, musculoskeletal and connective tissue disorders, general disorders and administration site conditions.

Sixteen patients (94.1%) experienced at least 1 TEAE. The majority of events were mild or moderate. Three patients on velaglucerase alfa had a severe or life-threatening AE; 1 patient experienced severe back pain and severe allergic dermatitis, 1 patient experienced severe prolonged activated partial thromboplastin time (aPTT) and 1 patient experienced life-threatening convulsion. Two patients on imiglucerase experienced severe AEs; 1 patient experienced severe arthralgia and 1 patient experienced severe chills. 8 patients (47.1%) on velaglucerase alfa had AEs considered possibly or probably related to study drug, including severe AEs of allergic skin reaction and severe prolonged aPTT. Six patients on imiglucerase experienced possibly or probably related AEs, including one event of severe rigors. Infusion-related AEs were experienced by 5 of 8 patients with study drug related AEs on velaglucerase alfa and 4 of 6 patients on imiglucerase.

Summary of Possibly/Probably Related TEAEs by SOC – Safety Population

System Organ Class Preferred Term[a]	Patients n(%) velaglucerase alfa 60 U/kg N = 17	 imiglucerase 60 U/kg N = 17
Any Adverse Event	8 (47.1)	6 (35.3)
Blood and lymphatic system disorders	1 (5.9)	0
Thrombocythaemia	1 (5.9)	0
Immune system disorders	1 (5.9)	0
Hypersensitivity	1 (5.9)	0
Nervous system disorders	3 (17.6)	2 (11.8)
Headache	2 (11.8)	2 (11.8)
Paraesthesia	1 (5.9)	0
Eye disorders	1 (5.9)	0
Dry eye	1 (5.9)	0
Vascular disorders	1 (5.9)	2 (11.8)
Hypotension	1 (5.9)	1 (5.9)
Flushing	0	1 (5.9)
Gastrointestinal disorders	1 (5.9)	0
Vomiting	1 (5.9)	0
Nausea	1 (5.9)	0
Skin and subcutaneous tissue disorders	2 (11.8)	1 (5.9)
Urticaria	2 (11.8)	0
Pruritus	1 (5.9)	0
Dermatitis allergic	1 (5.9)	0
Lichen planus	0	1 (5.9)
Rash	1 (5.9)	0
Musculoskeletal and connective tissue disorders	1 (5.9)	1 (5.9)
Arthralgia	1 (5.9)	0
Pain in extremity	1 (5.9)	0
Arthritis	0	1 (5.9)
Reproductive system and breast disorders	1 (5.9)	0
Pelvic pain	1 (5.9)	0
General disorders and administration site conditions	2 (11.8)	2 (11.8)
Pyrexia	0	1 (5.9)
Oedema peripheral	1 (5.9)	0
Chills	0	1 (5.9)
Face oedema	1 (5.9)	0
Chills	0	1 (5.9)
Feeling abnormal	0	1 (5.9)
Feeling cold	0	1 (5.9)
Feeling hot	0	1 (5.9)
Investigations	1 (5.9)	1 (5.9)
Activated partial thromboplastin time prolonged	1 (5.9)	0
Blood pressure systolic increased	0	1 (5.9)
Oxygen saturation decreased	0	1 (5.9)
Prothrombin time prolonged	1 (5.9)	0

In conclusion, the overall AE profile appears to be comparable between treatment groups of velaglucerase alfa and imiglucerase. However, no SAE occurred in the imiglucerase group compared to 3 SAEs on velaglucerase alfa and there was 1 case of severe prolonged aPTT on velaglucerase alfa compared to none on imiglucerase. Prolongation of aPTT is a potential risk that has to be further evaluated. For this purpose the CHMP requested a commitment for an analysis of aPTT values in both treatment groups as a follow-up measure. Additionally, bleeding disorders will be collected *via* register and included in the PSURs as closely monitored issues.

2.4.10.3. Serious adverse event/deaths/other significant events

No patient experienced a life threatening AE and no deaths were reported during studies with velaglucerase alfa. Of the 54 treatment-naïve patients who received velaglucerase alfa, 8 patients experienced a total of 12 SAEs.

Treatment-Naïve Patients, 0 to 9 Months Exposure
Four patients on velaglucerase alfa experienced a total of 5 SAEs. One SAE (allergic dermatitis) was considered related to study drug. A mild allergic skin reaction 214 days after initial dose and 7 days after the most recent administration was experienced by one patient. The skin reaction became more serious 10 days later; the patient was presented to the hospital and the event was resolved without sequelae. The skin reaction was considered severe and probably related to treatment. The patient continued on velaglucerase alfa at the same dose with added premedication of unspecified antihistamines and corticoids. Rechallenge was negative.

Treatment-Naïve Patients 0 to 12 Months Exposure
There were no SAEs in addition to those discussed in the 0 to 9 months exposure group.

Treatment-Naïve Patients Long-term Exposure (>9 Months)
Four patients experienced a total of 7 SAEs; none of these were considered treatment related.

Patients transitioned from imiglucerase
Four out of 40 patients experienced at least one SAE. In the 15 U/kg group, one patient experienced a moderate anaphylactoid, treatment related SAE upon receiving the first dose of velaglucerase alfa. The patient responded rapidly to discontinuation and supportive care, recovered without sequelae, and did not develop anti-velaglucerase alfa antibodies. Another patient in the 30 U/kg group experienced SAEs of severe face swelling and severe urticaria approximately 7 months after start of treatment. The patient required hospitalisation and the events, considered not related to the treatment, resolved without sequelae. Other SAEs were not considered to be treatment related.

HGT-GCB-039
The overview of SAEs identified in the study *HGT-GCB-039* are summarised below.

Listing of SAEs – Safety Population

Actual Treatment	Unique Subject Identifier	Reported Term for the Adverse Event	Dictionary-Derived Term (Preferred Term)	Start Date Time of Adverse Event	End Date Time of Adverse Event	Date of First Exposure to Treatment	Causality	Severity/ Intensity	Action Taken with Study Treatment
velaglucerase alfa 60 U/kg	039-165-0001	skin allergic reaction	Dermatitis allergic	2008-12-28	2008-12-31	12MAY2008	probably related	severe	dose temporarily withheld
	039-180-0003	thrombocytopenia (epistaxis)	Thrombocytopenia	2008-08-23	2008-08-24	11JUL2008	not related	moderate	dose unchanged
		thrombocytopenia (epistaxis)	Thrombocytopenia	2008-09-05	2008-10-30	11JUL2008	not related	mild	dose unchanged
	039-185-0001	convulsions	Convulsion	2008-10-29	2008-10-29	04JUL2008	not related	life threatening	dose unchanged
imiglucerase 60 U/kg	039-180-0002	thrombocytopenia (epistaxis)	Thrombocytopenia	2008-06-15	2008-06-18	08JUL2008	not related	severe	
	039-194-0002	probable sepsis	Sepsis	2008-05-15	2008-05-20	18JUL2008	not related	moderate	

In conclusion, in study HGT-GCB-039 SAE occurred only in patients treated with velaglucerase alfa, but only 1 of the 4 SAE, an allergic skin reaction, is considered probably treatment related. Since allergic skin reactions have also been described for imiglucerase, the difference is most likely a chance finding due to the low number of patients treated per group.

2.4.10.4. Laboratory findings

Investigations
In the overall safety pool, 6 treatment-naïve patients (11.1%) on velaglucerase alfa, 2 on 45 U/kg and 4 on 60 U/kg dose, experienced a prolonged activated partial thromboplastin time. No laboratory AEs have been reported for patients on imiglucerase.

In study HGT-GCB-039 analyses of serum chemistry and urinalysis parameters revealed no clinically important mean changes in either group with the exception of changes in aPTT. One patient on velaglucerase alfa reported a severe AE of prolonged aPTT (129.6 sec), which was considered probably treatment related. Prothrombin time was also prolonged (17.2 sec). Liver function tests (ALT, AST, and GGT) were normal throughout the study and the patient continued velaglucerase alfa treatment in the

extension protocol. One patient per each treatment group reported a moderate, not treatment related AE of thrombocytopenia. Data on all aPTT-measurements for the six patients who were found to have increased level during the study have been provided. The fact that all patients had an elevated aPTT at screening or baseline supports the assumption that the increase was associated with the underlying disease rather than the treatment as such. The literature data provided further support that elevated aPTT level is a known feature in Gaucher's disease. However, no summary of the characteristics of the six patients in the study has been given, thus the severity of disease, degree of liver affection or splenectomy status has not been accounted for.

Anti-velaglucerase alfa and anti-imiglucerase antibodies

In the overall safety pool of the 94 patients on velaglucerase alfa, one treatment-naïve patient was tested positive for anti-velaglucerase alfa antibodies. Of the 17 treatment-naïve patients treated with imiglucerase, 4 patients were tested positive for anti-imiglucerase antibodies. The adult male patient on velaglucerase alfa completed 12 months of treatment with 45 U/kg. Antibodies were characterised as IgG and neutralising and were detected only after 1 year of treatment. Patient's modified Hgb and platelet count baseline values were 12.25 g/dL and 33.5 x 10^9/L, respectively. Corresponding Week 53 values were 13.6 g/dL and 54.0 x 10^9/L, respectively. No AEs were reported during the study.

In the 4 patients on imiglucerase antibodies were characterised as IgG. IgG antibody in one patient was neutralising, and the patient also had neutralising anti-velaglucerase alfa antibodies. Cross-reaction between antibodies is not considered surprising since both proteins share extensive sequence homology. The patient experienced multiple infusion-related AEs throughout the study and eventually withdrew consent due to these events. Patients in the extension study TKT025EXT were tested negative for anti-velaglucerase alfa antibodies until data cut-off. Of the 40 patients who transitioned from imiglucerase to velaglucerase alfa, no patient tested positive for anti-velaglucerase alfa antibodies, including 3 patients tested positive for anti-imiglucerase antibodies at screening. In study HGT-GCB-039, all patients in the safety population were negative for both anti-imiglucerase and anti-velaglucerase alfa antibodies at baseline. No patient in the velaglucerase alfa group developed anti-velaglucerase alfa or anti-imiglucerase antibodies. Four (25.0%) patients in the imiglucerase group developed anti-imiglucerase antibodies. One of the patients had anti-velaglucerase alfa antibodies; neutralising antibodies for imiglucerase and velaglucerase alfa were present. Development of anti-velaglucerase alfa antibodies can be attributed to cross-reaction in the assay, as this patient had never been exposed to velaglucerase alfa. This patient experienced AEs of thrombocytopenia, flushing, upper abdominal pain, abdominal discomfort and others. Nasopharyngitis, rhinitis, convulsion, lichen planus, or influenza-like illness was reported among the 3 remaining patients positive for anti-imiglucerase antibody.

Overall laboratory findings do not indicate significant differences between treatment groups. Antibody formation appears to be numerically higher in patients on imiglucerase than on velaglucerase alfa. However absolute numbers are low and thus no definite conclusion is possible.

Summary of Anti-velaglucerase alfa and Anti-imiglucerase Antibodies Study HGT-GCB-039 – Safety Population

	Anti-velaglucerase alfa Antibody		Anti-imiglucerase Antibody	
	Velaglucerase alfa 60 U/kg N=17 n (%)	Imiglucerase 60 U/kg N=17 n (%)	Velaglucerase alfa 60 U/kg N=17 n (%)	Imiglucerase 60 U/kg N=17 n (%)
Negative	17 (100.0)	16 (94.1)	17 (100.0)	13 (76.5)
Positive	0	1 (5.9)	0	4 (23.5)
IgG	0	1 (5.9)	0	4 (23.5)
IgA	0	0	0	0
IgM	0	0	0	0
IgE	0	0	0	0
Neutralizing Antibodies	0	1 (5.9)	0	1 (5.9)

2.4.10.5. Safety in special populations

Subgroup analyses of AE for age, gender, and splenectomy status have been provided. The findings do not indicate differences in the AE profiles for age groups, gender, or splenectomy status. However, absolute numbers per group are too small for any definite conclusion.

2.4.10.6. Safety related to drug-drug interactions and other interactions

No data on drug-drug or drug-disease interactions with regard to safety have been provided and this is considered acceptable.

2.4.10.7. Discontinuation due to adverse events

The analyses of discontinuations due to AEs did not reveal any unexpected findings. In study HGT-GCB-039, there were no relevant differences in discontinuation due to AEs between treatment groups. Compliance was high in both groups. In the treatment-naïve group of the overall patient safety pool no patient on velaglucerase alfa discontinued due to an AE, while 4 of 54 (7.4%) patients discontinued early for reasons considered unrelated to study drug. One of 17 (5.9%) patients (039-071-0004) on 60 U/kg imiglucerase withdrew consent due to infusion-related AEs. The patient experienced warm feeling at Week 15, feeling cold at Week 19, flushing and cold feeling at Week 21 and severe rigors and decrease in oxygen saturation at Week 23. The patient tested positive for neutralising antibodies to imiglucerase and discontinued at Week 23. 2 of 40 (5%) patients transitioned from imiglucerase discontinued early. One patient (034-048-0001) transitioned from 50 U/kg imiglucerase and categorised in the 15 U/kg velaglucerase alfa group (see above) discontinued first infusion after 30 minutes due to an SAE of anaphylactoid reaction. The second patient withdrew consent at Week 31 because she did not feel the improvement in Gaucher-related symptoms justified continued participation.

Patient Early Discontinuations by Study – Safety Population

Study	Dose Level	Week of last infusion	Reason
Treatment-Naïve Patients			
velaglucerase alfa			
TKT025	60 U/kg	5[a]	Withdrawal of consent[f]
HGT-GCB-039	60 U/kg	17[b]	Patient lost to follow-up[g]
TKT025EXT	60 U/kg	21[c]	Withdrawal of consent
	60 U/kg	169	Participation terminated by Sponsor because patient's pregnancy test was positive
Note: No discontinuations at dose of 45 U/kg or 60 U/kg in study TKT032			
imiglucerase			
HGT-GCB-039	60 U/kg	23	Withdrawal of consent due to infusion-related AEs
Patients Transitioned from ERT with Imiglucerase			
TKT034	15 U/kg	1[d]	AE[h]
	15 U/kg	31[e]	Withdrawal of consent—Patient felt that they had not had sufficient improvement to justify continuation in the trial.[i]

Note: No discontinuations at dose of 30, 45 or 60 U/kg in TKT034

[a] Last infusion was Week 5.

[b] Last infusion was Week 17, recorded as lost to follow-up Week 26.

[c] Last dose in the extension study was Week 21, patient did not discontinue until 8 weeks later.

[d] Last and only infusion was at Week 1, infusion was not completed, 26 mL of 40 mL delivered.

[e] Last infusion was Week 31 (no missed infusions), discontinued Week 33.

[f] Patient discontinued for personal reasons.

[g] After the Week 17 infusion the patient had an SAE of convulsion, not related to study drug. Parents were initially willing to continue but the patient did not come in for further infusion..

[h] This was a SAE of anaphylactoid infusion reaction See narrative Patient 034-048-0001.

[i] Baseline value for hemoglobin was 10.4 g/dL and for platelet count was 88 $x10^9$/L. At the last assessment (Week 31) hemoglobin concentration was 10.8 g/dL and platelet count was 81 x 10^9/L.

2.4.10.8. Post marketing experience

There are no data available from the post marketing use of velaglucerase alfa.

2.5. Discussion on clinical safety

Exposure to velaglucerase alfa is limited, but in light of the low prevalence of type 1 Gaucher disease, it is considered adequate. The most relevant safety data are derived from study HGT-GCB-039, the only trial comparing velaglucerase alfa to imiglucerase the current standard of treatment for type 1 Gaucher disease patients eligible for ERT; safety evaluation in this trial is limited to the 17 patients per group enrolled. Separate analyses of AEs between patients treated for 9 or 12 months as provided were not supported and analyses of controlled, imiglucerase comparison, and uncontrolled data would have been preferred. For patients transitioned from imiglucerase the AE profile does not reveal any unexpected findings.

In study HGT-GCB-039 the duration of exposure and mean actual dose administered at each infusion were comparable between groups. The overall AE profile appears to be comparable between treatment groups. However, no SAE occurred in the imiglucerase group compared to 3 SAEs on velaglucerase alfa and there was 1 case of severe prolonged aPTT on velaglucerase alfa compared to none on imiglucerase. The event is adequately reflected in the SmPC. Re-analysis of the prolongation of aPTT has been requested by the CHMP. No patient on velaglucerase alfa developed anti-velaglucerase alfa antibodies throughout the study compared to 4 patients on imiglucerase developing anti-imiglucerase antibodies, but the number of patients available for comparison is too small for any definite conclusion. Infusion related AEs were balanced between groups. Overall, laboratory findings do not indicate significant differences between treatment groups. No deaths were reported for either group during the study. SAE occurred only in patients treated with velaglucerase alfa, but only 1 of the 4 SAE, an allergic skin reaction, is considered probably treatment related. Since allergic skin reactions have also been described for imiglucerase, the difference is most likely a chance finding due to the low number of patients treated per group.

Regarding safety in special populations subgroup analyses have been provided for age, gender, and splenectomy status. Overall AE profiles are considered comparable between age groups, female and male patients, and patients with and without spleen. There are no safety signals specific to the paediatric population. Infusion-related AEs are considered comparable between the groups. No data on drug-drug or drug-disease interactions with regard to safety have been provided. There were no relevant differences in discontinuation due to AEs between treatment groups and compliance was high in both groups.

For the overall data set there have been no unexpected findings in the analyses of SAEs and deaths; no death occurred during the trials. Six patients on velaglucerase alfa compared to none on imiglucerase developed a prolonged aPTT. Although these events appear to be related to the underlying disease rather than being a treatment effect, the limited data do not allow a definite conclusion and thus, prolonged aPTT is considered a potential risk to be included in the RMP. The event is also appropriately reflected in the SPC.

Antibody formation appears to be numerically higher in patients on imiglucerase than on velaglucerase alfa, but absolute numbers are low and thus no definite conclusion is possible. In the subgroup analyses of AE for age and gender, findings do not indicate differences in the AE profiles. As expected, infusion related AEs occurred with velaglucerase alfa treatment. No unexpected findings have been reported.

Safety related to drug-drug interactions and other interactions has not been provided which is considered acceptable.

Analyses of discontinuations due to AEs do not reveal any unexpected findings.

Sufficient information has been provided to allow the conclusion that velaglucerase alfa may be administered as home therapy. In order to identify patients at high risk of infusion related reactions, it is strongly recommended that at least the first three infusions are given in a clinical setting. This strategy is reflected in the SmPC.

2.6. Conclusions on the clinical safety

In conclusion the safety data provided do not indicate significant differences in safety between velaglucerase alfa and imiglucerase. Sufficient information has been provided to allow the conclusion that velaglucerase alfa may be administered as home therapy. Besides the prolonged aPTT, no

unexpected safety findings have been identified during the trials conducted with velaglucerase alfa. Nevertheless the evaluation is limited by the low number of patients exposed to velaglucerase alfa in these trials. This has been adequately considered in the Risk Management Plan and follow up measures have been agreed. There will be an Gaucher disease Observational Survey (GOS) set up in order to monitor the post-marketing status of velaglucerase alfa as requested by the CHMP.

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system, version 5.10a as described by the applicant fulfils the legislative requirements.

2.7.2. Risk management plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Infusion-related reactions	Routine pharmacovigilance As a part of safety data collection, recommend that IgE antibody testing (as per specific guidelines provided by Shire and as part of routine follow-up queries) is requested in all SAE cases of severe infusion-related reactions (ie suspected anaphylactic/anaphylactoid reactions). Gaucher Observational Survey (GOS)	SPC Section 4.4 Warnings and precautions for use provide the following information about the risk, its management and suggested preventive measures: Infusion-related reactions were the most commonly observed adverse reactions in patients treated in clinical studies. Most of the infusion-related reactions were mild. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia/body temperature increased. In treatment-naïve patients, the majority of infusion-related reactions occurred during the first 6 months of treatment. The management of infusion-related reactions should be based on the severity of the reaction, and include slowing the infusion rate, treatment with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of velaglucerase alfa during clinical studies. Antibodies may play a role in treatment-related reactions found with the use of velaglucerase alfa. To further evaluate the relationship, in cases of severe

		infusion related reactions and in cases of lack or loss of effect patients should be tested for the presence of antibodies and the results reported to the company.
Potential for reduced efficacy due to development of neutralizing antibodies to velaglucerase alfa	Routine pharmacovigilance As a part of safety data collection, recommend antibody testing (as per specific guidelines provided by Shire and as part of routine follow-up queries) is considered in AE cases involving patients who have a lack or loss of efficacy. Gaucher Observational Survey (GOS)	SPC Section 4.4. Warning and precautions for use informs that patients should be tested for the presence of neutralizing antibodies in cases of lack or loss of effect: Antibodies may play a role in treatment-related reactions found with the use of velaglucerase alfa. To further evaluate the relationship, in cases of severe infusion-related reactions and in cases of lack or loss of effect patients should be tested for the presence of antibodies and the results reported to the company. In the clinical trials, one of 94 (1%) patients developed IgG-class antibodies to velaglucerase alfa. In this one event, the antibodies were determined to be neutralising in an *in vitro* assay. No infusion-related reactions were reported for this patient. No patients developed IgE antibodies to velaglucerase alfa.
Increased activated partial thromboplastin time (aPTT)	Routine pharmacovigilance Gaucher Observational Survey (GOS)	SPC Section 4.8 Undesirable effects inform that aPTT prolonged was a common adverse reaction in clinical studies with velaglucerase alfa.
Off label use	Routine pharmacovigilance Gaucher Observational Survey (GOS)	The SPC Section 4.1 Therapeutic indications states that VPRIV is indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.
Lack of safety data for patients who transition to velaglucerase alfa and have a prior history of significant adverse drug reactions to other ERT, and insufficient safety data for patients who transition to velaglucerase alfa and who developed antibodies to previous ERT	Routine pharmacovigilance As a part of safety data collection, recommend that antibody testing (as per specific guidelines provided by Shire and as part of routine follow-up queries) is requested for all SAE cases involving patients who after transitioning to velaglucerase alfa developed severe (ie suspected anaphylactic/anaphylactoid reactions) infusion-related reactions. Gaucher Observational Survey (GOS) Clinical study HGT-GCB-058	SPC Section 4.4 Special warnings and precautions for use informs that treatment with velaglucerase alfa should be approached with caution in patients who have exhibited symptoms of hypersensitivity to other enzyme replacement therapy. Also, a recommendation for antibodies testing is given in cases of severe infusion-related reactions and in cases of lack or loss of effect.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.7.2.1. User consultation

The results of the user testing of the PIL demonstrate that study participants were able to identify and comprehend key safety messages. The results are considered supportive of the proposed PIL and the test in line with the requirements of the EMA guidelines.

2.7.3. Benefit-risk balance

2.7.3.1. Benefits

2.7.3.1.1. Beneficial effects

There is a considerable degree of variability in the clinical signs and symptoms of Gaucher disease, ranging from severely affected infants to asymptomatic adults. Type 1 Gaucher disease is the most common subtype; patients display a wide range of symptoms. The clinical features of type 1 Gaucher disease are dominated by accumulation of Gaucher cells in target organs liver, spleen, and bone marrow and thus include anaemia and thrombocytopenia due to splenic sequestration and bone marrow replacement, as well as splenomegaly and hepatomegaly. Besides symptomatic treatment, the goal of therapies is to reduce storage of GlcCer in affected tissues of GD patients leading to improvements in haemoglobin concentration (Hgb) and platelet count and reductions in spleen and liver volumes. The main endpoints of interest to assess the efficacy of treatments for type 1 Gaucher disease patients in clinical trials are changes in Hgb concentration, platelet count, and liver and spleen volume, since based on the literature, haematological and visceral disease therapeutic goals can generally be met more rapidly than designated goals for skeletal or pulmonary compartments.

In the pivotal trial HGT-GCB-039 effects of treatment with 60 U/kg velaglucerase alfa over 9 months were not inferior to those seen with 60 U/kg imiglucerase. Mean changes from baseline in Hgb were comparable between velaglucerase alfa and imiglucerase treatment groups and the primary endpoint of predefined non-inferiority criteria was met. For the ITT population, the mean absolute changes were 1.624 g/dL for velaglucerase alfa and 1.488 g/dL for imiglucerase. Results were consistent with the PP population. Responses were similar between treatment groups for subgroups paediatric (age 2 to 17 years), adult (age ≥18 years), gender, and splenectomy status. The secondary endpoint time to first Hgb response, defined as an increase of ≥1 g/dL from baseline, was similar between groups (log-rank p-value = 0.8965).

Regarding the secondary endpoints, the mean platelet counts increased with both treatments. At Week 41, the unadjusted mean change was 110.4 x 10^9/L in the velaglucerase alfa and 144.4 x 10^9/L in the imiglucerase group. The model-based estimated treatment difference in mean change at Week 41 was not statistically significant. The mean change in liver volume was comparable between groups and statistically not significantly different. Regarding the change in spleen volume results indicate a substantial reduction during treatment. Results are based on 7 patients per group with spleen. Effects on plasma chitotriosidase and CCL18 values were comparable between treatment groups. For adults changes in QoL measurements appear to be comparable between groups. The exploratory endpoints Hgb, platelet count, liver and spleen volume response categories showed comparable results between velaglucerase alfa and imiglucerase groups; response categories as proposed in the CHMP scientific advice were used.

Efficacy data from the supportive study TKT025 are consistent with a clinically significant positive effect of velaglucerase alfa dosed as 60 U/kg EOW on relevant markers of type 1 Gaucher disease. Effects were maintained throughout the 9 month duration of the trial.

In study TKT032, investigating two dose groups of velaglucerase alfa, 45 and 60 U/kg, effects on Hgb and platelet count were equal or greater in the 45 U/kg dose group, while the opposite was seen for effects on liver and spleen volume and time to first Hgb response, indicating an earlier response in the 60 U/kg; no formal comparison of dose groups was prespecified. However, velaglucerase alfa induced clinically relevant effects on Hgb, platelet count, and spleen and liver volumes comparable to those seen in the other clinical trials.

Overall, data from these trials support the assumption that velaglucerase alfa is effective in increasing haemoglobin concentration and platelet count as well as reducing spleen and liver volumes in type 1 Gaucher disease patients.

No clinical studies in special populations have been performed. Exploratory subgroup analyses of data from study TKT032 do not indicate differences in the response to treatment for either age or gender. The applicant did not provide analyses of efficacy data across the clinical trials. However, assessment of data from single trials indicates comparable effects of velaglucerase alfa on Hgb, platelet count and organ volumes across trials.No placebo controlled data have been provided, which is acceptable for the patient population investigated.

2.7.3.1.2. Uncertainty in the knowledge about the beneficial effects

Interpretation of the results is generally limited by the low number of patients investigated and by the fact that the majority of trials have been uncontrolled, the exception being the active-controlled trial HGT-GCB-039 with only 17 patients per arm. In this trial, there were also imbalances between treatment groups that might have affected the outcome. The median baseline Hgb was 11.4 g/dL in the velaglucerase alfa and 10.6 g/dL in the imiglucerase group. This difference between groups remained during the entire study. However, an analysis adjusting for the baseline haemoglobin concentration values confirmed the primary efficacy analysis and the baseline difference is considered to be to the disadvantage of the efficacy of velaglucerase alfa rather than imiglucerase and thus adding reassurance to the assessment of the efficacy of velaglucerase alfa. For platelet count baseline values were higher in the imiglucerase compared to the velaglucerase alfa group (181.2 vs. 161.1 x 10^9/L); the difference persisted at each assessment and appeared to increase in the latter half of the study. Part of the difference might be explained by the fact that all 4 children under the age of 5 years, 3 with spleen and 1 splenectomised, were randomised to imiglucerase indicating a more severe course of disease; children with more severe disease are expected to have a better response to treatment. Post hoc analyses suggest that patients in the 2 to 4 years age group have skewed the data; those three not splenectomised had large spleens and low platelet counts at baseline and appeared to have worse disease at the start of the study. There was also a considerable imbalance in mean spleen volume at baseline, but results indicate a comparable response on change in spleen volume between groups. Regarding the assessment of QoL measurements the interpretation is hampered by the insufficient data especially in children.

There are currently no final data from study TKT025EXT contributing to the efficacy evaluation of velaglucerase alfa. The preliminary data indicate that the treatment effect is maintained over an extended period of five years in spite of lowering of the dose by 50%. The applicant has committed to provide the final CSR in an acceptable timeframe after finalisation of the trial. For the two doses of imiglucerase used in study TKT032, no formal comparison has been pre-specified or provided.

2.7.3.2. Risks

2.7.3.2.1. Unfavourable effects

Exposure to velaglucerase alfa is limited, but in light of the low prevalence of type 1 Gaucher disease, considered adequate. The most relevant safety data are derived from study HGT-GCB-039; safety evaluation in this trial is limited to the 17 patients per group enrolled.

In study HGT-GCB-039 the overall AE profile appears to be comparable between treatment groups. No deaths were reported for either group during the study. SAE occurred only in patients treated with velaglucerase alfa, but only 1 of the 4 SAE, an allergic skin reaction, is considered probably treatment related. Since allergic skin reactions have also been described for imiglucerase, the difference is most likely a chance finding due to the low number of patients treated per group.

One case of prolonged aPTT occurred in the velaglucerase alfa group compared to none in the imiglucerase group. The event is adequately reflected in the SmPC.

No patient on velaglucerase alfa developed anti-velaglucerase alfa antibodies throughout the study compared to 4 on imiglucerase. However, infusion related AEs were balanced between groups. Overall laboratory findings do not indicate significant differences between treatment groups.

Regarding safety in special populations subgroup analyses have been provided for age, gender, and splenectomy status. Overall AE profiles are considered comparable between age groups, female and male patients, and patients with and without spleen. There are no safety signals specific to the paediatric population.

No data on drug-drug or drug-disease interactions with regard to safety have been provided. There were no relevant differences in discontinuation due to AEs between treatment groups and compliance was high in both groups.

For the overall data set there have been no unexpected findings in the analyses of SAEs and deaths; no death occurred during the trials.

Six patients on velaglucerase alfa compared to none on imiglucerase developed a prolonged aPTT. Although these events appear to be related to the underlying disease rather than being a treatment effect the limited data do not allow a definite conclusion and thus prolonged aPTT is considered a potential risk to be included in the RMP. The event is however appropriately reflected in the SPC.

Antibody formation appears to be numerically higher in patients on imiglucerase than on velaglucerase alfa , but absolute numbers are low and thus no definite conclusion is possible.

In the subgroup analyses of AE for age and gender, findings do not indicate differences in the AE profiles.

Infusion related AEs occurred with velaglucerase alfa treatment. No unexpected findings have been reported.

Safety related to drug-drug interactions and other interactions has not been provided which is considered acceptable.

Analyses of discontinuations due to AEs do not reveal any unexpected findings.

2.7.3.2.2. Uncertainty in the knowledge about the unfavourable effects

Evaluation of unfavourable effects is restricted by the limited data available. However, a planned register, called Gaucher disease Observational Survey (GOS), will collect additional data on treatment with velaglucerase alfa.

2.7.3.3. Benefit-risk balance

2.7.3.3.1. Importance of favourable and unfavourable effects

Changes in haemoglobin, platelet count, and organ volumes are considered relevant and sufficiently sensitive endpoints for the assessment of treatment efficacy. These endpoints contribute considerably to the disease burden and thus improvement in these parameters is expected to alleviate disease burden in patients with type 1 Gaucher disease. According to the literature these therapeutic goals can generally be met more rapidly than designated goals for skeletal or pulmonary compartments.

Except for the unexpected findings, antibody formation and infusion related events are considered the most relevant unfavourable effects for assessment of safety comparability between ERT groups. Antibody formation might reduce efficacy, as well as it might lead to infusion-related events. Infusion-related events might either jeopardise compliance or even render treatment impossible due to severe anaphylactic reactions.

2.7.3.3.2. Benefit-risk balance

Treatment of type 1 Gaucher disease patients with velaglucerase alfa leads to significant and clinically relevant improvements in haemoglobin concentration, platelet count, and spleen and liver organ volumes. These changes are sustained throughout the studies. The observed changes are considered comparable to those seen with the established ERT imiglucerase.

No unexpected safety findings except a prolongation of aPTT have been identified. Thus the data provided indicate that the benefits seen with velaglucerase alfa treatment outweigh the risks involved with this treatment and that the benefit-risk balance is comparable to that for the established ERT with imiglucerase. Thus, the benefit/risk balance is positive.

2.7.3.4. Discussion on the benefit-risk balance

Efficacy data from trial HGT-GCB-039 indicate that velaglucerase alfa 60 U/kg EOW in treatment naïve patients is not inferior to the currently licensed imiglucerase as assessed by increases in Hgb and platelet count and decreases in liver and spleen volumes. Data from supportive studies are in line with the findings in this pivotal trial. Patients transitioned from imiglucerase to velaglucerase alfa showed sustained clinical effects in Hgb and platelet count. Long term data do not indicate any inconsistent effects in increases in Hgb and platelet count, or decreases in liver and spleen volumes. Efficacy results were consistent between paediatric and adult patients and no gender related differences were seen. The adverse event profile is considered comparable to that of imiglucerase. Thus in consequence it is considered that the benefit outweighs potential risks with velaglucerase alfa treatment.

The absence of data from placebo-controlled trials is acceptable, placebo-controlled trials are not considered feasible in the patient population investigated due to ethical concerns.

In conclusion, the safety data provided do not indicate significant differences in safety between velaglucerase alfa and imiglucerase. Besides the prolonged aPTT, no unexpected safety findings have been identified during the trials conducted with velaglucerase alfa. Nevertheless the evaluation is limited by the low number of patients exposed to velaglucerase alfa in these trials. This should be adequately considered in the Risk Management Plan.

2.7.3.5. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Additional pharmacovigilance planning was needed to adequately monitor the safety of the product.
- No additional risk minimisation activities were required beyond those included in the product information.

2.7.4. Similarity with authorised orphan medicinal products

The CHMP is of the opinion that VPRIV is not similar to Zavesca within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

2.7.5. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of VPRIV in the treatment of patients with type 1 Gaucher disease was favourable and therefore recommended the granting of the marketing authorisation.

and

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers VPRIV not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Zavesca for the same therapeutic indication.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not completed yet as none of the measures are completed.