EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 November 2012
EMA/CHMP/697253/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Krystexxa

International non-proprietary name: **pegloticase**

Procedure No. **EMEA/H/C/002208**

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

AB	Antibodies
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event(s)
ASHI	Arthritis-specific health index, summary score of SF-36
AUC	Area under the curve
BSA	Body surface area
CD	Circular Dichroism
E2W	Every 2 Weeks
E4W	Every 4 Weeks
HMW	High molecular weight variants/forms
IEF	Isoelectric focusing
LMW	Low molecular weight variants/forms
MALDI-MS	matrix-assisted laser desorption/ionization mass spectrometry
mPEG	Monomethoxypoly(ethylene glycol)
mPEG-NPC	p- nitrophenylcarbonate derivative of mPEG
MS	Mass spectrometry
MW	Molecular Weight
PUA	Plasma uric acid
RI	Refractive Index
SOP	Standard Operating Procedure
SUA	Serum uric acid
UA	Uric acid
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Savient Pharma Ireland Ltd. submitted on 3 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Krystexxa, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

KRYSTEXXA is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors or uricosuric agents at the maximum medically appropriate dose, or for whom these drugs are contraindicated.

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/28/2011 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

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

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Krystexxa has been given a Marketing Authorisation in the U.S. on 14 September 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: **Martina Weise** Co-Rapporteur: **Ian Hudson**

The application was received by the EMA on 3 May 2011.

- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2011.
- During the meeting on 22 September 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 April 2012.
- During the CHMP meeting on 16-19 April 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 June 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 2 July 2012.
- During the CHMP meeting on 15-19 July 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of outstanding Issues on 17 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 3 September 2012.
- The Rapporteurs circulated the final Joint Assessment Report on the responses provided by the Applicant dated 11 October 2012.
- During the meeting on 15-18 October 2012, 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 Krystexxa on 18 October 2012.
- The CHMP adopted via written procedure on 7 November 2012 the revised CHMP Opinion and Assessment Report to include further details in the assessment report.

2. Scientific discussion

2.1. Introduction

Problem statement

Uric acid is the end metabolite in the purine catabolic pathway in humans. In most species, except the great apes, urate oxidase catalyzes the conversion of uric acid to allantoin. Uric acid, which is poorly soluble in water, is excreted in the urine. When the concentration of serum uric acid (SUA) is above the biochemical limit of solubility, 6.8 mg/dl, i.e. in the status of hyperuricaemia, monosodium urate crystals may precipitate in tissues.

Gout is characterized by a constellation of signs and symptoms typified by the occurrence of episodic acute inflammation in and around a joint or joints (a gout flare), the formation of gout tophi, gouty arthritis, and uric acid nephropathy (including uric acid renal stones). Chronic gout is a debilitating condition in which pain and dysfunction are caused by an accumulation of monosodium urate (MSU) crystals in tissues and joint spaces, caused by hyperuricaemia. Hyperuricaemia is defined as a serum urate level ≥ 6.8 mg/dL (404 µmol/L), the limit of urate solubility at physiological temperature and pH.

Urate-lowering therapy is the pharmaceutical approach to prevent recurrent flares and the development of complications: xanthine oxidase inhibitors, such as allopurinol or febuxostat, which block the synthesis of uric acid; uricosuric agents, such as probenecid and sulfinpyrazone, which are used alone or in combination with allopurinol to enhance the urinary excretion of uric acid in some patients. Although allopurinol is generally well tolerated, patients with gout may fail to normalize their serum uric acid even with the medically appropriate dose of allopurinol.

About the product

Pegloticase, the active substance in Krystexxa, is a polyethylene glycol (PEG)-modified recombinant mammalian uricase of the therapeutic class bio-uricolytic agent. Each subunit of the tetrameric enzyme is conjugated with several strands of a 10 kDa monomethoxypolyethylene glycol (mPEG). The rationale for the addition of mPEG to this molecule was to reduce the potential for immunogenicity and to increase circulation half-life compared to the non-PEGylated porcine enzyme.

Uricase catalyses the first step of the conversion of uric acid (UA) into the highly water-soluble end-stage metabolite allantoin, which is eliminated by renal excretion. Pegloticase was developed for parenteral therapy of gout in patients refractory or intolerant to conventional treatment with uricostatic or uricosuric drugs. The pharmacokinetic profile of pegloticase is such that sub-saturating SUA levels can be maintained for long periods, which is a precondition for eliminating tissue pools of MSU crystals.

The product is a colourless, clear, sterile solution containing 8 mg/ml of pegloticase. Pegloticase is packaged in sterile single-use glass vials filled to deliver 1 ml of study drug.

The proposed indication for pegloticase was:

KRYSTEXXA is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors or uricosuric agents at the maximum medically appropriate dose, or for whom these drugs are contraindicated.

The proposed dose is 8 mg given as an intravenous infusion every 2 weeks (wks).

The final approved indication is:

"KRYSTEXXA is indicated for the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated (see Section 4.4)."

2.2. Quality aspects

2.2.1. Introduction

The finished product is a concentrated solution for dilution prior to administration. It is presented as a single-use 2 mL glass vial containing 1 mL of pegloticase solution in normal phosphate buffered saline at a concentration of 32 mg of pegloticase/mL, corresponding to 8 mg uricase protein. Prior to administration to the patient by intravenous infusion, 1 mL of the finished product is diluted 1:250 with sterile sodium chloride infusion solution.

The active substance is pegloticase, a recombinant uricase of chimeric mammalian origin produced in *E. coli* to which monomethoxy poly (ethylene glycol) (mPEG) has been covalently attached. The active substance is presented as a solution buffered in sodium phosphate and sodium chloride at pH 7.3.

Uricase intermediate is a homotetramer of 136.8 kDa, consisting of four identical non-covalently-bound uricase monomeric subunits. Derivatisation of uricase with monomethoxypoly(ethylene glycol)-p-nitrophenyl carbonate (mPEG-NPC) with an average mass of 10 kDa results in the covalent attachment of an average of 10.2 ± 1.0 strands of mPEG per uricase monomeric subunit or 40.8 ± 4.0 strands of mPEG per uricase homotetramer, resulting in a MW of approx. 545 kDa.

2.2.2. Active Substance (Uricase Intermediate and Pegloticase Active Substance)

Manufacture

Pegloticase drug substance is manufactured by Bio Technology General, Kiryat Malachi, Israel.

Origin, source and history of cells, characterisation and testing

Generation of the expression plasmid, the production cell line, the cell banks and its characterisation has been adequately described. Uricase intermediate is produced in an *E. coli* strain. Characterisation and evaluation of stability of the cell line was based on Master Cell Bank (MCB) and End of Production (EoP) cells.

Cell Banking System

The cell banking system was established as two-tiered cell bank with a Master Cell Bank (MCB) used to generate the Working Cell Bank (WCB). A protocol for generation of future WCBs is provided.

Manufacture

The manufacturing process of pegloticase has been described with sufficient detail. It is divided in four main steps:

1. Fermentation/harvest: Production of the biomass, from thawing of a vial of frozen WCB to harvesting of the biomass from the main production fermentor;

2. Recovery: Separation of the biomass from the fermentor broth, disruption of the cells, separation and dissolution of the inclusion bodies containing the target protein;

3. Purification: Isolation and purification of uricase intermediate through several chromatographic and ultrafiltration steps and;

4. Pegylation/purification: Conjugation of mPEG to uricase intermediate and purification of pegloticase.

The fermentation/harvest stage comprises two sequential fermentation runs initiated by inoculation of two shake flasks from one vial of the WCB. At the required OD_{660} production of uricase is induced. Fermentation continues with supplemental feeds until harvesting is initiated by cooling of the culture followed by ultracentrifugation, diafiltration and concentration to result in a cell-slurry intermediate. Uricase is recovered from cells with mechanical disruption supported by lysis of cells with lysozyme to obtain inclusion bodies. Upon solubilisation of inclusion bodies uricase is recovered in its tetrameric native state. The solubilisate is initially refined through precipitation of process related protein (CPC) to yield crude uricase solubilisate as the retentate.

Purification of crude uricase to uricase intermediate is achieved by several column chromatography steps. The function of each step is sufficiently described.

The PEGylation stage is initiated with column chromatography-based concentration of uricase intermediate. The PEGylation reagent converts the concentrated uricase intermediate pool at predefined reaction conditions to a reaction product containing ~ 40 PEG-strands each of ~ 10 kDa per tetrameric uricase molecule. Application of a further chromatographic purification step and subsequent concentration and diafiltration into the final formulation buffer results in pegloticase active substance that is filled in glass bottles.

A traditional approach to development and control of the manufacturing process has been taken. The manufacturing steps are monitored by process controls that are adequately documented. The list of in-process controls has been amended with a comprehensive list of process parameters including their classification with respect to criticality. These data are used to support the control strategy.
Although the Applicant has not provided any process characterisation data in the dossier, the acceptance and target ranges or set points chosen for the process controls are generally explained and justified by the Applicant's understanding derived from development studies and the existing manufacturing experience.

The manufacturing process was validated in two separate campaigns both traditionally performed with three consecutive lots, respectively. The initial validation campaign focused on consistency of the manufacturing process in its entirety supported by additional scaled-down validation studies on column resin lifetime and calculation of clearance factors for process-related impurities.

PEGylation conditions in the first validation campaign were adjusted to reach a defined target PEGylation ratio for the uricase molecule of ~ 9 strands/uricase subunit.
Although the first process validation campaign was successfully completed a critical aspect of this process validation campaign was a shift in PEGylation conditions away from those used for manufacture of the Phase III clinical batch. The shift intended to reach a level of 9 PEG-strands per molecule subunit. Therefore, the second validation campaign further included a reversion of PEGylation conditions back to those used for manufacture of the Phase III Clinical batch (~ 10 strands /uricase subunit). The second validation campaign was successfully completed as well.

Manufacturing process development

Process development included six distinct stages of the pegloticase manufacturing process ranging from a laboratory-scale process (pre-development process), used to prepare material for initial pharmacokinetic studies of the product, via scale-up (development and pilot scale process) to process

A used for manufacture of the clinical lot. Process B, the proposed commercial process, included a shift in the ratio of PEG strands/subunit from ~10 strands / subunit (Process A) to a ratio of 9 strands / subunit. Process B material was used in a clinical Phase III follow-up study. In Process C (proposed commercial manufacturing process) additional filtration steps were included and the PEGylation ratio was changed back to ~ 10 strands/subunit (as in Process A). The evolution of the commercial process C from the development process is described with sufficient detail. Comparability studies were performed to support comparability of pilot scale material with clinical process A material as well as comparability of clinical process A material with both process B and process C material.

Characterisation and Impurities

In general, appropriate information has been provided on characterisation of uricase intermediate, which has been performed using suitable state-of-the-art analytical methods.

Characterisation studies comprise studies of the primary structure, modifications in the primary sequence (disulfide bonds, deamidation, oxidation, and acid isoforms) as well as studies on the presence of high and low molecular weight forms.

SEC-HPLC shows that uricase intermediate contains monomer which is comprised of four monomeric subunits, and high molecular weight (HMW) forms which include dimer and higher oligomers. In addition, the secondary structure as well as the enzymatic potency of uricase intermediate has been investigated. The tetrameric structure of uricase is essential for its catalysis of the oxidative cleavage of uric acid to produce allantoin, carbon dioxide and hydrogen peroxide. Uricase intermediate catalyzes the conversion of uric acid to allantoin.

Potential impurities in uricase intermediate are product-related impurities and process-related impurities. The testing currently applied for the control of product-related impurities give sufficient confidence on quality. In general, appropriate information has been provided on characterisation of Pegloticase active substance which used suitable orthogonal analytical methods and evaluation of representative active substance and finished product lots.

Characterization studies have also been performed on the pegloticase active substance. The extent and the sites of pegylation have been investigated as well as the enzymatic activity of pegylated uricase. Forced degradation studies have been performed to investigate potential degradation pathways and to conclude on appropriate analytical methods.

Information has been provided on the amount of methionine oxidation in pegloticase active substance. The presence of acidic forms was revealed by IEF investigation of the uricase subunit and the apparent heterogeneity in uricase has been addressed with respect to the pegloticase active substance.

The near-UV CD spectra used for investigation of the tertiary structure of Pegloticase active substance showed considerable differences between the unpegylated and the pegylated protein. This has been confirmed for a number of batches. Extent of PEGylation was determined and studies show enzymatic activity and immunogenicity as a function of the extent of PEGylation.

Specification

Release testing of uricase intermediate includes tests for appearance, pH, identity, protein content, specific activity, isomers, polymeric forms, product-related forms, endotoxin and bioburden.

In general, the description of the analytical methods is considered sufficient. Non-compendial tests have been validated, compendial tests have been qualified. The information provided on batch analyses of uricase intermediate as well as the provided justification of specification is considered acceptable.

Pegloticase active substance specifications include tests for appearance, pH, osmolality, identity, mPEG/monomer, specific activity, polymeric forms, product and process-related impurities, endotoxin and bioburden.

Batch data obtained from process B are deemed to be supportive with regard to batch analyses for Pegloticase active substance.

References standards of materials

Information regarding the qualification program for new Uricase Reference Standard (RS) as well the Pegloticase RS are considered acceptable.

Container Closure System

The container closure system for the uricase intermediate is a sterile, disposable plastic bag. The product contact surface is a low density polyethylene material.

The container closure system for the pegloticase drug substance is a clear Type 1 glass bottle with a polypropylene screw cap.

Stability

The applicant provides stability data for two batches of uricase stored in PE material substantiating stability of uricase over the proposed hold time of 54 days at 2-8 °C.

Based on the data provided, the proposed shelf-life of the Pegloticase active substance of 6 months when stored at 2-8°C is acceptable.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished Medicinal Product

Krystexxa finished product is a colourless, clear to slightly opalescent, sterile solution containing 32 mg/mL of pegloticase comprised of 8 mg/mL uricase protein conjugated to monomethoxypoly(ethylene glycol), (mPEG) in phosphate buffered saline. The finished product is presented in a 1 mL (nominal) fill in a single-use vial. There are no overages. During manufacture of the finished product, a target volume of the finished product solution is filled into the final container to ensure that the total dose volume of 1.0 mL can be delivered.

Pharmaceutical Development

The development of the finished product is adequately described. Minor changes were introduced during the finished product process development. These include changes to the manufacturing site, the batch size and the introduction of a two filter filtration step for commercial batches. Since these changes are considered to have no impact on the final product quality comparability studies are not required.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

The compatibility of Krystexxa and the commercially available sodium chloride solution (0.45% and 0.9%) was tested to evaluate pegloticase stability after dilution. No excipient of human or animal origin is used in the finished product. No novel excipient is used in the finished product.

Adventitious agents

According to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, (EMEA/410/01 rev. 3, July 2011) bovine milk is unlikely to present any risk of TSE contamination. Since the casein used for N-Z amine production is sourced from milk from healthy animals and collected under the same conditions as for human consumption and since no other ruminant materials are used in the preparation the casein can be considered compliant with the NfG.

The slip agent is a tallow derivative and has been manufactured under rigorous process conditions, therefore it is unlikely to represent a risk of TSE contamination.

Lysozyme is a raw material derived from hen's eggs and is used during the uricase intermediate manufacturing process (recovery step). The Applicant has performed a further risk assessment under special consideration of small, non-enveloped viruses. A literature-based estimation of the virus reduction ability of AEX and affinity chromatography has been performed and both methods were assumed to be effective in virus removal/inactivation. Although a theoretical evaluation of the virus reduction capacity of the manufacturing process might be used as supportive data, the process- and product-specific conditions of the processes to be compared deviate in essential details (i.e. matrix) and thereby hamper a meaningful comparison. Therefore the replacement of the animal-derived lysozyme by a recombinant product is considered a key measure to assure the virus safety of this material.

Manufacture of the product

The Krystexxa finished product is manufactured at Sigma-Tau PharmaSource, Inc. Indianapolis, Indiana (STPS).

The manufacturing process consists of sterile filtration, aseptic filling, inspection, labelling and packaging. No change in formulation occurs during finished product manufacturing. The manufacturing process is appropriately described and controlled. A rationale for the classification of all controls into in-process tests, critical and key processing parameters is presented. The in-process tests are limited by acceptance criteria.

The finished product production process only comprises, mixing of several glass bottles of one active substance lot, sterile filtration into a filling bag, transport to the fill site and filling into vials.

The final process was validated by producing six validation batches, three of them using active substance from process C. The validation data included results of all in-process tests and critical processing parameters. The results were within the predefined ranges or fulfilled the acceptance criteria. Overall, the validation results demonstrate that the finished product manufacturing process is under control and produces finished product of consistent quality.

Product specification

The drug product specification includes tests for appearance, identity, content, potency and purity. The list of tests is adequate to control drug product quality.

The analytical methods for testing pegloticase attributes in the finished product solution are identical to the methods used for active substance analysis. The release specification limits are based on statistical evaluation of the batch data obtained so far.

Results of all finished product batches produced so far are presented, among them four batches representing the commercial finished product (active substance process C) process and the clinic lot 5682003100 used in for phase III studies. All parameters fulfilled the acceptance criteria, thus confirming consistent finished product quality.

Reference standards or materials

There is no designated Krystexxa finished product reference standard other than that described in the active substance section.

Stability of the product

Stability studies were initiated with four Krystexxa finished product batches manufactured with Process C active substance. All stability data from the Krystexxa finished product process C available so far (maximum 18 months) met the acceptance criteria.

Although the active substance of process B has a slightly different PEGylation:protein ratio, it is not considered to impact on the degradation rate given the high degree of PEGylation in the molecule. Therefore, the stability data of the pilot scale lot can be used to support the proposed finished product shelf life of 24 months when stored at 2-8°C. A post-approval stability protocol is available.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In the Quality Dossier for Krystexxa (Pegloticase) the development, characterisation, manufacture and control of the intermediate uricase, the active substance Pegloticase and the finished product Krystexxa are adequately described. No major objections were raised during the evaluation, but the applicant was asked to address a number of other concerns mainly related to comparability of phase 3 and commercial active substance batches, control of uricase intermediate, pegloticase active substance and finished product. All issues raised during the evaluation have been adequately addressed by the Applicant. A number of recommendations have been identified which should be appropriately followed by the Applicant post authorisation.

Based on the review of data on quality, the CHMP consider that the application for Krystexxa can be approved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to provide reassurance on viral/TSE safety.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

2.3. Non-clinical aspects

2.3.1. Introduction

The design of the non-clinical testing program for pegloticase was based on the guidance provided by ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. The non-clinical testing strategy involved pharmacodynamic studies to evaluate pegloticase activity, pharmacokinetic studies to ascertain systemic disposition and metabolism, and toxicology studies to characterize the safety profile, including the immunogenic potential of the molecule.

In all of the non-clinical studies, pegloticase was formulated in phosphate buffered saline (PBS) as was the case for pegloticase administered in the clinical trials. The drug substance used in the toxicology studies was produced using the same process used to manufacture pegloticase for the clinical trials.

GLP

Studies on primary pharmacology of pegloticase were performed in compliance with GLP, with the exception of the study in knock-out mice.

All pivotal toxicological studies were conducted in accordance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Urate oxidase (uricase) catalyzes the conversion of uric acid (UA) to allantoin. Pegloticase is a recombinant mammalian (porcine/baboon variant) uricase produced in *E. coli*. The effect of PEG-uricase on SUA levels was determined in an *in vivo* a genetically modified mouse model (Uox-/-) where the endogenous uricase gene had been knocked-out. In this study, PEG-uricase was administered via the intraperitoneal route.

Furthermore the pharmacodynamics were investigated in four non-clinical single-dose toxicology studies and in five repeat (intermittent) dose toxicology studies, UA levels were measured following intravenous or intramuscular administration of pegloticase in rats and dogs.

Since the main species (rats and dogs) used in the preclinical studies possess the enzyme uricase and have already low endogenous baseline levels of UA, the pharmacodynamics of pegloticase was initially examined using an uricase-deficient knock-out mouse model. In this hyperuricemic model, pegloticase exhibited greater bioavailability and greater and more prolonged biological (UA-lowering) activity when the unmodified recombinant enzyme. In the uricase-deficient mouse model, the control mice developed the expected signs of diabetes insipidus, with impaired renal concentrating ability. However, in mice receiving pegloticase, the development of diabetes insipidus and nephropathy were prevented, and the renal concentrating ability remained similar to that in normal control (*Uox*+/+) mice.

In rats and dogs with endogenous uricase and already low baseline UA levels, pegloticase lowered UA levels further when administered IV, IM or SC. Thus, pegloticase was shown to be able to supplement the intrinsic activity of endogenous uricase in these species.

Overall, the pharmacological activity of pegloticase in non-clinical studies established the potential of pegloticase to lower UA levels for clinical use. Subsequent clinical studies demonstrated that a dose of 8 mg (3.51 mg/m^2) given IV on an every 2 week dosing schedule was effective in lowering UA levels in humans (5.3.5.1.1, C0403; 5.3.5.1.2, C0405; 5.3.5.1.3, C0406).

Secondary pharmacodynamic studies

Pegloticase is a recombinant enzyme which, according to the Applicant, has no known secondary pharmacodynamic activities in addition to its capability to convert UA to allantoin. Therefore, the CHMP endorses the Applicant's argument that an investigation of secondary pharmacodynamics was not applicable and no data for secondary pharmacodynamic studies has been provided.

Safety pharmacology programme

No separate safety pharmacology studies have been conducted for this biotechnology product but safety pharmacology endpoints were investigated in context of the toxicity studies, which is considered an acceptable approach. Pharmacodynamic effects on the cardiovascular system (in dogs) and a modified Irwin's Behavioural Screen (in dogs and rats) were performed as part of single and repeated dose toxicity studies. There were no unexpected organ system findings or effects on function in any of these non-clinical studies at pegloticase exposures greatly exceeding the clinical exposure that warranted further consideration for separate safety pharmacology studies.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed. This was considered acceptable to CHMP. However, concomitant medication was considered in the study population to study potential pharmacodynamic drug interactions in clinical studies.

2.3.3. Pharmacokinetics

Evaluation of absorption, distribution, metabolism and excretion (ADME) of pegloticase was performed in pharmacokinetic studies in rats, rabbits, pigs and dogs after single and repeat IV, SC and IM application.

Methods of analysis

Two methods were used to address ADME of pegloticase:

- ^{125}I- Pegloticase (radiolabel on lysine residue (s) of the protein) was used to assess the disposition of the radioactivity in the animals.
- A colorimetric method (measuring enzymatic activity) was used to determine pegloticase concentrations in biological fluids.

The measurement of the enzymatic activity was considered to be the most appropriate means to measure concentrations of pegloticase because of its large molecular size and high content of mPEG.

Absorption

Systemic exposure

In the single dose pharmocokinetic/toxicokinetic studies, the exposure to pegloticase tended to be higher in female rats compared to male rats, whereas exposure appeared to be comparable in male and female dogs. Exposure (AUC) after single IV application in dogs increased roughly as a function of the applied dose.

In the repeat dose pharmocokinetic/toxicokinetic studies in rats (SC) and dogs (SC, IV), peak/plateau levels and total (AUC) systemic exposures to pegloticase increased roughly as a function of the administered dose as well as the duration of the study. Plateau values in the 39 week chronic toxicity study in dogs with an IV application of doses up to 10 mg/kg every 7 days were reached after 84 days.

The mean total exposures following IV, SC and IM application tended to be higher in female rats compared to male rats, whereas in the dog studies the mean total exposure appeared to be comparable for the males and females.

Bioavailability

Bioavailability (F) following SC administration of pegloticase appeared to be lower in the rat (26%) compared to rabbit (84 – 95%), dog (48 – 50%) or pig (77%).

Mean bioavailability following IM administration of pegloticase tended also to be somewhat lower in the rat (44 - 76%) compared to the rabbit (88 – 98%), the dog (68 – 100%) or the pig (72%). For example, in a repeated dose dog study of four weeks duration with weekly IM dosing, the 1.5 mg/kg dose had a mean bioavailability of 100% in males and 91% in females for the terminal dose.

Plasma elimination half-life

In single and repeat dose pharmacokinetic/toxicokinetic studies, mean apparent plasma elimination half-life following IV administration of pegloticase appeared to be shorter in rats (23 – 84 hours) compared to rabbits (89 – 153 hours), dogs (94 – 216 hours), or pigs (178 hours).

In the rat, plasma elimination half-life of pegloticase following repeated IV administration of a dose of 0.7 mg/kg (34 – 43 hours) was similar to that seen after a single IV application of a dose of ~0.5 mg/kg (35 – 48 hours) and 15.2 mg/kg (54 - 68 hours). Also the plasma elimination half-life with repeated SC injections of doses of 3.4, 10.2 and 34 mg/kg did not show any dose-dependency with values ranging from 63 to 84 hours. Therefore, in the rat, elimination kinetics do not appear to be appreciably affected by the applied dose and administration mode.

In a single dose juvenile dog study, the elimination half-life for IV doses of 0.4, 1.5 and 10 mg/kg was 54, 96 and 104 hours (combined male and female values).

In a single dose adult dog study, the elimination half-life was 109, 139 and 187 hours (combined male and female values) for IV doses of 0.4, 1.5 and 10 mg/kg.

In the 12-week repeated dose toxicity study with IV doses of 0.5, 1.5 and 5 mg/kg the terminal plasma elimination half-life was 169, 167 and 227 hours (combined male and female values).

For IV dose of 0.4 mg/kg and 1.5 mg/kg, a half-live of 109 hours and 147 hours (combined male and female values), respectively, was observed following single application, whereas a final half-life of 163 hours and 221 hours (combined male and female values), respectively, was observed after repeated administration.

For an IM dose of 1.5 mg/kg a half-live of 217 hours (combined male and female values) was observed following single application, and a half-life of 222 hours (combined male and female values) was observed after repeated administration.
Therefore, in the dog, elimination half-life does appear to increase with the applied dose and with repeated IV application and appears to be shorter in juvenile animals than in adult animals.

The plasma elimination half-life of pegloticase after repeated IV administration in the Phase 2 clinical study for the 8 mg given every 2 weeks dose was 160 hours (ranging from 95.8 – 371 hours). In the Phase 3 clinical studies, the terminal half-life was 214 hours (ranging from 123 – 444 hours). Although this suggests that mean clinical exposure may be of a longer duration, values did to some extent overlap with the values determined for the dog and whereby affirmed the relevance of this species for evaluation of pegloticase toxicity. Furthermore, with regard to the repeat dose toxicity studies, total exposures in rats and dogs in these studies were much higher than those in the clinical investigations, assuring that cumulative exposures to pegloticase in the non-clinical toxicity studies were well beyond that anticipated clinically.

Clearance

In accordance with the observed shorter plasma elimination half-life, clearance appeared to be higher in rats (0.97 – 1.01 ml/hxkg) than in adult dogs (0.09 – 0.39 ml/hxkg).

In accordance with the observed shorter plasma elimination half-life, clearance appeared to be higher in juvenile dogs (0.41 – 0.72 ml/hxkg) than in adult dogs (values see above)

Volume of distribution

For the volume of distribution values of 78-95 ml/kg were reported for rat and values of 24 – 81 ml and 45 – 70 ml for adult and juvenile dogs, respectively. There appeared to be no gender differences.

These low values suggest that distribution of pegloticase is mainly confined to the circulating plasma volume.

Distribution

As described above, Vd-values suggest that distribution of pegloticase is mainly confined to the circulating plasma volume. From the single-dose tissue distribution studies in male and female rats given ^{125}I-pegloticase by the IV route, the distribution of the radiolabel to the tissues was consistent with the blood flow to the organs and total (specific) tissue radioactivity generally declined in parallel with blood/plasma elimination except in the thyroid and spleen. In these two organs, the elimination of radioactivity was much slower. For the thyroid, this probably represents the uptake of the radiolabel or protein fragments thereof. There was no evidence in the repeated dose toxicity studies that the thyroid was a target organ. Thus, for this organ, the radioactivity likely represents a pseudo-distribution of the label.

However, for the spleen, the residual radioactivity likely represents ^{125}I-pegloticase sequestered by the reticuloendothelial system (RES) in this organ. With either IV or SC administration, radioactivity in the spleen did not decline in parallel with blood or other organs over the 7 days of study. This observation correlates with the microscopic findings in the spleen (vacuolated macrophages) in the repeated dose toxicity studies.

Protein binding studies were not conducted since the molecular weight of pegloticase (>540 kDa) is much greater than that of albumin (66 kDa), making it unsuitable for the study of plasma protein binding using conventional techniques.

Radiolabelled studies to assess placental transfer were not conducted. However, in the rat embryo/foetal toxicity studies, pegloticase was not detected in pooled foetal samples, indicating that it does not cross the placenta.

Metabolism

The large size of pegloticase with the extensive PEG modification makes isolation and identification of the *in vivo* degradation products impractical. Therefore, the metabolism of pegloticase was followed by measurement of the amount of radioactivity precipitated by TCA in the blood and urine in male and female rats given ^{125}I-pegloticase by the IV or SC routes. To this aim ^{125}I-Bolton-Hunter reagent was coupled to free amino groups on pegloticase. In blood, TCA precipitated (indicates radiolabel attached to protein) radioactivity approached 100%. Greater than 89% of the radioactivity found in the urine was TCA soluble, indicating that extensive degradation of the radiolabelled protein had taken place, probably via vascular proteolytic activity and reticuloendothelial processing. Pegloticase protein degradation products were not further isolated or identified from urine.

Since the ^{125}I-label was coupled to the protein part of the pegloticase molecule, no direct evidence concerning the metabolic fate of the PEG-part of the pegloticase can be derived from the experiments performed with ^{125}I-pegloticase.

According to literature provided by the Applicant, the pharmacokinetics and organ uptake of PEGylated peptides and enzymes is affected in a predictable manner by their molecular size. As the molecular size increases, blood and body clearances decrease. PEGylation delays the elimination of these pharmaceuticals from the circulation by a variety of mechanisms, including decreasing renal clearance, proteolysis and immunogenicity. The metabolism of PEG itself is limited, and it is apparent that metabolic clearance of PEG decreases markedly as molecular weight increases. High molecular weight PEGs (>5000; typical of those used to PEGylate proteins) show little or no metabolism. Thus for PEGs typically used in biological products, metabolism will not play a major role in their elimination.

PEG of the size used to modify uricase and the large size of resulting pegloticase would indicate that for the PEG moiety, urinary excretion would be the route of elimination.

The presented literature data appear to be of relevance for an estimation of the metabolic fate/elimination of the PEG-part of the pegloticase molecule. Nevertheless, the CHMP considers it scientifically necessary to follow-up on this discussion, taking into account the occurrence of vacuolization in different cell types and the formation of anti-PEG antibodies during repeated dose toxicity studies with pegloticase. To further investigate the tissue deposition of pegloticase (tissue vacuolization) and the reversibility of this process, it is recommended that the applicant provides long-term data from an ongoing 12-month repeated dose toxicity study in dogs once available.

Excretion

The IV administration of ^{125}I-pegloticase to rats in the ADME studies demonstrated a slow elimination of the pegloticase-derived material from the blood with a half-life of 35.2 hours in males and 48.1 hours in females. However, the retention of radioactivity in the spleen and thyroid was different than for other tissues in which radioactivity declined as the radioactivity in the blood declined (see above). The excretion of ^{125}I-pegloticase occurred principally through the urine (approximately 70% of total administered radioactivity) as a soluble fraction, probably representing protein degradation products, while less than 10% of radioactivity were detected in the faeces.

Pharmacokinetic drug interactions

Pharmacokinetic drug interaction studies have not been performed. This appears to be acceptable with regard to the known high substrate specificity of uricase for uric acid.

2.3.4. Toxicology

To support the Phase 1 clinical trials, pegloticase was administered SC in single-dose and repeat-dose toxicity studies in rats and dogs. Furthermore, single-dose and repeat-dose toxicity studies in rats and dogs were also investigated via the IM route. However, the IV route of administration was thereafter developed as the SC route raised concern on the potential for immunogenicity. Hence, to support the Phase 2 and 3 clinical trials, which used IV route of administration, pegloticase was administered IV in single-dose studies in rats and dogs and in repeated dose toxicity studies in dogs. For the long term IV chronic toxicity studies, the dog was chosen since plasma half-life of pegloticase in dogs was closer to the pegloticase half-life determined in humans.

Single dose toxicity

Single-dose toxicity studies with pegloticase were conducted in rats and dogs via the IV, SC and IM route of application, involving a post-observation period of up to 28 days. Investigations usually included a measurement of body weight and food consumption, clinical observations, serum chemistry and macroscopic and microscopic evaluation of selected tissues following necropsies. Safety pharmacology endpoints (modified Irwin´s behavioural screen, electrocardiography) were included in some of the studies.

In the rat studies, single IV and SC doses of up to 72.5 mg (corresponding to a body surface area-based exposure ratio of 124 compared with human exposure) and an IM dose of 15.2 mg/kg were well tolerated. There were no adverse findings.

In the adult dog studies, single IV, SC and IM doses of up to 10, 29 and 1.5 mg/kg (corresponding to body surface area-based exposure ratios of 57, 165 and 8.5, respectively) were well tolerated. There were no adverse findings.

In conclusion, the acute dose toxicity studies in rats and adult dogs did not allow to define a non-clinical adverse effect level or a maximal tolerated dose for acute application of pegloticase. The applied dose levels provided a sufficiently high safety margin relative to human exposure for this biotechnology-derived product.

Overview of Single Dose Toxicity Studies

Species	Study ID	Route	N	Post-dose d	Dose mg/kg	Cmax µg/ml	AUC µgxh/ml	Exposure Ratio[1] AUC[2]	Exposure Ratio[1] BSA[3]	Note-worthy findings
Rat	10-4-0186-00	IV	5/sex/dose	14	72.5	-	-		124	
	10-4-0185-00	SC	5/sex/dose	14	72.5	-	-		124	
	WIL-441015	IM	12/sex/dose	14	15.2	57 (M) 134 (F)	6729 (M) 11326 (F)	32	26	NOAEL
		IV			15.2	319 (M) 315 (F)	15307 (M) 14821 (F)	55	26	NOAEL
Dog Juvenile	WIL-441011	IV	3/sex/dose	28	0.4	7 (M) 8 (F)	733 (M) 545 (F)	2.1	2.3	
					1.5	24 (M) 25 (F)	2948 (M) 3018 (F)	10	8.5	
					10	190 (M) 187 (F)	24488 (M) 24129 (F)	89	57	NOAEL
Dog Adult	WIL-441012	IV	3/sex/dose	28	0.4	8 (M) 8 (F)	1278 (M) 1230 (F)	3.4	2.3	
					1.5	27 (M) 28 (F)	5307 (M) 5135 (F)	18	8.5	
					10	156 (M) 141 (F)	33221 (M) 25784 (F)	102	57	NOAEL
	WIL-441016	IV	6/sex	28	1.5	29 (M) 29 (F)	4964 (M) 4734 (F)	19	8.5	NOAEL

		IM	x/ dose		1.5	23 (M) 26 (F)	6028 (M) 5376 (F)	21	8.5	NOAEL
	10-2-0187-00	SC	1/ sex/ dose	14	14.5	-	-		83	
			2/ sex/ dose		29	-	-		165	

1: Exposure compared with the clinical exposure
2: AUC: Values relative to exposure (AUC) of clinical responders in the phase 3 studies given 8 mg pegloticase every two weeks;
2: BSA (Body surface area): Values relative to exposure of patients (3.51 mg/m^2), based on a clinical dose of 8 mg and the average body weight of 99.3 kg in the Phase 2 and 3 clinical investigations.

Repeat dose toxicity

Repeated dose toxicity studies with pegloticase were conducted in rats and dogs. Investigations usually included a measurement of body weight and food consumption, clinical observations, serum chemistry and macroscopic and microscopic evaluation of selected tissues following necropsies. Safety pharmacology endpoints (modified Irwin´s behavioural screen, electrocardiography) were included in some of the studies.

In the rat, subchronic toxicity of SC doses up to 34 mg/kg was studied for 54 days (pegloticase administered every second day), followed by a 14 day recovery period.

In the dog, subchronic toxicity of SC doses (up to 17 mg/kg for 52 days, recovery period 28 days) and IM doses (up to 1.5 mg/kg for 28 days, recovery period 28 days) were evaluated.

In accordance with the IV application in the Phase 2 and 3 clinical studies, the pivotal repeat dose toxicity studies focused on the evaluation of the subchronic and chronic toxicity of IV applied pegloticase in the dog in studies of 4 weeks (application every 4th day, recovery period 4 weeks), 12 weeks (application every 5th day, recovery period 6 weeks) and 39 weeks duration (application every 7th day, recovery period 12 weeks). For the long term IV chronic toxicity studies, the dog was chosen since plasma half-life of pegloticase in dogs was closer to the pegloticase half-life determined in humans than plasma half-life in rats.

In the repeated dose toxicity studies there were no study drug-related deaths or relevant functional impairments. The only consistent finding concerning serum chemistry was the lowering of endogenous uric acid levels, which reflects the expected pharmacological effect of pegloticase.

Repeated Dose Toxicity Studies

Species	Study ID	Route	N	Duration d	Frequency	Recovery d	Dose mg/kg	Cmax µg/ml	AUC µgxwk/ml[1]	Exposure Ratio AUC	Noteworthy Findings
Rat	20-4-0188-00	SC	10-15/ sex/dose	54	every 2 d	-	3.4	16	160	7.2	NOAEL; no vacuoles
						-	10.2	48	443	20	Vacuoles in spleen
						14	34	157	1687	76	Vacuoles in spleen, partial reversal during recovery
Dog	20-2-0189-00	SC	2-3/ sex/dose	52	every 4 d	-	1.7	35	121	5.5	NOAEL; no vacuoles
						-	5.1	118	414	19	Vacuoles in spleen and submandibular lymph node
						28	17	414	3350	152	Vacuoles in spleen and submandibular lymph node, retained after recovery
	WIL-441017	IM	6/ sex/dose	28	every 7 d	28	0.4	10	30	1.4	No vacuoles
						28	1.5	50	153	6.9	NOAEL; no vacuoles
		IV				28	1.5	57	185	8.4	No vacuoles
	6432-106	IV	3/ sex/dose	84	every 5 d	42	0.5	24	232	11	Vacuoles in spleen (1 dog), no vacuoles after recovery
						42	1.5	75	745	34	Vacuoles in spleen, partial reversal after recovery
						42	5.0[2]	287	3018	137	Vacuoles in spleen, retained after recovery; NOAEL
	7533-100	IV	6/ sex/dose	273	every 7	84	0.4	15	263	12	Vacuoles in spleen, heart, liver (1 dog each), for spleen after recovery
						84	1.5	73	2167	98	Vacuoles in spleen, adrenal cortex. Retained in spleen; NOAEL;
						84	10	473	14253	645	Vacuoles in spleen, adrenal cortex, liver, heart, GI tract, retained after recovery

1: Values taken from Table 35, 2.6.4 Pharmacokinetics written summary, 2: recovery + challenge 0.5 mg/kg

Tissue vacuolization

The main relevant finding in the repeated dose toxicity studies was the occurrence of vacuolization in different tissues following repeated pegloticase application to rats and dogs. The severity of vacuolization and the number of tissues affected appeared to be dependent on the applied dose and the duration of exposure. Therefore, the number of tissues affected and the severity of vacuolization was greatest in the high dose (10 mg/kg) group in the 39-week dog repeated dose toxicity study in which vacuolization was observed in spleen, liver, duodenum, jejunum, adrenal cortex and heart. According to the presented study data, tissue vacuolization was not fully reversible during the applied recovery periods.

Anti-drug antibody formation

Antibody development in response to repeated pegloticase injections was observed in several studies, including pharmacokinetic studies in rats, rabbits and dogs, and repeat (intermittent) dose toxicity studies in rats and dogs. This is expected, because for the tested species, pegloticase represents a foreign protein and therefore possesses an inherent immunogenic potential to evoke an antibody response. Usually, antibody formation in animal studies is not predictive for anti-drug antibody formation in humans.

Weak antibody titers to m-PEG, and pegloticase were detected in most subchronic/chronic studies. The predominant immune response was directed against uricase. In the 12- and 39-week chronic toxicity study in dogs, anti-uricase antibodies/anti-pegloticase antibodies developed in most treated dogs, the response was not dose- or gender- related. There was a trend towards a decrease in titer and response during recovery for anti-uricase and anti-pegloticase antibodies. Anti-uricase/anti-pegloticase IgG

antibodies in all high responders did not affect pegloticase activity, i.e. the antibodies were not considered to be neutralizing. There was only a small anti-PEG response. There were no clinical manifestations associated with the presence of antibodies against uricase, pegloticase or m-PEG.

Intermittent dosing did not affect immune competence, and in the subchronic IV dog study, 4 week intermittent dosing followed by a recovery period and then challenge with pegloticase did not evoke any exaggerated immune response.

In the clinical trials, antibody titers to pegloticase have been detected in most treated patients. Although no neutralizing antibodies have been detected in patients receiving pegloticase, an increase in the clearance of pegloticase has been noted, possibly through immune complex formation via the PEG moiety. The toxicokinetic parameters determined in the repeat (intermittent) dose toxicity studies provided no evidence that there was any increase in clearance of pegloticase seen during these studies.

Genotoxicity

Pegloticase is a m-PEG conjugated recombinant mammalian uricase and regarded as a biotechnological product. The enzyme and the conjugated mPEG moiety are not considered to have a genotoxic potential. According to ICH S6 standard genotoxicity testing is not required for this type of product.

Carcinogenicity

Pegloticase is a m-PEG conjugated recombinant mammalian uricase. As the enzyme does not belong to any class of growth factor or hormone like peptides it is not considered to have a carcinogenic potential. In addition, in the repeated dose toxicity studies there were no findings that would indicate any carcinogenic potential. According to ICH S6 standard carcinogenicity testing is not required for this type of product.

Reproduction Toxicity

Embryo/foetal development

When pregnant rats were treated on gestation day 6 to 16 an increase in extramedullary haematopoiesis with dose-dependent increase in severity was observed in all treatment groups. While macrophages were not affected at 5 mg/kg (low dose) and 10 mg/kg (mid dose) administered IV every other day, in the pivotal study one out of eight mid dose dams showed vacuolated macrophages at 20 mg/kg as well as all high dose dams at 40 mg/kg with the same administration regimen as in the dose range finding study. In both studies uric acid levels were decreased by gestation day 17 when compared to pre dose levels on gestation day 6. Toxicokinetic investigations in dams showed a dose proportional increase in pegloticase plasma levels. In pooled litter samples pegloticase values were below the LLOQ. No drug-related effects were observed in foetuses of all treated groups. There was one malformed control foetus (localized foetal oedema) in the dose range finding and three foetuses with malformations (one control foetus with anal atresia and vertebral agenesis with anury; one low dose foetus with exencephaly and open eyelids and additionally *spina bifida* and absent gonads, another low dose foetus with vertebral malformation) in the pivotal study.

Studies in juvenile animals

In a single dose IV study in juvenile dogs aged 7 – 8 weeks old, a dose-dependent decrease in relative heart weights, reaching statistical significance in females of the mid (1.5 mg/kg) and high dose (10 mg/kg) groups, was observed. Furthermore, electrocardiographic evaluations which were performed pre dose (day -9), one hour post dose on the treatment day, and after a recovery period of 21 days

showed an increased incidence of dogs with second degree atrioventricular block on day 21 post dose, while no such finding was observed in any of the control group dogs. As no second degree atrioventricular block was observed one hour post-dosing in juvenile dogs, and pharmacokinetic considerations do not suggest any causal relationship with the second degree atrioventricular blocks demonstrated electrocardiographically 21 days after pegloticase administration, a causal relationship appears to be unlikely.

Toxicokinetic data

Toxicokinetic parameters have been determined in the single and repeat dose toxicity studies (see above).

Local Tolerance

Separate local tolerance studies were not performed. The assessment of local tolerance was part of the single dose and repeat (intermittent) dose toxicity studies conducted. This approach is considered acceptable.

There were no pegloticase injection site findings in the seven single dose studies. In the 54-day SC repeated dose rat study, there was a dose and treatment related change in all three pegloticase dose groups at the site of the SC injection. Slight oedema and inflammation were observed indicating that the pegloticase formulation caused a slight local response in the subcutaneous tissue of the rats after repeated injection.

In the 52-day SC repeat dose dog study and in the three (4-week, 12-week and 39-week) IV repeated dose dog studies, there were no pegloticase injection site findings.

Other toxicity studies

Studies have been performed to evaluate the immunogenic potential of pegloticase and to characterize potential effects on macrophage function. These studies are discussed above (see Repeated dose toxicity).

2.3.5. Ecotoxicity / environmental risk assessment

As the active ingredient pegloticase is an enzyme and thus a protein the applicant did not provide an environmental risk assessment. With reference to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) the applicant pointed out that this approach is supported by the given guideline where it is stated that vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted from an ERA because they are unlikely to result in significant risk to the environment. The justification for not providing an environmental risk assessment for the active ingredient pegloticase is considered acceptable.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The primary pharmacology of pegloticase in the mentioned non-clinical studies established the potential of pegloticase to lower UA levels for clinical use. Subsequent clinical studies demonstrated that a dose of 8 mg (3.51 mg/m^2) given IV on an every 2 week dosing schedule was effective in lowering UA levels in humans.

With regard to safety pharmacology, according to ICH S6 "Preclinical safety evaluation of biotechnology-derived pharmaceuticals", it is important to investigate the potential for undesirable pharmacological activity of biotechnology-derived pharmaceuticals on the major physiological systems in appropriate animal models. To this aim, functional indices may be investigated in separate studies or incorporated in the design of toxicity studies. The approach taken by the Applicant to investigate safety pharmacology endpoints in context of the toxicity studies is therefore in accordance with the recommendation laid down in ICH S6 and additional separate safety pharmacology studies are not considered warranted.

Pharmacokinetics

The pharmakocinetics were investigated of pegloticase in plasma from rats, rabbits, dogs, and pigs following single or repeat- (intermittent) dosing by the IV, subcutaneous, and IM routes (these were assessed using a colorimetric assay).

The CHMP noted that the analytical methods applied do not provide direct information concerning the pharmacokinetics of the PEG-part of pegloticase, which does not show enzymatic activity and is not labelled by ^{125}I when using the Bolton Hunter method. Therefore, the Applicant was asked to provide a more detailed discussion concerning the pharmacokinetics of the PEG-part of pegloticase, taking also into account the observation of tissue vacuolization in the repeated dose toxicity studies with pegloticase. Further data will become available with the final report of the 24-month vacuole study in dogs, which was recommended to be provided once available (see below).

In single and repeat dose pharmacokinetic/toxicokinetic studies, mean apparent plasma elimination half-life following IV administration of pegloticase appeared to be shorter in rats (23 – 84 hours) compared to rabbits (89 – 153 hours), dogs (94 – 216 hours), or pigs (178 hours). With regard to the repeat dose toxicity studies, total exposures in rats and dogs in these studies were much higher than those in the clinical investigations, assuring that cumulative exposures to pegloticase in the non-clinical toxicity studies were well beyond that anticipated clinically.

Toxicology

Repeated dose toxicity studies with pegloticase were conducted in rats and dogs. Investigations usually included a measurement of body weight and food consumption, clinical observations, serum chemistry and macroscopic and microscopic evaluation of selected tissues following necropsies.

Repeated dose toxicity

Reaction products of uricase-mediated uric acid degradation

Uricase is an enzyme not physiologically present in humans. Allantoin and hydrogenperoxide are formed as reaction products during uricase-mediated degradation of uric acid. During therapy with pegloticase, patients will therefore be exposed to these degradation products in an amount exceeding the normal physiological exposure. The repeated dose toxicity studies did not allow to define a maximal tolerated dose (MTD) for subchronic and chronic application of pegloticase. Nevertheless, the applied dose levels provided a sufficiently high safety margin relative to human clinical exposure for this biotechnology-derived product, amounting for the high dose in the 39 week dog toxicity study in an exposure-based safety margin of 645.

The CHMP asked the Applicant to tabulate reported concentrations of allantoin in normal animals and humans, and compare this to allantoin exposure expected in humans treated with pegloticase. The Applicant has provided an estimation of the additional amount of these reaction products formed during pegloticase therapy and a discussion concerning their toxicological properties. Allantoin formed by pegloticase from urate does not appear to represent a relevant safety problem. According to the

Applicant, the amount of H_2O_2 produced during pegloticase therapy can be expected to be decomposed by red blood cells via catalase. The contraindication listed in the SmPC together with the warning statement for SmPC section 4.4 concerning potential haemolysis and/or methaemoglobinaemia during KRYSTEXXA treatment were considered sufficient by the CHMP to cover relevant aspects related to an increased hydrogen peroxide production during Krystexxa treatment.

Also, maintaining plasma urate levels at <1 mg/dL with pegloticase did not increase plasma levels of F2-isoprostanes, considered to be relevant biomarkers for oxidative stress, and pegloticase was even shown to lower in F2-isoprostanes levels over time on treatment. In order to prevent possible haemolytic anaemia induced by hydrogen peroxide, cellular metabolic disorders known to cause haemolytic anaemia (like G6PDH deficiency) are included as contraindications for use in the SmPC. Furthermore, "Genetic Polymorphism (G6PD deficiency, cytochrome b5 reductase deficiency and other metabolic disorders known to cause haemolytic anaemia)" is indicated as missing information in the RMP.

Tissue vacuolization

The main relevant finding in the repeated dose toxicity studies was the occurrence of vacuolization in different tissues following repeated pegloticase application to rats and dogs. The severity of vacuolization and the number of tissues affected appeared to be dependent on the applied dose and the duration of exposure; vacuolization was not fully reversible during the applied recovery periods.

As reported for other pegylated products, vacuolization appears to be related to the presence of macrophages in some of the affected tissues. However, the CHMP noted that in the present studies with pegloticase other cell types (e.g. in the aorta outflow area of the heart) appeared also to be involved.

For macrophages, the presence of the vacuoles may reflect their normal function, as part of the reticuloendothelial system, to remove from circulation and possibly degrade any large molecules, cellular debris or foreign material that they encounter. The vacuoles may be interpreted to reflect the fact that the macrophages could not rapidly degrade the pegloticase and therefore, retained it in their cytoplasm, probably in isolated phagosomes.

In the repeated dose toxicity studies there was no case, at any dose or duration of application, of a test animal developing a systemic disease that would suggest that the defensive functions of the macrophages had been compromised by the presence of the vacuoles in their cytoplasm. Furthermore, there was no evidence at any dose of a study animal developing any condition that would indicate that the presence of vacuoles in cells from any organ had an adverse effect upon the health of the animal.

However, significant decreases in the TNF response to a LPS challenge were seen in total splenocytes and macrophages from rats dosed for 4 weeks with pegloticase doses of 4.3, 10.2 and 34 mg/kg. The effects were most prominent in the high-dose group, but also observed for the lower dose groups. Since there were no vacuoles reported in the low- and mid-dose groups, it was difficult to establish a functional relationship between TNF-release upon LPS challenge and the presence of vacuoles.

Overall, the information available concerning potential adverse consequences related to the occurrence of tissue vacuolization, in particular in cells other than macrophages, during chronic therapy with pegloticase should be investigated further. The Applicant is already conducting an additional 12-month chronic toxicity study in dogs with a 12-month recovery period to further characterize effects of pegloticase on tissue vacuolization, and the CHMP recommended these results to be provided once available.

<u>Reproductive and developmental toxicity</u>

A single embryofoetal development study in rats was included in the MAA dossier. This study in rats does not indicate direct or indirect harmful effects with respect to reproductive toxicity. Additional reproductive toxicity studies are ongoing: rat fertility study (WIL-441020), rabbit embryo/foetal developmental toxicity study (WIL-441021), rat pre-and postnatal development study (WIL-441025). The final reports should be available by the end of 2012. The CHMP recommended these results to be provided once available.

Section 4.6 of the SmPC states that 'embryofetal development study in rats does not indicate direct or indirect harmful effects with respect to reproductive toxicity' and section 5.3 of the SmPC includes a wording 'in the pregnant rat study there was no evidence of embryotoxicity or teratogenicity at 46 times the clinical exposure (AUC)'.

2.3.7. Conclusion on the non-clinical aspects

In general, the available data on non-clinical pharmacology, pharmacokinetics and toxicology of pegloticase is considered comprehensive to support the granting of a marketing authorisation for pegloticase from a non-clinical point of view.

The CHMP noted that further non-clinical studies are ongoing, whose results will provide relevant information regarding the formation, effects and reversibility of intracellular cytoplasmic vacuoles after i.v. administration of pegloticase (12-month repeated dose toxicity study in dogs) and reproductive toxicity of pegloticase (rat fertility study, rabbit embryo/foetal developmental toxicity study, rat pre- and postnatal development study). The CHMP therefore recommended that the results of these studies will be provided as soon as available, this has been agreed by the applicant in their letter of recommendation.

The Genetic Polymorphism (G6PD deficiency, cytochrome b5 reductase deficiency and other metabolic disorders known to cause haemolytic anaemia) has been addressed in the SmPC. SmPC section 4.3 includes a contraindication for Glucose-6-phosphate dehydrogenase (G6PD) deficiency and other cellular metabolic disorders known to cause haemolysis and methaemoglobinaemia. SmPC section 4.4 includes: "It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methaemoglobin reductase) or other cellular metabolic disorders are at increased risk for haemolysis and/or methaemoglobinaemia. If haemolysis and/or methaemoglobinaemia occur in patients receiving KRYSTEXXA, treatment should be immediately and permanently discontinued and appropriate measures initiated." SmPC section 4.8 lists haemolysis as an adverse reaction with not known incidence. This has also been addressed in the risk management plan as important identified risk.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, pegloticase is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme for pegloticase consisted of two Phase I studies investigating pharmacokinetics (PK), safety and tolerability of single subcutaneous (SC) and IV doses of pegloticase, one Phase II study investigating safety and efficacy of multiple IV doses of pegloticase, two placebo-controlled (pivotal) Phase III studies of 8 mg PEG-uricase in two dose regimens in hyperuricemic subjects with symptomatic gout, an open-label, Phase IIIb extension study for patients participating in

the two pivotal studies, and an exploratory study to investigate re-challenge with pegloticase. The list of clinical trials can be found in the tabular overview below (see Table 1).

Table 1 Tabular overview of clinical studies

Study	Study Objective	Study Design	Number of Subjects Treated	Dosage Regimen; Route of Administration	Duration of treatment	Study Status
Phase I						
C0401	Single dose PK, tolerability, safety	Open label, escalating single dose	13	Pegloticase SC; 4 mg (n=4), 8 mg (n=4), 12 mg (n=4), 24 mg (n=1)	1 day (FU 21day)	Completed
C0402	Single dose PK, tolerability, safety	Open label, escalating single dose	24	Pegloticase IV infusion; 0.5 mg (n=4), 1.0 mg (n=4), 2.0 mg (n=4), 4.0 mg (n=4), 8.0 mg (n=4), 12.0 mg (n=4)	1 day (FU 8wks)	Completed
Phase II						
C0403	Multiple dose PK, efficacy, tolerability, safety	Randomized, open label, parallel group	41	Pegloticase IV infusion; 4 mg/2 wk (n=7), 8 mg/2 wks (n=8). 8 mg/4 wks (n=13) 12 mg/4 wk (n=13)	18 wks	Completed
Phase III						
C0405	Efficacy, safety	Randomized, double-blind, placebo-controlled, parallel group	104; Pegloticase: (n=84); Placebo: (n=20)	Pegloticase IV infusion; 8 mg/2 wks 8 mg/2 wks (n=43); 8 mg/4 wks (n=41); Placebo	26 wks	Completed
C0406	Efficacy, safety	Randomized, double-blind, placebo-controlled, parallel group	108; Pegloticase: (n=85) Placebo: (n=23)	Pegloticase IV infusion; 8 mg/2 wks 8 mg/2 wks (n=42); 8 mg/4 wks (n= 43); placebo	26 wks	Completed
C0407	Long-term efficacy, safety	Open label extension	151; Pegloticase: (n=149); No treatment: (n=2)	Pegloticase IV infusion; 8 mg/2 wks 8 mg/2 wks (n=82); 8 mg/4 wks (n=67); no treatment (observational arm)	Up to 30 mo	Completed
C0409	Safety and clinical effect of re-exposure	Open label re-exposure	7	Pegloticase IV infusion; 8 mg/2 wk	6 mo	Completed

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

2.4.2. Pharmacokinetics

Pegloticase has been developed as recombinant PEGylated uricase with a prolonged circulating half-life of enzymatically active uricase. The enzyme uricase can be found in an extensive variety of organisms but is absent in humans and many other primates. The outer surface of the tetrameric uricase enzyme is encased in a hydrated PEG "cloud" also impacting the pharmacokinetics of the compound.

The formulation for intravenous use was kept unchanged throughout the development phase and therefore no comparative biopharmaceutical studies were performed.

Pharmacokinetic (PK) and Pharmacodynamic (PD) data have been generated from five studies all conducted in patients with severe refractory gout (see Table 2).

Table 2 Overview of PK/PD studies

Study	Design	Dose (mg)	No pat	Patients (gender, mean age)
401	open-label single dose SC	4 8 12 24	4 4 4 1	**13** 10M/3F 56.1 y
402	open-label single dose IV	0.5 1 2 4 8 12	4 4 4 4 4 4	**24** 20M/4F 56.7 y
403	open-label multiple dose IV	4 every 2 wks (6 inf) 8 every 2 wks (6 inf) 8 every 4 wks (3 inf) 12 every 4 wks (3 inf)	7 8 13 13	**41** 35M/6F 58.1 y
405/406	double-blind population PK IV	8 every 2 wks 8 every 4 wks		**163** 131M/32F 55.6

- **Analytical methods**

Different analytical methods were validated and used in the course of clinical development. During Phase 1, pegloticase activity was determined using a radiochemical HPLC method to quantify the amount of [8-14C] uric acid remaining after pegloticase oxidation of UA in standard samples (study C0402). In the Phase 2 and 3 studies, a fluorimetric method was used for the determination of active pegloticase in human serum. The presence of anti-pegloticase antibodies was detected by means of an enzyme-linked immunosorbent assay (ELISA).

Absorption / Distribution / Elimination

Study 401 was initiated to determine the bioavailability and PK of pegloticase following SC administration. The mean plasma urate was reduced from 11 mg/dL to 3 mg/dL after 7 days. However 3 patients had injection site reactions, and while the circulating half-life of the enzyme was unexpectedly prolonged in 8 patients, with activity detectable after 21 days, there was also evidence of accelerated clearance in the other 5 patients with no detectable enzyme activity after 10 days, possibly associated with the development of anti-PEG antibodies. As a result, the Phase 1 study was terminated and no further development of SC administration of pegloticase was pursued.

Study 402 was an open-label, single-dose study of intravenously administered pegloticase was conducted in 24 subjects with symptomatic gout. The primary objective was to assess the PK profile, tolerability and safety of PEG uricase, administered as a single intravenous infusion. Another objective was to evaluate the dose response effect on plasma uric acid levels. Escalating doses of pegloticase (0.5, 1.0, 2.0, 4.0, 8 or 12 mg) were administered as a 1-hour infusion. Blood samples were collected pre-dose and at 1.5, 4, 8, 24 hours, 2, 4, 7, 8, 10, 14 and 21 days post-dose. Non-compartmental PK and PD analyses were conducted using data from 23 of the 24 subjects which were also included in the PK analyses (one subject had only 2 detectable concentrations).

The results of study 402 are summarized in Table 3. Although sample size is rather limited and high variability does not allow a final conclusion, C_{max} for uricase appeared to be roughly dose proportional. However, there seemed to be no increase in AUC above the 8 mg dose. Study results further indicated a dose of 2 mg or greater to be sufficient to keep uric acid levels below the solubility level of 6.8 mg/dL in serum. The mean uricase half-life was found to be at least 1 week, though high data variability is noted.

Compartmental PK/PD modelling results suggested that pegloticase doses of 2 mg or greater could maintain mean pegloticase levels above EC50 and consequently uric acid levels below its solubility limit of 6.8 mg/dL for up to one week.

Table 3 Mean (CV%) Pharmacokinetic parameters by dosing group for Protocol C0402

Parameter	0.5 mg (n=4)	1 mg (n=3)	2 mg (n=4)	4 mg (N=4)	8 mg (N=4)	12 mg (n=4)
AUC_{inf} (mcg.h/mL)	22.1 (55.3%)	108 (33.1%) *	92.0 (90.3%)	183 (76.6%)	422 (11.4%)	394 (38.7%)
AUC_{0-t} (mcg.h/mL)	11.2 (55.6%)	46.0 (69.7%)	69.6 (80.9%)	131 (70.3%)	292 (10.0%)	289 (38.8%)
C_{max} (mcg/mL)	0.076 (18.2%)	0.223 (32.1%)	0.397 (29.9%)	0.653 (19.4%)	1.20 (10.8%)	1.66 (15.7%)
$T_{½}$ (h)	203 (57.5%)	332 (15.3%) *	153 (63.9%)	167 (75.6%)	300 (7.05%)	163 (40.1%)

Study 403 was a randomized, open-label, multi-centre, parallel-group Phase 2 study. Altogether 41 subjects with refractory gout and hyperuricaemia were enrolled. Each subject received 3 or 6 IV infusions of pegloticase, infused over approximately 30-60 minutes. The dosing regimens were chosen based on the outcome of previously performed studies (namely 401 and 402) and were 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks or 12 mg every 4 weeks.

The primary efficacy objective of this study was to assess the effect of multiple doses of PEG-uricase on uric acid levels, time to normalization of uric acid (i.e. ≤6 mg/dL of uric acid in plasma), and duration of uric acid normalization in the above-mentioned population. The secondary efficacy objective was to assess PK and PD parameters of multiple doses of PEG-uricase in this patient population.

Pharmacokinetics of pegloticase in serum were best described by a 1-compartment model with linear elimination. The final PK/PD model included a direct inhibitory Emax model to describe an inhibitory effect of pegloticase on uric acid. Covariates investigated for inclusion in the PK/PD model were age, sex, race, body weight, ideal body weight and antibody levels. No influence on CL and Vc appeared to come from factors like age, sex, race, body weight, and antibody levels. Simulations indicated

pegloticase given as 2 h- IV infusion every 2 or 4 weeks at an 8 mg dose to best control uric acid levels below the threshold of 6 mg/dL. This dosing regimen is also supported by the long half-life of pegloticase.

Table 4 Summary of Non-compartmental PK parameters for subjects in Protocol C0403 following administration of single and multiple doses of pegloticase [median(range)]

Treatment	Cycle	AUC_{0-24} (mcg·h/mL)	AUC_{0-168} (mcg·h/mL)	AUC_{0-t} (mcg·h/mL)	C_{max} (mcg/mL)	Half-life (h)	CL (L/h)
4 mg every 2 weeks	1	17.0 (15.0-18.9)	NC	18.1 (15.0-170)	0.800 (0.768-1.14)	NC	NC
	6	34.2 (22.7-51.9)	251 (132-369)	132 (97.1-657)	1.62 (1.51-2.94)	414 (210-617)	0.00609 (0.00609-0.00609)
8 mg every 2 weeks	1	50.3 (20.5-71.7)	355 (245-489)	608 (264-838)	2.95 (1.98-4.81)	274 (198-308)	0.00734 (0.00536-0.00141)
	6	122 (61.1-186)	710 (326-1034)	1361 (326-2734)	5.96 (2.87-8.89)	160 (95.8-371)	0.00681 (0.00447-0.0114)
8 mg every 4 weeks	1	41.4 (15.7-92.9)	269 (151-759)	304 (151-1751)	2.50 (1.34-5.14)	280 (239-296)	0.00673 (0.00314-0.0138)
	6	46.5 (25.4-72.8)	403 (231-577)	231 (81.2-3936)	2.81 (1.92-4.56)	399 (61.6-940)	0.00349 (0.00349-0.00349)
12 mg every 4 weeks	1	59.6 (30.7-114)	478 (252-765)	1047 (97.6-2574)	3.52 (1.53-5.79)	329 (181-403)	0.00767 (0.00393-0.00121)
	6	84.0 (63.5-139)	519 (398-567)	670 (398-1821)	4.64 (3.28-6.18)	119 (92.8-282)	0.00671 (0.00659-0.00683)

Studies 405 and 406 were two multicentre, randomized, double-blind, placebo-controlled, three-arm, parallel treatment group Phase 3 trials with a 24 week treatment period. Each subject was expected to participate in the study for up to 26 weeks, including a 2-week screening period and the 24 week treatment period. Each subject received 8 mg pegloticase IV every 2 weeks or 8 mg pegloticase IV every 4 weeks (alternating with placebo infusion every 2 weeks) or matching placebo control. Samples for PK analysis were collected before each dose administration, as well as 2 and 24 hours after the end of dose administration following doses 1 (week 1), 5 (week 9) and 11 (week 21). Additional samples were also collected 7 days after the end of dose administration following Doses 5 and 11, 2 hours and 7 days after the end of dose administration following Doses 6 and 12, and 14 days after the end of dose administration following Dose 12. In the event of an early termination, a sample was also collected at this time. Samples for analysis of antibodies to pegloticase and PEG were collected pre-dose before dose 1 (week 1), dose 2 (week 3), dose 3 (week 5), dose 5 (week 9), dose 7 (week 13), dose 9 (week 17), dose 11 (week 21) and approximately 14 days after dose 12 (week 25).

A population PK analysis was performed using NONMEM VI in order to robustly characterize the pharmacokinetics of pegloticase. A total of 163 subjects (131 men and 32 women) from both protocols

were included in the pharmacokinetic analysis. Only subjects who received active drug and who had at least one detectable pegloticase concentration were included in the population PK analysis.

Table 5 Summary of Population Pharmacokinetic Parameters for Subjects in Studies C0405 and C0406

Parameter	Mean	Coefficient of Variation (%)	
		Inter-subject	Intra-subject
Vc if no increase in anti-pegloticase (L)	4.73	24.7	18.2
Vc if increase in anti-pegloticase (L)	5.93		
CL if no increase in anti-pegloticase (L/h)	0.0145	39.6	17.0
CL if increase in anti-pegloticase (L/h)	0.0191		

Covariates investigated included demographic variables (height, weight, ideal body weight, body mass index, age, body surface area, sex) as well as serum uric acid levels at screening, creatinine clearance (calculated using the Cockroft-Gault equation), number of gout flare ups, overall antibody level against pegloticase and PEG, presence of tophi, presence of hypertension or diabetes and allergy or gastrointestinal intolerance to allopurinol. The only significant covariates included in the PK model were body surface area and anti-pegloticase antibody response on Vc and CL. Although creatinine clearance on CL and anti-pegloticase antibody response on Vc were associated with the greatest decreases in objective function, they were not included as covariates in the model, because their inclusion in the model did not provide pharmacologically plausible results. Anti-pegloticase antibody level on Vc should have been added to the model, since this covariate was associated with the most important decrease in objective function. However, when this covariate was added to the model, anti-pegloticase antibodies were not a significant covariate on CL, when it would be expected that the antibodies should have an effect on pegloticase elimination. Creatinine clearance on CL was the covariate that produced the second-greatest decrease in objective function (after anti-pegloticase antibody level on Vc), but the inclusion of this covariate was not deemed appropriate as no renal elimination of unchanged pegloticase is observed (it is possible that uremic toxins accumulating with decreased renal function could inhibit transporters thereby decreasing access to sites of metabolism). Since the inclusion of anti-pegloticase antibody level on Vc and creatinine clearance on CL did not lead to final models that were realistic from a pharmacologic perspective, the analysis using BSA on CL as the second covariate was pursued since the effect of creatinine clearance on clearance was not a primary covariate, while anti-pegloticase antibodies did become a selected covariate on CL in the forward analysis. The inclusion of the anti-pegloticase antibody response in the final model indicates that the presence of antibodies is associated with an increased volume of distribution as well as an increased systemic clearance. Treatment group was not a significant covariate; therefore, population PK parameters were the same regardless of the dosing frequency (every 2 weeks or every 4 weeks).

Table 6 Summary of Pharmacokinetic Parameters for Subjects in Protocols C0405 and C0406

Parameter	Treatment	
Mean* (CV%) median (range)	8 mg IV Pegloticase given every 2 weeks	8 mg IV Pegloticase given every 4 weeks
AUC0-T	445 (32.3%)	440 (29.2%)

(mcg·mL/h)	430 (223 – 1040)	413 (277 – 1037)
Cmax (mcg/mL)	2.17 (30.1%) 2.17 (1.25 – 4.77)	1.56 (31.1%) 1.55 (0.891 – 3.20)
tmax (h)	2.25 (26.0%) 2.00 (1.92 – 4.25)	2.23 (25.8%) 2.00 (2.00 – 5.08)
Kel (h-1)	0.00339 (21.1%) 0.00337 (0.00156 – 0.00565)	0.00319 (23.3%) 0.00312 (0.00153 – 0.00531)
Half-life (h)	214 (23.4%) 206 (123 – 444)	229 (24.4%) 222 (130 – 452)

*Geometric means and CV% for AUC0-τ and Cmax parameters and arithmetic means for all other parameters

Data from food-interaction studies

No specific studies have been performed. Given the type of medicinal product, route of administration, and target population information provided on pharmacokinetics and PK/PD relation are considered acceptable by the CHMP.

Dosing and dose in special populations

No specific studies have been performed. Group imbalances were apparent in the dose finding study C0403 making the selection of the appropriate dose difficult. PK dose proportionality (AUCinf) was not sufficiently shown. Based on population PK analyses, only BSA was correlated with the clearance and volume of distribution. The population included a substantial proportion of elderly patients, the median age being 57 years. Dose subgroup analyses indicated that PUA responses might be influenced by absolute bodyweight (BW) and might be modified in the elderly and in patients with renal impairment. This is supported by data from population pharmacokinetic analysis revealing an influence of the BSA and of the patient's creatinine clearance on the clearance of pegloticase. This has not been further evaluated by the Applicant but might have an impact on dose selection for patients with renal impairment and different weight.

Higher AE rates were reported for most SOCs in the elderly and in patients with impaired renal function, these likely to be correlated. However, there was no obvious unexpected safety signal that would justify a dose adjustment in these patients. The statement that data are very limited in patients with severe renal impairment has been added in the SmPC. Further evaluation of the optimal dose in patients with over 100 kg BW is deemed to be necessary. The Applicant commits to conduct such a dose finding study. Meanwhile, the SmPC contains an appropriate warning.

Pharmacokinetic interaction studies

No interaction studies have been conducted with pegloticase. Additionally, 41% of patients developed antibodies against the PEG moiety. As no interaction studies were conducted it cannot be excluded at present that these antibodies could reduce the efficacy of other PEGylated agents (e.g. interferon) that might be used in future. This has been adequately reflected in the SmPC.

Pharmacokinetics using human biomaterials

No studies have been performed with pegloticase regarding metabolism, using human biomaterials, protein binding, or distribution studies using human biomaterials. Given the type of medicinal product, route of administration, and target population information provided on pharmacokinetics and PK/PD relation are considered acceptable by the CHMP.

2.4.3. Pharmacodynamics

Mechanism of action

In humans, uric acid is the terminal metabolite of purine degradation. Pegloticase catalyzes the oxidation of uric acid to allantoin. Allantoin is an inert and highly soluble purine metabolite. It is readily

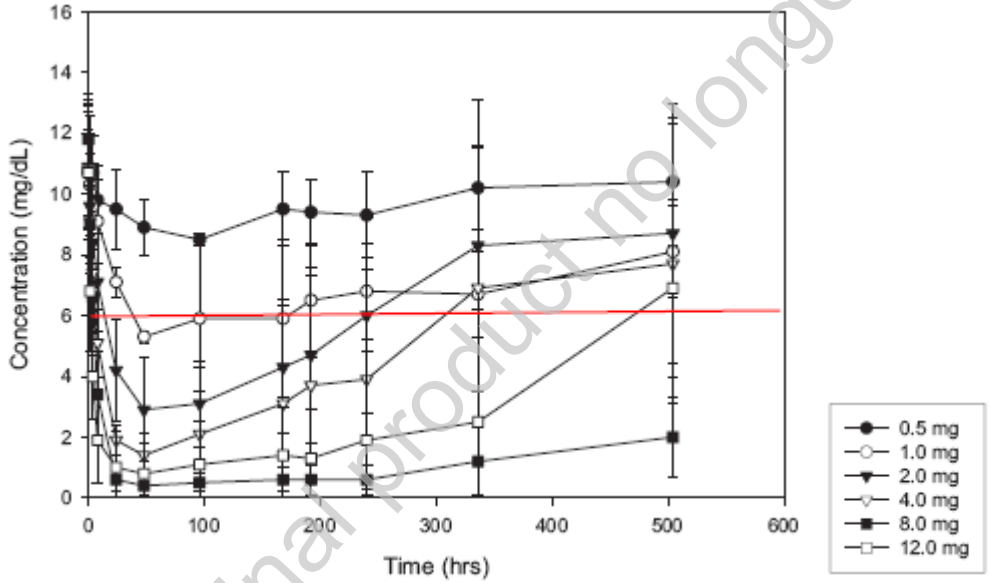
eliminated. Pegloticase is a uric acid specific enzyme and as such might have a very specific effect. Elimination of allantoin is not explicitly presented.

Primary and Secondary pharmacology

The Phase I programme established that pegloticase administered intravenously had an acceptable profile of tolerability and safety, after it was shown that subcutaneous administration was less well tolerated.

Study 402 examined the efficacy, immunogenicity, tolerability, pharmacokinetics and pharmacodynamics of pegloticase following IV administration. Six groups of 4 patients received single IV doses of 0.5, 1, 2, 4, 8 or 12 mg of protein. Following doses of 4-12mg the plasma urate fell within 24-72 hours from a mean ± SEM of 11.1 ± 0.6mg/dL to 1.0 ± 0.5 mg/dl. The plasma half-life of uricase activity ranged from 6-14 days but area under the curve measurements of the plasma urate suggested that plasma urate levels were maintained in the range 1.2- 4.7 mg/dL for 21 days following infusion of these doses. The study identified a clear pharmacodynamic relationship between the IV administered pegloticase dose, uricase activity, and the plasma uric acid concentration achieved. Anti-PEG IgG antibodies developed in 9 patients who had more rapid clearance of enzyme but there were no associated allergic reactions.

Figure 1 Study 402: Mean (SD) plasma UA concentration over time



2.4.4. Discussion on clinical pharmacology

Irrespective of certain limitations regarding sample size, and some differences between studies probably caused by model misspecification, manufacturing site change, and bioanalytical assay differences, the clinical pharmacology results characterize the PK and PD profiles of pegloticase. The main conclusions supported by the data are:

- An 8 mg dose is expected to provide sufficient control of hyperuricemia in patients with chronic gout who have failed alternative urate-lowering therapies, a population currently without alternative treatment options.
- The long half-life and low EC50 support the use of a two weeks dose administration interval.

- Potential for some accumulation in the pegloticase 8 mg every two weeks dosing regimen is predicted by the PK modeling; however, this is not of large enough magnitude to give rise to concern (confirmed by the safety profile in patients continuously exposed to pegloticase 8 mg every two weeks for 30 months or more).
- Dose subgroup analyses indicated that PUA responses might be influenced by absolute bodyweight (BW) and might be modified in the elderly and in patients with renal impairment.

In a single-dose, dose-escalating study, following 1-hour intravenous infusions of 0.5, 1, 2, 4, 8 or 12 mg of pegloticase in 24 patients with symptomatic gout (n=4 subjects/dose group), plasma uric acid decreased with increasing pegloticase dose or concentrations. The duration of suppression of plasma uric acid appeared to be positively associated with pegloticase dose. Sustained decrease in plasma uric acid below the solubility concentration of 6 mg/dl for more than 12.5 days was observed with doses of 8 mg and 12 mg.

2.4.5. Conclusions on clinical pharmacology

The mode of action of pegloticase was well characterised by the PK/PD studies providing a sound rationale for the frequency of dosing being tested in the Phase III. The frequency of dosing seems to be sufficiently supported by the results of the pivotal studies.

2.5. Clinical efficacy

The efficacy of pegloticase was investigated in three trials, a dose-response study (403) and two double-blind placebo-controlled replicate pivotal Phase III trials (405 & 406). They were all conducted in the target population of patients with gout refractory to conventional therapy. Two additional studies were performed (407 & 409), for safety purposes mainly: long-term safety and safety of re-exposure after a treatment interruption of at least one year.

Table 7 Overview of clinical efficacy/safety studies

Study ID	No. of study centres locations	Design	Treatment posology	Study objective	Subj by arm treated/ completed	Duration wks	Gender M/F	Median Age	Diagnosis Inclusion criteria	Primary Endpoint
403	9/US	Random. Open-label Multiple dose	4mg/2 wks 8mg/2wks 8mg/4wks 12mg/4wks	PK/PD	7/4 8/8 13/8 13/6	10 10 8 8	7/0 5/3 11/2 12/1	51 64 64 60	Symptomatic refractory gout	Plasma UA level
405	29/US Canada	Random. Double-blind	Placebo 8mg/2wks 8mg/4wks	Efficacy Safety	20/19 43/30 41/27	26	15/5 30/13 35/6	57 58 55	Symptomatic refractory gout	% subj with PUA <6mg/dL
406	27/US Mexico	Random. Double-blind	Placebo 8mg/2wks 8mg/4wks	Efficacy Safety	23/20 42/29 43/32	26	21/2 38/4 34/9	54 54 54	Symptomatic refractory gout	% subj with PUA <6mg/dL
407	46/US, Canada, Mexico	Open-label Extension 405 & 406	8mg/2wks 8mg/4wks	Efficacy Safety	80/43 69/27	Up to 30 mo	62/18 55/14		Symptomatic refractory gout	Long-term safety
409	4/US	Open-label Re-exposure	8mg/2wks	Efficacy Safety	7/4	6 mo	6/1	64	Symptomatic refractory gout	Safety at re-exposure

2.5.1. Dose response study

Study C0403

Randomized, open-label, multi-centre, parallel-group study of multiple doses of pegloticase, administered by IV infusion, in 41 patients in patients with hyperuricemia and symptomatic gout.

The dose finding study C0403 assessed a total of 41 patients distributed across 4 dosing groups: 4 mg/2 wks (resulting 6 infusions over a period of 10 wks), 8 mg/2 wks (resulting 6 infusions over a period of 10 wks), 8 mg/4 wks (resulting 3 infusions over a period of 8 wks), 12 mg/4 wks (resulting 3 infusions over a period of 8 wks).

The patients' characteristics showed distinct differences in the BMI between the groups. The mean bodyweight in the 4mg/2weeks group was very high with 115.26kg (BMI 36.38) whereas the patients in the 8mg/2 weeks group weighted 76.95kg (BMI 27.12). In the 4mg/2weeks group there was no female patient and in the 8mg/2weeks group the rate of men were 62.5%. Also the age was 10 years lower in the 4mg/2weeks group and SUA at baseline was 1mg/dL lower than with 8mg.

The percentages of ITT population treatment responders in the 4mg 2-week, the 8mg 2-week, the 8mg 4-week, and the 12mg 4-week treatment regimens were 4/7 (57.1%), 7/8 (87.5%), 7/13 (53.8%), and 8/13 (61.5%), respectively. No statistically significant differences were observed between the treatment comparisons of interest (ie, 4mg 2-week vs. 8mg 2-week, 8mg 2-week vs. 8mg 4-week, and 8mg 4-week vs. 12mg 4-week) for the ITT population.

The dose-finding study lacked power to show statistically significant differences between the efficacies of the included dosing regimens according to the pre-specified primary endpoint (normalization of PUA to < 6 mg/dL for 80% of the time during entire treatment period). Nevertheless, using this response criterion, the best regimen was 8mg/2 wks with a proportion of responders (87%) almost twice that achieved with the 8mg/4 wks (46%) when early drop-outs were imputed as non-responders.

2.5.2. Main studies

The two pivotal Phase III studies 405 & 406 used the same protocol and will be described together.

Study C0405:

Randomized, Multicentre, Double-blind, Placebo-controlled Efficacy and Safety Study of 8 mg PEG-uricase in Two Dose Regimens in Hyperuricemic Subjects with Symptomatic Gout

Study C0406:

Randomized, Multicentre, Double-blind, Placebo-controlled Efficacy and Safety Study of 8 mg PEG-uricase in Two Dose Regimens in Hyperuricemic Subjects with Symptomatic Gout

Methods

Study Participants

Main inclusion criteria

- outpatients of either gender;
- age 18 or older;
- hyperuricemic with a screening serum uric acid (SUA) ≥ 8 mg/dL;
- subjects with symptomatic gout (at least 3 gout flares experienced in the 18 months prior to entry, or at least 1 tophus, or gouty arthritis);

- subjects in whom conventional therapy was contraindicated or had been ineffective, i.e., history of hypersensitivity or of failure to normalise SUA with at least 3 months treatment with allopurinol at the maximum labelled dose [800 mg/day in the U.S.] or at a medically appropriate lower dose based on dose-limiting toxicity or dose-limiting comorbidity.

Main exclusion criteria

- Unstable angina pectoris, uncontrolled arrhythmia, non-compensated congestive heart failure
- Uncontrolled hypertension (> 150/95 mmHg)
- History of end-stage renal disease requiring dialysis
- Haemoglobin < 8 g/dL (males) and < 7 g/dL (females)
- Organ transplant recipient
- Prior treatment with pegloticase, or other recombinant uricase, or any concomitant therapy with a PEG-conjugated drug
- G6PD deficiency
- History of anaphylactic reaction to a recombinant protein or porcine product, or hypersensitivity to PEG

Treatments

Patients were randomised to one of three groups:

- pegloticase 8 mg/2 wks,
- pegloticase 8 mg/4 wks (alternating every 2 weeks with placebo)
- or placebo/2 wks.

All patients received an IV infusion of either pegloticase or placebo (250 mL) over a 2-hour period every 2 wks. Subjects were to remain at the study site for at least 2 additional hours of observation in order monitor for infusion reactions (IR).

Study duration was approximately 26 wks, including 2 wks for screening and 24 wks (6 months) of treatment. After completing the study, subjects were given the option of continuing active treatment up to an additional 30 months through the separate OLE protocol (Study 407), or they could enter at any time into an observation Phase.

Gout flare prophylaxis and treatment

All patients were required to use a gout flare prophylaxis drug regimen starting 1 week before the first administration of study drug and for the whole duration of the trial. This consisted of colchicine at a dose individualised for each subject by the investigator (0.6 to 1.2mg/d) or an NSAID, associated with a proton pump inhibitor (PPI) for gastric prophylaxis, if necessary.

All subjects who experienced a gout flare after the screening visit, received an anti-inflammatory treatment, pre-specified at screening from among three possible options: NSAIDs and a PPI, colchicine; or corticosteroids. Narcotic analgesics, acetaminophen, or tramadol, prescribed at the discretion of the investigator, could be used to attain effective analgesia in conjunction with gout flare treatment.

Infusion reaction prophylaxis

All subjects received a standardised pre-treatment prophylaxis regimen consisting of:

- 60mg of fexofenadine *po* the night before study drug infusion,
- 60mg of fexofenadine and 1000mg of acetaminophen *po* the morning of the infusion,
- and hydrocortisone 200mg IV immediately prior to the infusion of study drug.

Management of infusion reactions

If a subject experienced an IR (= an AE during the infusion or within the 2 hours post-infusion), the following procedures were undertaken: abbreviated physical exam, vital signs, 12-lead ECG, blood sample for measurement of tryptase (as a marker for mast cell degranulation).

The rate of infusion had be slowed by half (250 mL/4 hours instead of 250 mL/2 hours), or stopped. If the AE resolved, the infusion may have proceeded to completion, either at the original rate or at a slower rate. If the AE failed to resolve within one hour, or if in the investigator's opinion the subject was experiencing an anaphylactic reaction, the infusion had to be terminated. Subjects who were considered to have possibly experienced an anaphylactic reaction did not receive a subsequent infusion of study drug without the written authorisation of the Sponsor's Medical Monitor. After the first experience of an infusion reaction, the next infusion could be initiated at a slower rate and/or with an increased volume of dilution. In addition, the patient could receive 20mg prednisone the night prior to the next infusion.

Objectives

Primary objective

To demonstrate superiority of pegloticase vs. placebo in reducing plasma uric acid (PUA) as determined by the percentage of subjects achieving and maintaining PUA concentrations < 6 mg/dL for at least 80% of the time assessed during Months 3 and 6 combined.

Secondary objectives

To determine the effect of pegloticase as reflected by:

- the reduction of tophus burden,
- the improvement of patient reported outcomes (PROs) using the Medical Outcomes Survey Short Form-36 (SF-36) and Health Assessment Questionnaire Disability Index (HAQ-DI),
- the reduction of the number of swollen and tender joints,
- the reduction of incidence and frequency of gout flares.

Safety objectives

To describe the AE profile of pegloticase, in particular:

- to determine the incidence of infusion reactions (IRs) and gout flares,
- to determine the incidence of clinically manifest allergic reactions,
- to characterize the potential for antibody response to pegloticase by laboratory evaluation.

Outcomes/endpoints

Primary endpoint

Normalisation of PUA to < 6 mg/dL for 80% of the time during Months 3 and 6 combined (i.e., PUA responder).

Patients were treated every two weeks with either pegloticase or placebo for a treatment period of 6 months. Week 1 was defined as the first day of treatment, so patients were treated on weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 and 25.

Following randomisation patients had blood samples taken for measurement of plasma uric acid (PUA) on the day of first treatment (week 1) and at weeks 3, 5, 7, 9, 10, 11, 12, 13, 15, 17, 19, 21, 22, 23, 24 and 25. At weeks 1, 9, 11, 21 and 23 both pre and 2 hours post-dose samples were taken (otherwise only a pre-dose measurement was taken). On weeks 1, 9, and 21 samples were also taken 24 hours after treatment.

The primary analysis of this endpoint was based on a responder analysis. A patient was classified as a responder if he/she maintained PUA < 6mg/dL for at least 80% of the time during months 3 and 6 combined.

A PUA time curve was derived using the linear trapezoidal rule. The proportion of time that the PUA level was below 6 mg/dL was defined as the ratio of the time during months 3 and 6 which the PUA level remained below 6 mg/dL to the entire time interval during each of months 3 and 6.

Assessments used for evaluation of primary end-point

Month 3	Month 6
Week 9 (pre-dose, post-dose, + 24 hours), 10, 11 (pre-dose, post-dose), 12, 13	Week 21 (pre-dose, post-dose, + 24 hours), 22, 23 (pre-dose, post-dose), 24, 25

Subjects who withdrew from the study before Month 6 were considered non-responders. Any subject with missing data at week 9 (pre-dose), week 13, week 21 (pre-dose) or week 25 had the baseline value imputed for those measurements.

Secondary endpoints

- Other endpoints related to PUA: percentage of time that patients were measured with PUA < 6 mg/dL (non hyperuricaemic time) for months 3 and 6 separately, mean PUA (area under the PUA time curve divided by the corresponding time interval), reduction in mean PUA from baseline, and percent reduction in mean PUA from baseline
- Reduction of tophus burden

  Photographs of each subject's hands and feet and up to two other representative sites of tophaceous disease were obtained at baseline and at Weeks 13, 19, and 25 using a standardized digital photography method. A blinded central reader assessed the photographs for size of each target tophus using the MedStudio® image analysis software package. To be considered measurable, tophi were ≥ 5 mm in the longest dimension at baseline and had borders distinguishable. Up to two tophi representative of the subject's tophus burden but which could not be accurately measured (e.g., due to location, shape or other factors), could also be evaluated at the reader's discretion.

  The response of each individual tophus was categorized according to change from baseline using quantitative or semi-quantitative assessment as: complete response (CR), marked response, improved, partial response (PR), stable disease (SD), progressive disease PD), unable to evaluate. The overall categorical tophus response of CR, PR, SD, or PD was based on the best response reported among all tophi (measurable and unmeasured) for an individual subject. If any one tophus showed complete response (CR), the overall response was reported as CR if there was no evidence of progressive disease (PD). If, however, any single tophus showed progression, or if a new tophus

appeared during the study, the overall response for that subject was progressive disease (PD), regardless of the response of any other tophi.

Time to tophus resolution was defined as the earliest assessment time at which one of the target tophi showed complete resolution.

- Number of swollen or tender joints

  A standard examination of 54 joints was performed by the clinician at baseline, and Weeks 13, 19, and 25. The number of swollen and tender joints, tenosynovitis, and painful and swollen bursae were summarized descriptively. A Clinician's Global Assessment (CGA) of disease activity was also quantified using a 100-mm VAS from 0 (very good) to 100 (very bad).

- Incidence and severity of gout flares

  Gout flares were self-reported by patients and confirmed by the investigators.

- Patients Reported Outcomes

  - SF-36 quality of life [QoL]

    The SF-36 was completed at baseline and Weeks 13, 19, and 25. The 8 domains of the SF-36 (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) were used to calculate three summary scores, mental (MCS), physical (PCS), and Arthritis-Specific Health Index (ASHI) components; this score was weighted to measure bodily pain, other aspects of physical and role functioning, and well-being particular to arthritic conditions.

  - HAQ-DI (physical function)

    Health Assessment Questionnaire–Disability Index measures disability over the past week by grouping 20 questions into 8 domains of function: dressing, arising, eating, walking, hygiene, reach, grip, and activities. The highest score for each of the 8 domains is summed (range: 0 to 24) and divided by 8 to yield, on a continuous scale, a Functional Disability Index (range: 0 to 3), with higher score indicative of increased functional disability. The HAQ includes a patient's assessment of pain measured using a 100-mm VAS and a global assessment (PGA) of how well the subject is doing despite arthritis using a 100-mm VAS scale (where 0 = very well and 100 = very poor). The scale is not included in the validated version of the Spanish HAQ questionnaire and, therefore, subjects using the Spanish version of the questionnaire were not included in this analysis.

Sample size

Approximately 120 patients were to be screened in each trial in order to randomise 100 patients across the three treatment arms. With 40 patients in each pegloticase arm and 20 patients in the placebo arm, the study had 80% power to detect a difference of 35% vs. 5% in responder rate with a significance level of 5% for each comparison.

As pre-specified in the protocol, the evaluation of secondary endpoints was to be based on pooled analyses from the two replicate studies. If 70% of patients had tophi at study entry, the combined data from the two studies had 80% power to detect a difference of 31% vs. 5% in overall tophi CR rate with a significance level of 5% for each comparison.

Randomisation

The randomisation, which used a 2:2:1 (placebo) ratio, was balanced across study centres in the USA, Canada, Mexico, and was stratified by presence/absence of tophi. The randomisation was central using an interactive voice response (IVR) system.

Blinding (masking)

Pegloticase and placebo were supplied in identical single-use glass vials containing a sterile solution in phosphate buffered saline or phosphate buffered saline alone, respectively. To ensure blinding, all patients received an infusion every 2 weeks; for the 8mg/4 wks dosing regimen, half of the injections were of placebo.

Statistical methods

The primary analysis was a responder analysis, where responders were defined as subjects whose PUA concentrations remained < 6 mg/dL for at least 80% of the time during months 3 and 6 combined. Responder rates were compared between each of the pegloticase treatment groups and placebo using Fisher's exact test.

Analysis populations

- *Intent-To-Treat (ITT)*: all randomised subjects who had received at least one dose of study medication and had some follow-up data
- *Per-protocol (PP)*: all subjects of the ITT population who completed 6 months of the study without major protocol deviations
- *Tophus-evaluable (TE)*: all subjects with a tophus at baseline and any subjects who developed a tophus over the course of the study

Primary analysis

Responder rates were compared between each of the pegloticase treatment groups and placebo using Fisher's exact test. This was done separately for each trial with the ITT population as primary analysis. The same analysis was performed in the PP population as a supportive analysis.

Analyses of secondary endpoints

Pooled analyses of the two trials were performed for all secondary endpoints.

- The PUA endpoints were analysed using two-sample t-test or non-parametric test if needed.
- The CR rates for tophi were compared using Fisher's exact test and two sample Wilcoxon test for ordinal scores (1 to 4). Kaplan-Meier plots were used to describe time to tophus resolution.
- Number of swollen/tender joints, CGA, QoL and VAS scores were compared using two-sample t-test and changes from baseline were analysed using a linear model with covariate as the baseline value. Last observation was carried forward for the final visit information.
- The numbers of gout flares experienced during the first 3-month period and during the last 3-month period were compared using two sample t-tests. The incidence of gout flares was compared using the Fisher's exact test. Shift tables were used to display the change in incidence and severity of gout flares during the first 3 mo as compared to the last 3 mo of the study by treatment group. The weekly flare burden was determined by assigning a flare score for each day in the study (0 = no flares, 1 = mild flares, 2 = moderate flares, and 3 = severe flares) based on the most severe flare reported for each day; the weekly flare burden was calculated as the average score for the 7-day period, i.e., from 0 to 3 (with higher scores reflecting a more severe condition). Last observational was carried forward for the final visit information.

Results

Participant flow

Overall, 128 and 134 subjects were screened in study 405 and 406, respectively. Out of these, 109 and 116 subjects, respectively, were randomised; the most frequent screening failures were due to laboratory tests that did not meet selection criteria. Overall, **212 patients** (out of 225) were treated and they were all included in the ITT analysis.

The disposition of the study patients is shown in Table 8.

Table 8 Disposition of patients in studies 405 & 406 – adapted from CSRs

(including corrections after database lock in study 406 CSR p.45)

	Pegloticase 8mg/2 wks			Pegloticase 8mg/4 wks			Placebo			Total	
	405	406	*Total*	405	406	*Total*	405	406	*Total*	405	406
No Subjects Screened										128	134
Screening Failure										19	18
Exclusionary Lab Value										13	15
Subject Withdrew										3	2
Other										3	1
Randomized	**44**	**46**	***90***	**43**	**46**	***89***	**22**	**24**	***46***	**109**	**116**
Not Dosed	1	4	***5***	2	3	***5***	2	1	***3***	5	8
Analysis sets											
Intent-to-Treat	**43**	**42**	***85***	**41**	**43**	***84***	**20**	**23**	***43***	**104**	**108**
Per-Protocol	30	29	***59***	26	32	***58***	18	20	***38***	74	81
Tophus-Evaluable	29	33	***62***	31	33	***64***	14	15	***29***	74	81
Completed Study	30	29	***59***	27	32	***59***	19	20	***39***	**76**	**81**
	70%	69%	***69%***	66%	74%	***70%***	95%	87%	***91%***	**73%**	**75%**
Continued on OLE	29	28	***57***	26	30	***56***	18	20	***38***	73	78
Withdrew from Study	13	13	***26***	14	11	***25***	1	3	***4***	28	27
	30%	31%	***31%***	34%	26%	***30%***	5%	13%	***9%***	27%	25%
Non-compliance	0	0	***0***	1	0	***1***	0	0	***0***	1	0
Adverse Event	8	8	***16***	9	8	***17***	0	1	***1***	17	17
Withdrew Consent	3	4	***7***	3	3	***6***	0	1	***1***	6	8
Lost to Follow-up	0	0	***0***	0	0	***0***	1	1	***2***	1	1
Protocol Violation	1	0	***1***	0	0	***0***	0	0	***0***	1	0
Death	1	1	***2***	1	0	***1***	0	0	***0***	2	1

Recruitment

Study 405 was conducted in 29 centres in US and Canada from June 2006 to October 2007.

Study 406 was conducted in 27 centres in US and Mexico from June 2006 to October 2007.

Subject were randomised from June 2006 to March 2007 and followed for 6 months.

Conduct of the study

Administrative structure

The studies were monitored by a CRO (Kendle International), which also conducted the statistical analysis and prepared the CSR.

Several central laboratories were used:

- Princeton Radiology Pharmaceutical Research for the reading of the target tophus photographs
- ICON Clinical Laboratories for the routine laboratory tests, including G6PD, tryptase and CH50 determinations

- Charles River Laboratories Preclinical Services Montreal for the assays of uric acid, PEG-uricase activity and PEG-uricase antibodies

Study audits

The Sponsor audited the CRO and laboratories as well as a number of investigator sites: 5 sites in study 405 and 6 sites in study 406.

The FDA inspected the Sponsor, Charles River Laboratories and 3 investigator sites.

Protocol amendments

Three protocol amendments were made, which introduced minor changes to the statistical plan, inclusion criteria, and study procedures.

Baseline data

Baseline characteristics are presented for the pooled data in the ITT population, i.e. 212 patients.

The patients enrolled in the pivotal studies were aged between 23 and 89 years, 55 years on average, with a sex ratio of 4:1. There were a majority of White patients (67%) but Hispanic and Black patients were also represented. Of note, African Americans are known to develop hyperuricaemia more commonly than White persons. The patients were clearly overweight as evidenced by a mean BMI of 33 kg/m^2 and weight of 100 kg; obesity is a well-known factor associated with gout, as are the metabolic syndrome, hypertension, congestive heart failure, and renal insufficiency. Indeed, co-morbidities in the study population included hypertension (> 70%), metabolic disorders (> 60%), renal failure and nephrolithisasis (> 40%), and cardiac disorders (> 30%) (data not shown). The majority of patients did not drink alcohol, a trigger for recurrent flares (data not shown).

The overall mean duration since first gout attack was 17 years and the number of gout flares reported over the last 18 months was about 10 (i.e. > 6 per year), the majority of which were crippling (63%). Overall, 73% exhibited tophi. More than half the patients (58%) had a chronic arthropathy and 22% had undergone surgery for gout; as many as 16% had renal complications of gout.

As required by protocol, all patients had a history of hypersensitivity or failure to normalise SUA with allopurinol. The most frequent reason was related to hypersensitivity (40% of the cases) followed by lack of efficacy, and dosing limited by GI intolerance or renal impairment.

In the pooled analysis, the treatment arms appeared reasonably well-balanced with respect to demographics and disease characteristics. Of note, there were some differences between the two studies; patients were slightly older, more overweight, with more co-morbidities and more severe gout in study 405 than in study 406.

Numbers analysed

The number of infusions administered to each patient (out of a total of 12) is summarised in Table 9.

Table 9 Number of infusions (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo	Total
	Every 2 Weeks (N = 85)	Every 4 Weeks[1] (N = 84)	(N = 43)	(N = 212)
Number of Infusions per Subject				
N	85	84	43	212
Mean (SD)	10.0 (3.46)	10.1 (3.41)	11.7 (1.21)	10.4 (3.17)
Median	12.0	12.0	12.0	12.0
Min, Max	1, 12	1, 12	6, 12	1, 12
Number of Infusions, n (%):				
1-2	5 (5.9)	5 (6.0)	0 (0.0)	10 (4.7)
3-4	6 (7.1)	5 (6.0)	0 (0.0)	11 (5.2)
5-6	6 (7.1)	5 (6.0)	1 (2.3)	12 (5.7)
7-8	2 (2.4)	5 (6.0)	1 (2.3)	8 (3.8)
9-10	5 (5.9)	4 (4.8)	1 (2.3)	10 (4.7)
11-12	61 (71.8)	60 (71.4)	40 (93.0)	161 (75.9)
≥ 13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1 Infusions in the pegloticase 8 mg/4 weeks dose group include pegloticase alternating with placebo every other dose.

While the vast majority of patients received their full treatment in the placebo arm, these data reflect a high discontinuation rate (about 30%) in the pegloticase arms, with no difference between the two regimens (consistent with Table 12). Treatment withdrawal occurred as early as after the first infusion and no pattern was evident.

Outcomes and estimation

A. Primary endpoint

With regard to the primary endpoint, normalisation of PUA to below 6 mg/dL at both Month 3 and Month 6, pegloticase was shown effective in both pivotal Phase III trials and in the pooled analysis. Significantly more subjects in both 8 mg pegloticase every 2 wks (E2W) and every 4 wks (E4W) treatment arms were responders compared to subjects receiving placebo (Table 10).

Table 10 Treatment response (ITT population) - from individual CSRs

Study 405

	ITT Population			PP Population		
	8 mg Pegloticase		Placebo	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 43)	Every 4 Weeks (N = 41)	(N = 20)	Every 2 Weeks (N = 30)	Every 4 Weeks (N = 26)	(N = 18)
PUA less than 6 mg/dL for at least 80% of the time in Month 3						
n (%)	25 (58.1)	13 (31.7)	1 (5.0)	23 (76.7)	9 (34.6)	1 (5.6)
95% CI[1]	35.6, 70.7	9.6, 43.9		52.6, 89.6	7.9, 50.2	
P-value[2]	<0.001	0.024		<0.001	0.031	
PUA less than 6 mg/dL for at least 80% of the time in Month 6						
n (%)	20 (46.5)	11 (26.8)	0 (0.0)	20 (66.7)	11 (42.3)	0 (0.0)
95% CI[1]	31.6, 61.4	13.3, 40.4		49.8, 83.5	23.3, 61.3	
P-value[2]	<0.001	0.011		<0.001	<0.001	
Responders: PUA less than 6 mg/dL for at least 80% of the time in Months 3 and 6 combined						
n (%)	20 (46.5)	8 (19.5)	0 (0.0)	20 (66.7)	8 (30.8)	0 (0.0)
95% CI[1]	31.6, 61.4	7.4, 31.6		49.8, 83.5	13.0, 48.5	
P-value[2]	<0.001	0.044		<0.001	0.014	

Study 406

	ITT Population			PP Population		
	8 mg Pegloticase		Placebo	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 42)	Every 4 Weeks (N = 43)	(N = 23)	Every 2 Weeks (N = 29)	Every 4 Weeks (N = 32)	(N = 20)
PUA less than 6 mg/dL for at least 80% of the time in Month 3						
n (%)	19 (45.2)	21 (48.8)	1 (4.3)	17 (58.6)	21 (65.6)	1 (5.0)
95% CI[1]	23.7, 58.1	27.4, 61.6		33.3, 73.9	41.6, 79.7	
P-value[2]	<0.001	<0.001		<0.001	<0.001	
PUA less than 6 mg/dL for at least 80% of the time in Month 6						
n (%)	17 (40.5)	18 (41.9)	0 (0.0)	17 (58.6)	18 (56.3)	0 (0.0)
95% CI[1]	25.6, 55.3	27.1, 56.6		40.7, 76.5	39.1, 73.4	
P-value[2]	<0.001	<0.001		<0.001	<0.001	
Responders: PUA less than 6 mg/dL for at least 80% of the time in Months 3 and 6 combined						
n (%)	16 (38.1)	21 (48.8)	0 (0.0)	16 (55.2)	21 (65.6)	0 (0.0)
95% CI[1]	23.4, 52.8	33.9, 63.8		37.1, 73.3	49.2, 82.1	
P-value[2]	<0.001	<0.001		<0.001	<0.001	

B. Secondary endpoints

Mean PUA

Mean PUA values were significantly lower for both pegloticase groups than for placebo at Month 3, Month 6, and Month 3 and 6 combined ($p < 0.001$) (Tables 11 and 12).

Table 11 Mean PUA (ITT population) - study 405

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 43)	Every 4 Weeks (N = 41)	(N = 20)
Month 3:			
n	39	36	20
Mean (mg/dL) (SD)	3.00 (3.481)	6.03 (3.779)	8.36 (2.199)
P-value[1]	<0.001	0.014	
Month 6:			
n	31	28	19
Mean (mg/dL) (SD)	2.89 (4.126)	5.80 (3.535)	8.29 (1.605)
P-value[1]	<0.001	0.006	
Months 3 and 6:			
n	31	28	19
Mean (mg/dL) (SD)	2.63 (3.632)	5.88 (3.426)	8.28 (1.668)
P-value[1]	<0.001	0.007	

[1] P-value based on two sample t-test to compare corresponding pegloticase group vs. placebo.

Table 12 Mean PUA (ITT population) - study 406

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 42)	Every 4 Weeks (N = 43)	(N = 23)
Month 3:			
n	34	38	23
Mean (mg/dL) (SD)	2.95 (3.076)	4.25 (4.074)	8.69 (2.342)
P-value[1]	<0.001	<0.001	
Month 6:			
n	30	32	21
Mean (mg/dL) (SD)	3.54 (4.176)	4.06 (3.946)	9.24 (2.755)
P-value[1]	<0.001	<0.001	
Months 3 and 6:			
n	30	32	21
Mean (mg/dL) (SD)	3.23 (3.567)	3.88 (3.770)	8.88 (2.218)
P-value[1]	<0.001	<0.001	

[1] P-value based on two sample t-test to compare corresponding pegloticase group vs. placebo.

Tophus resolution

Overall, 155 patients were evaluable for this endpoint. Differences in Overall tophus response, analyzed by categories of response, were significantly greater for pegloticase 8 mg E2W compared to placebo at every post-baseline tophus measurement including Final Visit. For the pegloticase 8 mg E4W arm, the difference was only significant at Week 19 (Table 13). This analysis was consistent between the two studies and the pooled analysis.

Table 13 Overall tophus response (ITT population) – from pooled analysis

Overall Response of Tophus Assessment	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 62) n (%)	Every 4 Weeks (N = 64) n (%)	(N = 29) n (%)
Week 13 (Visit 11, Dose 7)			
Complete Response (CR)	10 (21.7%)	4 (8.3%)	0 (0.0%)
Partial Response (PR)	11 (23.9%)	9 (18.8%)	4 (16.0%)
Stable Disease (SD)	20 (43.5%)	28 (58.3%)	13 (52.0%)
Progressive Disease (PD)	5 (10.9%)	7 (14.6%)	8 (32.0%)
Number of subjects with evaluable tophi	46	48	25
P-value[1]	0.002	0.068	—
P-value[2]	0.011	0.292	—
Week 19 (Visit 14, Dose 10)			
Complete Response (CR)	16 (36.4 %)	12 (27.9%)	2 (7.7%)
Partial Response (PR)	11 (25.0%)	9 (20.9%)	3 (11.5%)
Stable Disease (SD)	12 (27.3%)	19 (44.2%)	14 (53.8%)
Progressive Disease (PD)	5 (11.4%)	3 (7.0%)	7 (26.9%)
Number of subjects with evaluable tophi	44	43	26
P-value[1]	0.001	0.004	—
P-value[2]	0.010	0.063	—
Week 25 (Visit 20, 14 Days After Dose 12)			
Complete Response (CR)	18 (45.0%)	11 (26.2%)	2 (8.0%)
Partial Response (PR)	8 (20.0%)	10 (23.8%)	6 (24.0%)
Stable Disease (SD)	10 (25.0%)	16 (38.1%)	11 (44.0%)
Progressive Disease (PD)	4 (10.0%)	5 (11.9)	6 (24.0%)
Number of subjects with evaluable tophi	40	42	25
P-value[1]	0.002	0.061	—
P-value[2]	0.002	0.109	—
Final Visit			
Complete Response (CR)	21 (40.4%)	11 (21.2%)	2 (7.4%)
Partial Response (PR)	12 (23.1%)	12 (23.1%)	6 (22.2%)
Stable Disease (SD)	14 (26.9%)	21 (40.4%)	13 (48.1%)
Progressive Disease (PD)	5 (9.6%)	8 (15.4%)	6 (22.2%)
Number of subjects with evaluable tophi	52	52	27
P-value[1]	0.001	0.142	—
P-value[2]	0.002	0.200	—

1 An ordinal score (for categorical analysis) was assigned for each response and used to compute the P-value, which was based on two sample Wilcoxon test to compare corresponding pegloticase groups vs. placebo.
2 P-value based on Fisher's exact test to compare percent of CR between corresponding pegloticase groups vs. placebo.

The Overall tophus response was assessed in relation to the PUA responder status. Within each pegloticase arm, a greater number of subjects who were PUA responders demonstrated complete resolution of tophi (41-62%) than subjects who were non-responders, although a certain proportion of non-responder patients had a complete response (11-26%) at Final Visit.

Resolution of tophi has been shown with urate-lowering therapy and some experts contend that SUA should be lowered to < 5 mg/dL in patients with tophaceous gout. The velocity of tophi reduction has been shown to be linearly related to the mean SUA during therapy. With conventional therapy, resolution of tophi takes an average of 20 months (Perez-Ruiz et al, 2002).

Number of swollen or tender joints

The mean baseline number of swollen and tender joints was higher in the placebo arm as compared with the pegloticase arms. For both endpoints, statistically significant changes from baseline were seen in both pegloticase arms but not in the placebo arm. The differences from placebo were not statistically significant for swollen joints for either pegloticase regimen; however, for tender joints both groups did achieve superiority to placebo (Tables 14 and 15). PUA responders had a greater decrease in the number of swollen and tender joints than PUA non-responders.

Table 14 Number of swollen joints (ITT population) – from pooled analysis

	8 mg Pegloticase						Placebo
	Every 2 Weeks			Every 4 Weeks			
	Responders (N = 36)	Non-Responders (N = 49)	Total (N = 85)	Responders (N = 29)	Non-Responders (N = 55)	Total (N = 84)	(N = 43)
Baseline Visit							
n	35	49	84	29	54	83	43
Mean (SD)	10.5 (11.71)	7.7 (10.60)	8.9 (11.09)	10.3 (11.47)	9.9 (9.21)	10.1 (9.99)	13.2 (13.70)
P-value[1]	—	—	0.059	—	—	0.149	—
Week 25 (Visit 20, 14 Days After Dose 12)							
n	36	25	61	29	34	63	38
Mean (SD)	2.1 (3.76)	3.8 (6.03)	2.8 (4.85)	2.3 (3.43)	4.8 (6.29)	3.6 (5.28)	10.2 (12.79)
P-value[1]	—	—	<0.001	—	—	<0.001	—
Change From Baseline To Week 25							
n	35	25	60	29	33	62	38
Mean (SD)	-8.6 (10.34)	-3.4 (9.40)	-6.4 (10.21)	-8.0 (9.34)	-3.4 (5.25)	-5.6 (7.75)	-2.1 (12.18)
P-value[1]	—	—	0.059	—	—	0.081	—
P-value[2]	—	—	<0.001	—	—	<0.001	0.306
Final Visit							
n	36	43	79	29	49	78	43
Mean (SD)	2.1 (3.76)	5.6 (8.44)	4.0 (6.91)	2.3 (3.43)	5.7 (8.24)	4.4 (7.02)	10.5 (13.40)
P-value[1]	—	—	<0.001	—	—	0.001	—
Change From Baseline To Final Visit							
n	35	43	78	29	48	77	43
Mean (SD)	-8.6 (10.34)	-3.0 (10.00)	-5.5 (10.47)	-8.0 (9.34)	-3.3 (6.20)	-5.1 (7.83)	-2.6 (11.64)
P-value[1]	—	—	0.166	—	—	0.170	—
P-value[2]	—	—	<0.001	—	—	<0.001	0.146

Table 15 Number of tender joints (ITT population) – from pooled analysis

	8 mg Pegloticase						Placebo
	Every 2 Weeks			Every 4 Weeks			
	Responders (N = 36)	Non-Responders (N = 49)	Total (N = 85)	Responders (N = 29)	Non-Responders (N = 55)	Total (N = 84)	(N = 43)
Baseline Visit							
n	35	49	84	29	54	83	43
Mean (SD)	11.7 (13.30)	11.6 (12.84)	11.7 (12.95)	12.3 (15.26)	10.4 (12.56)	11.1 (13.51)	14.1 (14.75)
P-value[1]	—	—	0.336	—	—	0.244	—
Week 25 (Visit 20, 14 Days After Dose 12)							
n	36	25	61	29	34	63	38
Mean (SD)	2.7 (6.42)	6.4 (10.25)	4.2 (8.33)	2.4 (4.56)	5.7 (8.28)	4.2 (6.97)	13.1 (15.93)
P-value[1]	—	—	<0.001	—	—	<0.001	—
Change From Baseline To Week 25							
n	35	25	60	29	33	62	38
Mean (SD)	-8.9 (11.96)	-7.7 (12.11)	-8.4 (11.93)	-9.9 (12.78)	-3.9 (8.85)	-6.7 (11.18)	-0.9 (12.77)
P-value[1]	—	—	0.004	—	—	0.018	—
P-value[2]	—	—	<0.001	—	—	<0.001	0.678
Final Visit							
n	36	43	79	29	49	78	43
Mean (SD)	2.7 (6.42)	6.5 (9.71)	4.8 (8.54)	2.4 (4.56)	5.5 (7.72)	4.3 (6.85)	12.9 (16.14)
P-value[1]	—	—	<0.001	—	—	<0.001	—
Change From Baseline To Final Visit							
n	35	43	78	29	48	77	43
Mean (SD)	-8.9 (11.96)	-6.1 (11.93)	-7.4 (11.95)	-9.9 (12.78)	-3.9 (8.47)	-6.1 (10.64)	-1.2 (12.30)
P-value[1]	—	—	0.008	—	—	0.024	—
P-value[2]	—	—	<0.001	—	—	<0.001	0.515

1 P-value based on two sample t-test to compare corresponding pegloticase groups vs. placebo.
2 P-value based on paired t-test within treatment.

The clinician's global assessment of disease activity (CGA) reflected a greater improvement from baseline to Week 25 for both pegloticase regimens as compared with placebo (p <0.001 and p = 0.003, respectively) (data not shown).

When combined (i.e. number of swollen or tender joints), the change from baseline to week 25 was significant in both treatment arms (data not shown). Overall, these results provide evidence of significant clinical benefit for patients with gout arthropathy.

Gout flares

Following the initiation of pegloticase treatment, the incidence of gout flares increased during Months 1-3 as expected, as this also occurs with other urate-lowering treatments. In contrast, during Months 4-6, patients who received pegloticase 8 mg E2W had a statistically significant reduction in the incidence of gout flares compared with placebo (p = 0.007) (Table 16 and Figure 2).

During Months 1-3, the severity of gout flares was typically moderate in both pegloticase arms. The frequency of severe flares was 22-23% in the pegloticase arms vs. 5% in the placebo arm. During Months 4-6, there was a reduction in the number of subjects experiencing severe flares in the pegloticase arms (7-9%) vs. 14% in the placebo arm (Table 17).

Table 16 Incidence of flares (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Months 1-3			
n/N (%)	64/85 (75.3%)	68/84 (81.0%)	23/43 (53.5%)
P-value[1]	0.016	0.002	
Months 4-6			
n/N (%)	28/69 (40.6%)	39/69 (56.5%)	29/43 (67.4%)
P-value[1]	0.007	0.321	

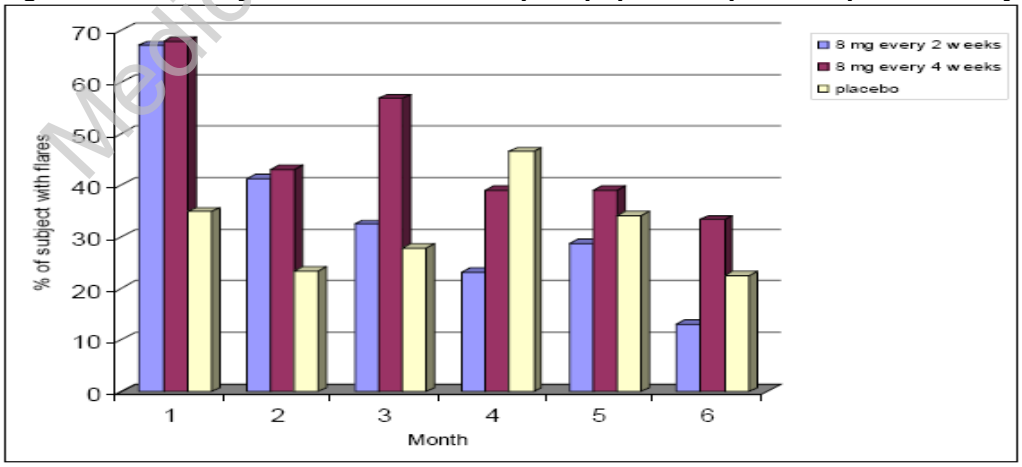
Note: "n" represents number of subjects who experienced flares during the period. "N" within the cells represents number of subjects with office visits during the period.
1 P-value from Fisher's exact test to compare number of subjects reporting flares vs. placebo.

Table 17 Severity of flares (ITT population) – from pooled analysis

Severity	8 mg Pegloticase		Placebo
	Every 2 weeks (N = 85) n (%)	Every 4 weeks (N = 84) n (%)	(N = 43) n (%)
During Study Period[1]			
N[2]	85	84	43
None	20 (23.5)	14 (16.7)	8 (18.6)
Mild	7 (8.2)	11 (13.1)	9 (20.9)
Moderate	37 (43.5)	38 (45.2)	20 (46.5)
Severe	21 (24.7)	21 (25.0)	6 (14.0)
Months 1-3			
N[2]	85	84	43
None	22 (25.9)	16 (19.0)	21 (48.8)
Mild	7 (8.2)	14 (16.7)	9 (20.9)
Moderate	37 (43.5)	35 (41.7)	11 (25.6)
Severe	19 (22.4)	19 (22.6)	2 (4.7)
Months 4-6			
N[2]	69	69	43
None	41 (59.4)	30 (43.5)	14 (32.6)
Mild	11 (15.9)	12 (17.4)	8 (18.6)
Moderate	12 (17.4)	21 (30.4)	15 (34.9)
Severe	5 (7.2)	6 (8.7)	6 (14.0)

Note: Missing severity response for gout flare was imputed as severe unless the subject experienced another occurrence within the same period for which severity was recorded.
Note: If the same subject in a given treatment had more than one occurrence, only the most severe occurrence was taken.
1 During the study period = first dose to 4 weeks after last dose.
2 N represents the number of subjects who had a visit within each time period.

Figure 2 Monthly incidence of flares (ITT population) – from pooled analysis



As expected and in spite of prophylactic treatment, gout flares occurred more frequently at the initiation of therapy with pegloticase as compared with placebo, especially in the first month, and they were also more severe. However, after the first 3 months of treatment, the effect of the E2W regimen was manifest as patients experienced significantly less flares in comparison with placebo. In contrast, with the E4W regimen, the percentage of patients experiencing flares was still numerically higher during Months 5 & 6 than with placebo. Therefore, only the E2W regimen has shown a favourable effect on gout flares.

Patient Reported Outcomes

SF-36

As a reference for comparison purposes, in a healthy normal population (age 55-64 for males and females combined) the average scores are approximately 47 for Physical Component Summary (PCS) scores and 52 for Mental Component Summary (MCS) scores. In the study population, these scores were lower at baseline, especially the physical component. Both pegloticase regimens produced significantly greater changes from baseline than placebo for the physical component but not for the mental component (Tables 18 and 19). The changes were much greater in PUA responders than PUA non-responders (data not shown).

Table 18 SF-36 PCS score (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Baseline Visit			
N	83	84	43
Mean (SD)	35.16 (10.901)	33.26 (9.842)	31.01 (11.098)
P-value[1]	0.046	0.244	—
Final Visit			
N	79	77	43
Mean (SD)	39.31 (11.128)	38.36 (10.303)	30.71 (11.750)
P-value[1]	<0.001	<0.001	—
Change From Baseline To Final Visit			
N	77	77	43
Mean (SD)	4.38 (9.364)	4.94 (8.487)	-0.30 (8.966)
P-value[1]	0.009	0.002	—

1 P-value from two sample t-test used to compare means of the corresponding treatment group vs. placebo.

Table 19 SF-36 MCS score (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Baseline Visit			
n	83	84	43
Mean (SD)	49.42 (12.739)	45.40 (11.752)	47.91 (11.981)
P-value[1]	0.523	0.259	—
Final Visit			
n	79	77	43
Mean (SD)	51.94 (10.318)	45.54 (12.224)	50.27 (10.295)
P-value[1]	0.394	0.034	—
Change From Baseline To Final Visit			
n	77	77	43
Mean (SD)	2.13 (10.807)	0.08 (10.229)	2.36 (9.643)
P-value[1]	0.907	0.235	—

The mean ASHI scores at baseline were similar across treatment arms. At the final visit, both pegloticase arms had statistically significantly higher mean ASHI scores than placebo, indicating improvement in bodily pain and functional impairment after receiving treatment with pegloticase ($p \leq 0.003$). For the between treatment comparisons, the changes from baseline were statistically significantly different for both pegloticase regimens ($p = 0.003$) (Table 20). The changes were much greater in PUA responders than PUA non-responders (data not shown).

Table 20 SF-36 ASHI score (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Baseline Visit			
n	83	84	43
Mean (SD)	54.38 (28.467)	47.81 (24.279)	45.81 (27.288)
P-value[1]	0.107	0.675	—
Final Visit			
n	79	77	43
Mean (SD)	70.77 (29.726)	63.43 (29.124)	46.74 (28.097)
P-value[1]	<0.001	0.003	—
Change From Baseline To Final Visit			
n	77	77	43
Mean (SD)	16.50 (28.769)	15.03 (25.114)	0.93 (22.826)
P-value[1]	0.003	0.003	—

HAQ-DI

Mean HAQ-DI scores decreased (i.e., reflected improvement in physical functioning) from baseline to Final Visit in both pegloticase arms, whereas they showed little change in the placebo arm. The mean changes from baseline in each pegloticase arm were statistically significantly greater than for placebo ($p \leq 0.026$) (Table 21).

Table 21 HAQ-DI (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Baseline Visit			
n	83	84	43
Mean (SD)	1.10 (0.855)	1.21 (0.858)	1.24 (0.954)
P-value[1]	0.418	0.858	—
Final Visit			
n	79	78	43
Mean (SD)	0.91 (0.834)	0.98 (0.904)	1.26 (0.904)
P-value[1]	0.033	0.102	—
Change From Baseline To Final Visit			
n	77	78	43
Mean (SD)	-0.22 (0.637)	-0.20 (0.554)	0.02 (0.408)
P-value[1]	0.026	0.025	—

Mean HAQ pain scores decreased from baseline to Final Visit in both pegloticase arms but increased in the placebo arm. The improvement was statistically significant for the pegloticase 8 mg every 2 weeks regimen only ($p = 0.04$) (Table 22). The changes were much greater in PUA responders than PUA non-responders (data not shown).

Table 22 HAQ assessment of arthritic pain (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Baseline Visit			
n	84	84	43
Mean (SD)	44.21 (27.698)	45.06 (26.994)	53.91 (28.063)
P-value[1]	0.066	0.087	—
Final Visit			
n	79	78	43
Mean (SD)	31.97 (28.241)	37.10 (28.195)	55.28 (28.149)
P-value[1]	<0.001	0.001	—
Change From Baseline To Final Visit			
n	78	78	43
Mean (SD)	-11.45 (33.795)	-6.91 (27.003)	1.37 (30.044)
P-value[1]	0.040	0.124	—

The baseline mean HAQ Patient Global Assessment (PGA) score was lower in the pegloticase 8 mg E2W arm in comparison to the other arms but the differences were not statistically significant. Mean HAQ PGA scores decreased (improved) from baseline to Final Visit in both pegloticase arms whereas it increased slightly in the placebo arm. The improvement was statistically significant for both pegloticase regimens ($p \leq 0.02$) (Table 23). The changes were much greater in PUA responders than PUA non-responders (data not shown).

Table 23 HAQ PGA (ITT population) – from pooled analysis

	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85)	Every 4 Weeks (N = 84)	(N = 43)
Baseline Visit			
n	73	78	40
Mean (SD)	42.44 (24.811)	49.79 (24.882)	51.58 (24.933)
P-value[1]	0.064	0.714	—
Final Visit			
n	69	72	40
Mean (SD)	30.43 (25.225)	37.13 (24.691)	52.40 (26.249)
P-value[1]	<0.001	0.003	—
Change From Baseline To Final Visit			
n	68	72	40
Mean (SD)	-11.85 (28.036)	-12.64 (26.997)	0.83 (24.988)
P-value[1]	0.020	0.011	—

1 P-value from two sample t-test used to compare means of the corresponding treatment group vs. placebo.

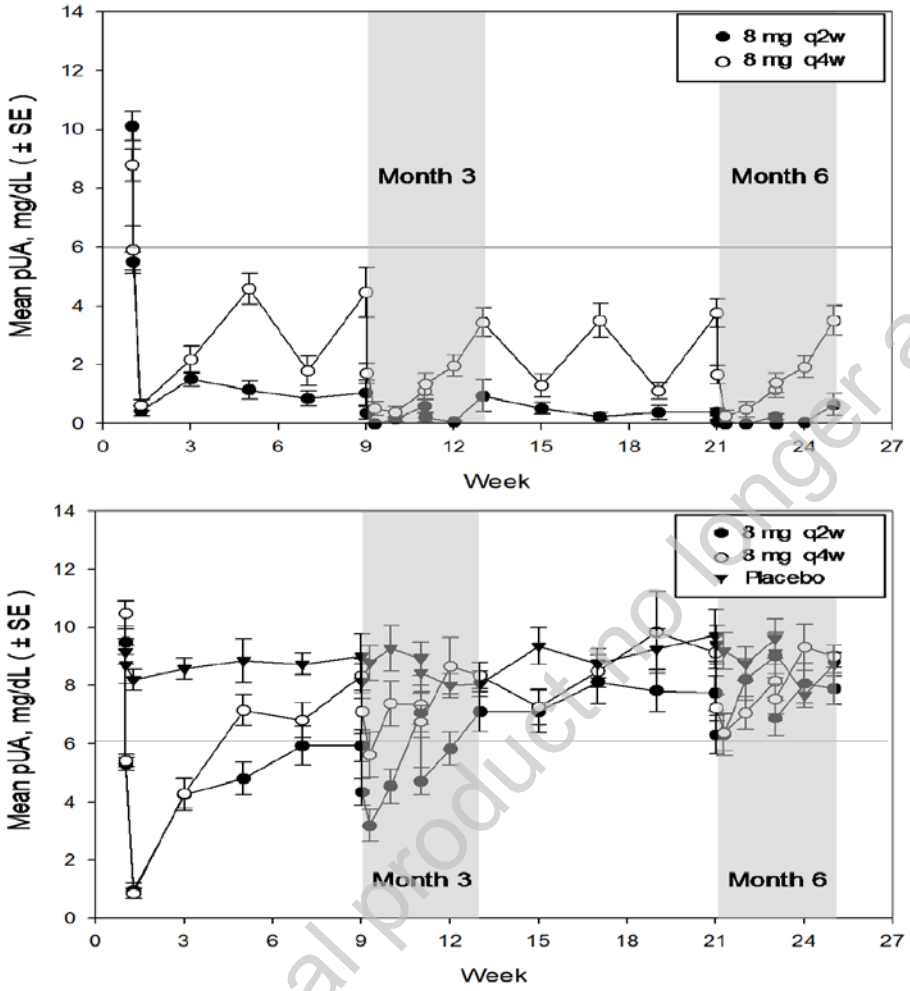
At baseline, the various scores reflected the impact of the disease on the patients' physical functioning and bodily pain. In particular, the baseline HAQ-disability index (mean 1.1 - 1.2) suggested a moderate level of physical impairment and the baseline VAS score (around 50) a moderate level of pain. In general, a significant improvement was reported for the various scores (except for the mental SF-36 component, which was not very affected at baseline) in both pegloticase arms; these results provide supportive evidence of patient benefit.

Ancillary analyses

The terms responder and non-responder are defined by the primary endpoint but the PUA data clearly show that all subjects who received pegloticase responded with a rapid normalisation of PUA within the

first day. Some of these subjects had a persistent normalisation for the entire 6-month study period (including over months 3 and 6) and can be referred to as “persistent responders” while those subjects that did not maintain PUA below 6 mg/dL for the entire 6-month study period (including months 3 and 6) can be referred to as “transient responders” (Figure 3). Loss of PUA response may be attributable to more rapid clearance of drug due to the presence of anti-pegloticase antibodies. In contrast to subjects receiving pegloticase, mean PUA levels in placebo subjects never normalised.

Figure 3 Mean (±SEM) PUA in responders and non responders



While there were no placebo responders (no decrease in PUA below 6 mg/dL), a statistical difference was observed in both studies between each of the active treatment arms and the placebo arm, although it was borderline in study 405 for the every 4 weeks (E4W) regimen. This regimen produced less consistent response estimates than the every 2 weeks (E2W) regimen with proportions as different as 20% and 49% in studies 405 and 406, respectively. Nevertheless, it can be accepted that efficacy has been shown for both regimens.

Summary of main efficacy results

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

Table 24 Summary of Efficacy for trial 405

Title: Randomized, Multicenter, Double-blind, Placebo-controlled Efficacy and Safety Study of 8 mg PEG-uricase in Two Dose Regimens in Hyperuricemic Subjects with Symptomatic Gout			
Study identifier	C0405		
Design	Randomized, multicenter, double-blind, 3-arm parallel treatment groups, placebo-controlled, randomization in a 2:2:1 ratio to 8 mg pegloticase every 2 weeks; 8 mg pegloticase every 4 weeks; or placebo		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months 1 week not applicable
Hypothesis	Superiority of pegloticase vs. placebo in maintaining PUA < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined		
Treatments groups	Arm 1		8 mg pegloticase i.v. every 2 weeks for 24 weeks; 44 randomized, 43 in ITT (received at least one dose of study drug)
	Arm 2		8 mg pegloticase i.v. every 4 weeks, alternating with placebo, for 24 weeks; 43 randomized, 41 in ITT
	Arm 3		Placebo every 2 weeks for 24 weeks, 22 randomized, 20 in ITT
Endpoints and definitions	Primary endpoint	PUA Response	Endpoint was the proportion of subjects in whom PUA was normalized to less than 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. Subjects who withdrew before Month 6 were considered non-responders.
	Secondary: Reduction in Tophus burden	Overall Tophus Response	Overall tophus response was based on the best response among all tophi (measurable and unmeasured) at each visit. Complete response was defined as 100% decrease in the area of the tophus for measured tophi or disappearance of the tophus for unmeasured tophi. However, if any single tophus showed progression, or if a new tophus appeared during the study, the overall response for that subject was Progressive Disease, regardless of the response of any other tophi.
	Secondary: Patient Reported Outcomes (PRO)	SF-36 Physical Component Score (PCS)	The SF-36 is a PRO instrument comprised of a 36-item self-reported inventory which serves to assess health-related limitations in 8 dimensions. The summary analysis of physical component score was calculated. For the purpose of comparison, in a healthy normal population (age 55-64 for males and females combined) the average PCS score is 47.

	Secondary: Patient Reported Outcomes	SF-36 Mental Component Score (MCS)	The summary analysis of mental component score was calculated. For the purpose of comparison, in a healthy normal population (age 55-64 for males and females combined) the average MCS score is 52.
	Secondary: Patient Reported Outcomes	SF-36 Arthritis-Specific Health Index (ASHI)	The ASHI is calculated from dimensions of the SF-36 and is weighted to measure bodily pain, other aspects of physical and role functioning, and well-being particular to arthritic conditions.
	Secondary: Patient Reported Outcomes	Health Assessment Questionnaire Disability Index (HAQ-DI)	The HAQ-DI is a self-reported functional status instrument that was completed by the subject. The index serves to measure disability over a 1-week period using 20 questions covering 8 domains of function.
	Secondary: Patient Reported Outcomes	Health Assessment Questionnaire Pain Scale	Pain Severity was also recorded on the HAQ Questionnaire using a 100-mm horizontal Visual Analog Scale (VAS), in response to the statement: (1) "How much pain have you had because of your illness IN THE PAST WEEK?" (where 0 = no pain and 100 = severe pain).
	Secondary: Patient Reported Outcomes	Health Assessment Questionnaire Global Assessment	Patient's Global Assessment was recorded on the HAQ Questionnaire using a 100-mm horizontal VAS , in response to the statement "Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line" (where 0 = very well and 100 = very poor).
	Secondary: Gout Flares	Incidence of Gout Flares	Gout flares were recorded throughout the study and reported in 3-month periods. There is no validated instrument to assess gout flares. For this study, self-reported gout flares were confirmed by the Investigator through questioning, if not through direct observation. The occurrence, severity, and duration of each flare (confirmed by the Investigator) were recorded.
Database lock	15-FEB-2008		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to Treat (had at least one dose of study drug) At Months 3 and 6 combined			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	43	41	20
	PUA Responder rate (% of subjects with PUA<6 mg/dl)	46.5%	19.5%	0
	95% CI	31.6, 61.4	13.3, 40.4	
Effect estimate per comparison	PUA Response	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Fisher's exact test		
		P-value	0.001	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Fisher's exact test		
		P-value	0.044	
Notes	PUA responder analysis reports the proportion of subjects whose PUA was normalized for 80% of the time during Months 3 and 6 combined.			
Analysis description	Secondary Endpoint-Overall Tophus Response			
Analysis population and time point description	Tophus-evaluable Population (TEP): all subjects with a tophus at baseline (as identified by the Investigator) and any subjects who developed new tophi during the study, as identified by either the Investigator or the Central Reader (RadPharm). Assessed at subject's Final Visit (Last observation carried forward-LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	26	23	13
	Final Visit: %CR	30.8	21.7	0
Effect estimate per comparison	Overall Tophus Response	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Fisher's Exact Test		
		P-value: Final Visit	0.035	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Fisher's Exact test		
		P-value: Final Visit	0.136	

Notes	Overall Tophus Response reports the proportion of subjects who had an overall tophus response of Complete Response at the time of their last study visit (i.e., at least one of the subject's target tophi disappeared, while no new tophus appeared or no other target tophus got worse)			
Analysis description	SF-36 Physical Component Score			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	39	38	20
	Change from Baseline (Mean)	4.94	4.06	-0.13
	SD	9.122	8.305	11.777
Effect estimate per comparison	Change in PCS	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.072	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.120	
Notes	Change from Baseline in PCS reports the mean change from baseline to Final visit (LOCF).			
Analysis description	SF-36 Mental Component Score			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	39	38	20
	Change from Baseline (Mean)	1.89	-0.60	4.34
	SD	11.561	8.555	10.552
Effect estimate per comparison	Change in MCS	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.429	
		Comparison groups	Pegloticase every 4 wks vs. placebo	

		Two-sample t-test		
		P-value		0.059
Notes	Change from Baseline in MCS reports the mean change from baseline to Final visit (LOCF).			
Analysis description	SF-36 ASHI Score			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	39	38	20
	Change from Baseline (Mean)	19.08	13.04	6.81
	SD	29.838	23.147	25.956
Effect estimate per comparison	Change in ASHI	Comparison groups		Pegloticase every 2 wks vs. placebo
		Two-sample t-test		
		P-value		0.124
		Comparison groups		Pegloticase every 4 wks vs. placebo
		Two-sample t-test		
		P-value		0.354
Notes	Change from Baseline in ASHI reports the mean change from baseline to Final visit (LOCF). A higher ASHI score indicates less arthritis-related disability.			
Analysis description	Health Assessment Questionnaire Disability Index (HAQ-DI)			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	39	38	20
	Change from Baseline (Mean)	-0.24	-0.15	-0.04
	SD	0.678	0.591	0.494
Effect estimate per comparison	Change in HAQ-DI	Comparison groups		Pegloticase every 2 wks vs. placebo
		Two-sample t-test		
		P-value		0.264

		Comparison groups		Pegloticase every 4 wks vs. placebo
		Two-sample t-test		
		P-value		0.503
Notes	Change from Baseline in HAQ-DI reports the mean change from baseline to Final visit (LOCF), where a lower number is better.			
Analysis description	HAQ Pain Scale			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	40	38	20
	Change from Baseline (Mean)	-14.53	-3.50	-3.80
	SD	30.669	27.710	28.631
Effect estimate per comparison	Change in Pain Scale	Comparison groups		Pegloticase every 2 wks vs. placebo
		Two-sample t-test		
		P-value		0.197
		Comparison groups		Pegloticase every 4 wks vs. placebo
		Two-sample t-test		
		P-value		0.969
Notes	Change from Baseline in Pain reports the mean change from baseline to Final visit (LOCF), where 0=no pain and 100=severe pain			
Analysis description	HAQ Patient Global Assessment			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	40	37	20
	Change from Baseline (Mean)	-17.70	-11.65	1.90
	SD	27.690	30.345	26.501
Effect estimate per comparison	Change in Global Assessment	Comparison groups		Pegloticase every 2 wks vs. placebo
		Two-sample t-test		

		P-value	0.011
		Comparison groups	Pegloticase every 4 wks vs. placebo
		Two-sample t-test	
		P-value	0.099
Notes	Change from Baseline in HAQ Global Assessment reports the mean change from baseline to Final visit (LOCF), where 0=very well and 100=very poor		
Analysis description	Incidence of Gout Flares		
Analysis population and time point description	Intent to treat population Months 1-3 and Months 4-6		

Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	43	41	20
	Months 1-3 n/N (%)	31/43 (72.1)	31/41 (75.6)	12/20 (60.0)
	Months 4-6 n/N (%)	11/37 (29.7)	20/33 (60.6)	15/20 (75.0)

Effect estimate per comparison	Gout Flare Incidence	Comparison groups	Pegloticase every 2 wks vs. placebo
		Fisher's exact test	
		P-value Months 1-3	0.390
		P-value Months 4-6	0.002
		Comparison groups	Pegloticase every 2 wks vs. placebo
		Fisher's exact test	
		P-value Months 1-3	0.242
		P-value Months 4-6	0.375
Notes	The number of subjects reporting gout flares (incidence) was captured throughout each month of the 6-month study treatment period. The incidence was compared between each pegloticase treatment arm and placebo for treatment differences during the first 3 months (Month 1 to Month 3) and last 3 months (Month 4 to Month 6). These periods were chosen because of the expected early transient increase in gout flares in the treatment arms.		

Table 25 Summary of Efficacy for trial 406

Title: Randomized, Multicenter, Double-blind, Placebo-controlled Efficacy and Safety Study of 8 mg PEG-uricase in Two Dose Regimens in Hyperuricemic Subjects with Symptomatic Gout			
Study identifier	C0406		
Design	Randomized, multicenter, double-blind, 3-arm parallel treatment groups, placebo-controlled, randomization in a 2:2:1 ratio to 8 mg pegloticase every 2 weeks; 8 mg pegloticase every 4 weeks; or placebo		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months 1 week not applicable
Hypothesis	Superiority of pegloticase vs. placebo in maintaining PUA < 6 mg/dL for at least 80% of the time during Months 3 and 6 combined		
Treatments groups	Arm 1		8 mg pegloticase i.v. every 2 weeks for 24 weeks; 46 randomized, 42 in ITT (received at least one dose of study drug)
	Arm 2		8 mg pegloticase i.v. every 4 weeks, alternating with placebo, for 24 weeks; 46 randomized, 43 in ITT
	Arm 3		Placebo every 2 weeks for 24 weeks, 24 randomized, 23 in ITT
Endpoints and definitions	Primary endpoint	PUA Response	Endpoint was the proportion of subjects in whom PUA was normalized to less than 6 mg/dL for at least 80% of the time during Months 3 and 6 combined. Subjects who withdrew before Month 6 were considered non-responders.
	Secondary: Reduction in Tophus burden	Overall Tophus Response	Overall tophus response was based on the best response among all tophi (measurable and unmeasured) at each visit. Complete response was defined as 100% decrease in the area of the tophus for measured tophi or disappearance of the tophus for unmeasured tophi. However, if any single tophus showed progression, or if a new tophus appeared during the study, the overall response for that subject was Progressive Disease, regardless of the response of any other tophi.
	Secondary: Patient Reported Outcomes (PRO)	SF-36 Physical Component Score (PCS)	The SF-36 is a PRO instrument comprised of a 36-item self-reported inventory which serves to assess health-related limitations in 8 dimensions. The summary analysis of physical component score was calculated. For the purpose of comparison, in a healthy normal population (age 55-64 for males and females combined) the average PCS score is 47.
	Secondary: Patient Reported Outcomes	SF-36 Mental Component Score (MCS)	The summary analysis of mental component score was calculated and reported. For the purpose of comparison, in a healthy normal population (age 55-64 for males and females combined) the average MCS score is 52.

	Secondary: Patient Reported Outcomes	SF-36 Arthritis-Specific Health Index (ASHI)	The ASHI is calculated from dimensions of the SF-36 and is weighted to measure bodily pain, other aspects of physical and role functioning, and well-being particular to arthritic conditions. The ASHI score was calculated and reported.
	Secondary: Patient Reported Outcomes	Health Assessment Questionnaire Disability Index (HAQ-DI)	The HAQ-DI is a self-reported functional status instrument that was completed by the subject. The index serves to measure disability over a 1-week period using 20 questions covering 8 domains of function.
	Secondary: Patient Reported Outcomes	Health Assessment Questionnaire Pain Scale	Pain Severity was also recorded on the HAQ Questionnaire using a 100-mm horizontal Visual Analog Scale (VAS), in response to the statement: (1) "How much pain have you had because of your illness IN THE PAST WEEK?" (where 0 = no pain and 100 = severe pain).
	Secondary: Patient Reported Outcomes	Health Assessment Questionnaire Global Assessment	Patient's Global Assessment was recorded on the HAQ Questionnaire using a 100-mm horizontal VAS , in response to the statement "Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line" (where 0 = very well and 100 = very poor).
	Secondary: Gout Flares	Incidence of Gout Flares	Gout flares were recorded throughout the study and reported in 3-month periods. There is no validated instrument to assess gout flares. For this study, self-reported gout flares were confirmed by the Investigator through questioning, if not through direct observation. The occurrence, severity, and duration of each flare (confirmed by the Investigator) were recorded.
Database lock	15-FEB-2008		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to Treat (had at least one dose of study drug) At Months 3 and 6 combined		

Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	42	43	23
	PUA Responder rate (% of subjects with PUA<6 mg/dl)	38.1%	48.8%	0
	95% CI	23.4, 52.8	33.9, 63.8	

Effect estimate per comparison	PUA Response	Comparison groups	Pegloticase every 2 wks vs. placebo
		Fisher's exact test	
		P-value	<0.001
		Comparison groups	Pegloticase every 4 wks vs. placebo
		Fisher's exact test	
		P-value	<0.001
Notes	PUA responder analysis reports the proportion of subjects whose PUA was normalized for 80% of the time during Months 3 and 6 combined.		
Analysis description	Secondary Endpoint-Overall Tophus Response		
Analysis population and time point description	Tophus-evaluable Population (TEP): all subjects with a tophus at baseline (as identified by the Investigator) and any subjects who developed new tophi during the study, as identified by either the Investigator or the Central Reader (RadPharm). Assessed at subject's Final Visit (Last observation carried forward-LOCF)		

Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	26	29	14
	Final Visit: %CR	50.0	20.7	14.3

Effect estimate per comparison	Overall Tophus Response	Comparison groups	Pegloticase every 2 wks vs. placebo
		Fisher's Exact Test	
		P-value: Final Visit	0.040
		Comparison groups	Pegloticase every 4 wks vs. placebo
		Fisher's Exact test	
		P-value: Final Visit	1.000
Notes	Overall Tophus Response reports the proportion of subjects who had an overall tophus response of Complete Response at the time of their last study visit (i.e., at least one of the subject's target tophi disappeared, while no new tophus appeared or no other target tophus got worse)		
Analysis description	SF-36 Physical Component Score		

Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	38	39	23
	Change from Baseline (Mean)	3.79	5.80	-0.44
	SD	9.694	8.682	5.801
Effect estimate per comparison	Change in PCS	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.063	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.003	
Notes	Change from Baseline in PCS reports the mean change from baseline to Final visit (LOCF).			
Analysis description	SF-36 Mental Component Score			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	38	39	23
	Change from Baseline (Mean)	2.38	0.75	0.64
	SD	10.124	11.708	8.641
Effect estimate per comparison	Change in MCS	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.495	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.968	
Notes	Change from Baseline in MCS reports the mean change from baseline to Final visit (LOCF).			
Analysis description	SF-36 ASHI Score			

Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	38	39	23
	Change from Baseline (Mean)	13.86	16.96	-4.19
	SD	27.776	27.055	18.816
Effect estimate per comparison	Change in ASHI	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.008	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.002	
Notes	Change from Baseline in ASHI reports the mean change from baseline to Final visit (LOCF). A higher ASHI score indicates less arthritis-related disability.			
Analysis description	Health Assessment Questionnaire Disability Index (HAQ-DI)			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	38	40	23
	Change from Baseline (Mean)	-0.21	-0.25	0.08
	SD	0.599	0.519	0.317
Effect estimate per comparison	Change in HAQ-DI	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.041	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.009	
Notes	Change from Baseline in HAQ-DI reports the mean change from baseline to Final visit (LOCF), where a lower number is better.			

Analysis description	HAQ Pain Scale			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	38	40	23
	Change from Baseline (Mean)	-8.21	-10.15	5.87
	SD	36.936	26.251	31.141
Effect estimate per comparison	Change in Pain Scale	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.132	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.033	
Notes	Change from Baseline in Pain reports the mean change from baseline to Final visit (LOCF), where 0=no pain and 100=severe pain			
Analysis description	HAQ Patient Global Assessment			
Analysis population and time point description	Intent to treat population Final Visit (LOCF)			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	28	35	20
	Change from Baseline (Mean)	-3.50	-13.69	-0.25
	SD	26.832	23.341	24.019
Effect estimate per comparison	Change in Global Assessment	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Two-sample t-test		
		P-value	0.668	
		Comparison groups	Pegloticase every 4 wks vs. placebo	
		Two-sample t-test		
		P-value	0.047	

Notes	Change from Baseline in HAQ Global Assessment reports the mean change from baseline to Final visit (LOCF), where 0=very well and 100=very poor			
Analysis description	Incidence of Gout Flares			
Analysis population and time point description	Intent to treat population Months 1-3 and Months 4-6			
Descriptive statistics and estimate variability	Treatment group	Pegloticase every 2 wks	Pegloticase every 4 wks	Placebo
	Number of subjects	42	43	23
	Months 1-3 n/N (%)	33/42 (78.6)	37/43 (86.0)	11/23 (47.8)
	Months 4-6 n/N (%)	17/32 (53.1)	19/36 (52.8)	13/23 (60.9)
Effect estimate per comparison	Gout Flare Incidence	Comparison groups	Pegloticase every 2 wks vs. placebo	
		Fisher's exact test		
		P-value Months 1-3	0.015	
		P-value Months 4-6	0.595	
		Comparison groups	Pegloticase every 2 wks vs. placebo	
		Fisher's exact test		
		P-value Months 1-3	0.001	
		P-value Months 4-6	0.599	
Notes	The number of subjects reporting gout flares (incidence) was captured throughout each month of the 6-month study treatment period. The incidence was compared between each pegloticase treatment arm and placebo for treatment differences during the first 3 months (Month 1 to Month 3) and last 3 months (Month 4 to Month 6). These periods were chosen because of the expected early transient increase in gout flares in the treatment arms.			

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

Pooled analysis across the two pivotal studies

The pooled analysis of the pivotal studies C0405 and C0406 confirms the statistically significant and clinically relevant PUA reduction shown for the pegloticase within the single pivotal studies. Overall the 8mg/2 weeks shows more decrease of PUA-levels and more constant PUA concentrations. Clinical improvement is also of greater magnitude for the 8mg/2 weeks dosing than given 8mg/4 weeks.

Primary endpoint

With regard to the primary endpoint, normalisation of PUA to below 6 mg/dL at both Month 3 and Month 6, pegloticase was shown effective in both pivotal Phase III trials and in the pooled analysis. Significantly more subjects in both 8 mg pegloticase every 2 wks and every 4 wks treatment groups were responders compared to subjects receiving placebo; there were no placebo-responders (Table 26).

Table 26 Treatment response (ITT population)

Study 405	N	PUA responders	p-value**
Pegloticase 8 mg/2 wks	43	47% [32%, 61%]*	< 0.001
Pegloticase 8 mg/4 wks	41	20% [7%, 32%]	0.044
Placebo	20	0%	
Study 406	**N**	**PUA responders**	**p-value***
Pegloticase 8 mg/2 wks	42	38% [23%, 53%]	< 0.001
Pegloticase 8 mg/4 wks	43	49% [34%, 64%]	< 0.001
Placebo	23	0%	
Pooled Data	**N**	**PUA responders**	**p-value***
Pegloticase 8 mg/2 wks	85	42% [32%, 53%]	< 0.001
Pegloticase 8 mg/4 wks	84	35% [24%, 45%]	< 0.001
Placebo	43	0%	

** 95% CI for the difference in responder rate vs. placebo ** p-value vs. placebo using Fisher's exact test*

Secondary endpoints

Please make reference to the pooled data presented in outcomes and estimations of the secondary endpoints.

Additional analyses

The following additional analyses are shown below: the overall duration of treatment in studies C0405, C0406, and C0407, efficacy data with regard to PUA results from the two pivotal 6 months studies C0405 and C0406, and the new long term efficacy analyses in patients treated for at least 1 year in studies C0405, C0406, and C0407 and an analysis of PUA responder with different cut-offs (50%, 60% 70% and 80% of time >6mg/dL.

These analyses show that overall 76 patients received 8mg/2w and 67 patients received 8mg/4w for 100% of their pegloticase treatment time. 65 patients received pegloticase under both regimens (8mg/2w and 8mg/4w), i.e. switched between regimens within the studies.

With regard to treatment duration over one year only 33 patients could be identified as having received a stable therapeutic dose regimen of 8mg/2w (Table 27).

Table 27 Number of Subjects and Pegloticase Treatment Duration for 100% of Time

	8 mg Pegloticase			Total number
	Every 2 weeks	Every 4 weeks	Every 2 or 4 weeks	
100% of Time, N (subjects)	**76**	**67**	**65**	**208**
Treatment duration (months)[1]				
Mean (SD)	13.5 (11.64)	10.9 (10.44)	23.4 (8.26)	-
<6 months	36 (47.4%)	39 (58.2%)	0	75
6 – 12 months	7 (9.2%)	4 (6.0%)	11 (16.9%)	22
12 months and beyond	33 (43.4%)	24 (35.8%)	54 (83.1%)	111
• 12-24 months	8	12	15	35
• 24-36 months	25	12	39	76

N=number of subjects per treatment group
[1]Include time on pegloticase treatment in studies C0405, C0406, and C0407

The results with respect to efficacy (and safety, see below) especially the loss of efficacy during prolonged treatment due to formation of antibodies against pegloticase of a treatment given every 4 weeks compared to the frequency every 2 weeks are distinctly different as can be seen in the PUA analyses of the three dose regimens (Table 28).

Table 28 PUA Responder[1] Status – All Subjects Treated with Pegloticase for at least 52 Weeks (Subjects on Pegloticase Treatment 100%)

	Subjects on pegloticase regimen		
	8q2 100% time N=33	**8q4 100% time N=24**	**8q2 or 8q4 N=54**
Months 1-3			
Responder[1] n, (%)	23 (69.7%)	13 (54.2%)	34 (63.0%)
Month 4-6			
Responder[1] n, (%)	23 (69.7%)	13 (54.2%)	31 (57.4%)
Month 7-9			
Responder[1] n, (%)	23 (69.7%)	10 (41.7%)	26 (48.1%)
Month 10-12			
Responder[1] n, (%)	22 (66.7%)	11 (45.8%)	25 (46.3%)
Beyond 12 Months			
Responder[1] n, (%)	20 (60.6%)	12 (50.0%)	23 (42.6%)
ALL Months			
Responder[1] n, (%)	16 (48.5%)	8 (33.3%)	22 (40.7%)

[1] Responder = subjects achieving and maintaining PUA < 6 mg/dL at least 80% of the time
[2] The two-sided 95%CI for the binomial proportion is derived from the Wilson score statistic

As there were more responders in female patients than in male patients, it was hypothesised that this outcome may be related to differences in body weight and consequently differences in dose per kg BW. Additional data submitted by the applicant showed a relationship between the responder rate and body weight in the 8mg/2w treatment arm (see table below, responder at 3 and 6 months, p-value=0.053).

Weight	**Responder N=36**	**Non-Responder N=49**	**Responder rate N=85**
<70kg	4 (11.1%)	3 (6.1%)	57%
70 to 100kg	22 (61.1%)	22 (44.9%)	50%
100 to 120kg	6 (16.7%)	14 (28.6%)	30%
>120kg	4 (11.1%)	10 (20.4%)	28%

Clinical studies in special populations

All studies were conducted in the target population, no further pharmacokinetic studies in special populations have been performed. However, impaired renal function is a common status in the target

population and respective covariates have been considered in the PopPK analysis in addition to weight, age, and gender.

Supportive studies

Study C0407 (OLE)

The Multi-centre Open-Label Extension Study C0407 includes a variety of data with different impact on the outcome e.g. different duration of treatment or switching of dosing, hence data from this study to support efficacy demonstration requires use the post hoc analysis. This analysis was made for responders in studies C0405/6 and only for patients who received approx. continuously the therapeutic dose. In this subgroup analysis a trend is indicated that clinical improvement is continued (week 101: status of individual tophus resolution (all improved, CR=73%), tender and swollen joints (0.4 and 1.3 respectively, baseline = 8.9 and 11.7), clinically relevant improvements compared to baseline in pain, patient global assessment, HAQ-DI and SF-36 Physical component) and gout flares decreased to a mean number of flares per patient of 0.02 (baseline = 0.13). The CHMP noted however that this analysis is based only on 19 patients hence it does not substantially contribute to efficacy data.

Study C0409

It is noted that the non-randomized, multicentre, open-label re-exposure study C0409 could not substantially contribute to efficacy data because only 3 patients received the full course over 24 weeks.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design of the two replicate Phase III trials is considered adequate including the choice of the study population, which corresponds to the restricted indication sought by the Applicant, and the selection of placebo as comparator given the absence of any treatment for gout refractory to conventional urate-lowering agents. Patients had to stop any urate-lowering agent at least one week before the first study infusion. These selection criteria define a population of patients with symptomatic gout and hyperuricaemia that failed to respond to allopurinol (in the EU, the maximum dose for severe condition is 900 mg daily). Moreover, allopurinol is contraindicated in patients with allopurinol (potentially life-threatening) hypersensitivity and its posology needs to be reduced in patients with impaired renal function.

The primary objective (reduction of SUA below the threshold of 6 mg/dL) is a valid surrogate endpoint, which is consistent with the therapeutic target for any prophylaxis of gout in clinical practice. Importantly, the selected secondary endpoints are indicative of direct benefit to the patients: reduction of tophi burden, of the number of swollen and tender joints, of the incidence and severity of gout flares, as well as improvement of quality of life. SUA, acute gout attacks, tophus burden, and the SF-36 instrument as a measure of quality of life are all validated outcome measures (OMERACT 9).

Based on the results of this Phase II study, 4mg IV every 2 wks was defined as the minimally effective dose; both dose regimens 8mg/2 wks or 8mg/4 wks were effective, and 12mg/4 wks did not provide additional benefit beyond that of the 8mg groups, thereby defining a dose-response plateau. Although the 8mg/2 wks and 8mg/4 wks treatment achieved the same degree of plasma UA decrease, an every 2 wks infusion regimen appeared to offer a more rapid and more prolonged reduction of plasma UA. On the basis of safety and efficacy results of this Phase II study, the pegloticase dose selected for advancement to Phase III pivotal trials was 8 mg to be administered IV every 2 wks or every 4 wks. Based on the results of the Phase I trial, the selection of the dose regimens tested in this Phase II trial and its design are considered adequate.

The studies appear to have been adequately conducted. The statistical analyses are generally considered acceptable.

Efficacy data and additional analyses

In a pooled analysis, the proportion of responders that maintain a low PUA concentration (< 6 mg/dL) up to the 6th month of the double-blind trial is numerically higher with the E2W regimen (42%) as compared with the E4W regimen (35%) whereas there is no responder in the placebo arm, a highly significant difference ($p < 0.001$) for both pegloticase arms. Furthermore, while large fluctuations of PUA concentration are observed with the E4W regimen, sustained low to undetectable PUA concentrations can be achieved with the E2W regimen. Of note, essentially all subjects show an initial rapid decline in PUA concentration, but in those who develop high titres of anti-pegloticase antibodies, exposure to pegloticase becomes insufficient to catabolise excessive UA and PUA concentration eventually returns to pre-treatment levels. The analyses of different cut-off values for the definition PUA responders (PUA <6 mg/dL 50%, 60%, 70% or 80% of time) show the robustness of results over 6 months.

Sustained low PUA concentrations translate into clinical benefit to the patient as reflected by a significant effect on tophi, which is only significant for the E2W regimen with 40% of the patients exhibiting at least one tophus completely resolved at the Final Visit within the first 6 months of therapy vs. 7% on placebo ($p = 0.002$). However, when missing data were considered as failures, these percentages were 29% vs. 7% ($p < 0.05$), respectively. This is an objective sign of clinical efficacy that was observed over a short period of time. Other clinical benefits to the patient include a significant reduction in the number of tender joints ($p < 0.02$) and a favourable impact on quality of life, as reflected in the Physical Component Summary of the SF-36 questionnaire ($p < 0.01$) in both pegloticase arms.

As with all urate-lowering therapies, treatment with pegloticase was expected to lead to an increase in gout flares during the initiation of therapy. It is important to note that the self-reported history of gout flares in the pre-study period was 1.38 flares per 3 month for all subjects. Gout flare prophylaxis (colchicine or NSAID) for all subjects started at least 1 week before their first study drug administration, unless medically contraindicated or not tolerated. About 80% of the patients experience gout flares within the first 3 months of pegloticase therapy. Subsequently, the benefit of the treatment becomes evident as the incidence of gout flares decreases over time in comparison to placebo, the difference being only significant for the E2W regimen (pegloticase 41%, placebo 67%; $p = 0.007$). However, the CHMP noted that this reduction of gout flare incidence for the E2W regimen was only observed for a selected subgroup as the patients who discontinued the study before month 4 were excluded from this analysis; in a worst-case analysis imputing dropouts as incident cases of gout flare, no significant difference was seen.

In a post-hoc descriptive analysis in various subgroups, responder rates ranged from 31% to 60% with the E2W regimen and were usually higher then those observed with the E4W regimen, which ranged from 26% to 47%. Efficacy vs. placebo (0% response) was evident in all subgroups but their size precludes any conclusion on potential small differences in efficacy. Nevertheless, the finding that efficacy does not decrease with age and impaired renal function is reassuring. Patients up to 89 years of age have been treated in the pivotal trials. As for renal impairment, the number of patients with creatinine clearance < 50 mL/min at baseline was limited (38 in the pegloticase arms) and only 14 had severe renal impairment (CrCL < 30 mL/min). This has been reflected in the SmPC and, given the prevalence of renal complications associated with severe chronic gout, further data will be collected post-authorisation in patients with severe renal impairment.

A small number of patients (33) were treated for at least one year at a stable dose of 8mg/2w. Sixty-one percent (61%) were responders beyond 12 months and the overall responder rate in this post hoc analysis was 48.5%. The long-term efficacy results (PUA responder rates) in patients treated with a stable, unchanged dose of pegloticase (8mg/2w or 8mg/4w) for at least 52 weeks showed a higher proportion of responders in the 8mg/2w group compared to 8mg/4w regimen at all analysed time points. Insofar, the interval of 2weeks is supported by the presented data. However, subgroup analyses indicate that PUA responses might be influenced by absolute bodyweight (BW) and might be modified in the elderly and in patients with renal impairment. This is supported by data from population pharmacokinetic analysis revealing an influence of the BSA and of the patient's creatinine clearance on the clearance of pegloticase. This might have an impact on dose selection for patients with renal impairment and different weight. However, as no obvious unexpected safety signals have been seen in the elderly and in patients with impaired renal function, a dose adjustment in these patients seems not justified. This is reflected in the SmPC. With regard to the efficacy in patients over 100kg BW, the SmPC indicates the lower response rates that were observed in these patients but also clarifies that the available data are not conclusive.

2.5.4. Conclusions on the clinical efficacy

The primary endpoint percentage of PUA responders achieving the primary efficacy endpoint (PUA < 6 mg/dL for at least 80% of the time during Months 3 and 6) was significantly and clinically relevantly greater in the patients receiving pegloticase 8 mg/2 wk and partially 8 mg/4 wk when compared to placebo treated patients.

The secondary endpoints showed for the intended therapeutic dose that the continuously lowering of plasma uric acid under the threshold of crystallisation induces a clinical improvement. For clinically relevant parameters as function, pain or tender and swollen joints a meaningful improvement for the claimed therapeutic dose could be shown compared to placebo at week 25. The mean decrease of PUA is mainly maintained over time so that uric acid can also be released from the tissue which is documented in gout tophi dissolving from 3-5 month of treatment on. The long-term efficacy results (PUA responder rates) in patients treated with a stable, unchanged dose of pegloticase (8mg/2w or 8mg/4w) for at least 52 weeks show a higher proportion of responders in the 8mg/2w group compared to 8mg/4w regimen at all analysed time points. However, subgroup analyses indicate that PUA responses might be influenced by absolute bodyweight (BW). The CHMP has recommended and the applicant has agreed to further explore the optimal dose in patients with over 100 kg BW in a dedicated study. This together with this information in the SmPC is considered adequate.

2.6. Clinical safety

Patient exposure

Pegloticase is claimed for long-term treatment. The safety of pegloticase is supported by the results of 7 clinical studies in patients with refractory gout, including two Phase I studies (C0401 and C0402), one Phase II study (C0403), two replicate pivotal Phase III studies (C0405 and C0406), as well as an open label extension (OLE) to Phase III (C0407), as well as a small, open-label study (C0409) evaluating safety and efficacy of re-exposure to pegloticase after a prolonged drug-free interval in patients who participated in earlier studies of IV administered pegloticase. The clinical studies with pegloticase in gout are summarized in Table 2.7.4-1. Pegloticase was IV infused in all studies except for C0401 in which pegloticase was administered subquanteously.

The IV studies included in total 277 patients with symptomatic gout despite previous treatment with conventional therapy (e.g. xanthine oxidase inhibitors); 273 patients received at least one dose of pegloticase.

In studies C0405/C0406/C0407, 108 patients were started on the claimed dose regimen 8mg/2 weeks (when including patients in the placebo arm that were treated with pegloticase in the extension study) and 100 patients were started on the 8mg/4 weeks regimen. Out of these, 57 and 45, respectively, were treated for at least 18 months (maximum duration 31 months). However, since patients were allowed to switch from one regimen to the other in the course of the extension study, only 33 patients were maintained on the claimed dose regimen 8mg/2 weeks for at least 12 months.

On the basis of the pivotal studies (C0405/6) only very common AEs could be detected over a treatment period of up to 6 month. The long-term safety database is limited and this is reflected in the SmPC; however, this is considered acceptable given the last line indication and potential therapeutic benefit to the patient. This will be further addressed in post-authorisation studies. The two dose regimens were not considered comparable with regard to safety because the dosing frequency has a distinct influence on the patient's reactions to pegloticase.

The table below presents the summary of adverse events (AEs) in the pooled pivotal studies C0405 and C0406 (safety population).

Table 29 Summary Table of Adverse Events including Gout Flares and Infusion Reactions (Safety Population)

	8 mg pegloticase		Placebo
	Every 2 weeks N=85	Every 4 weeks N=84	N=43
Number of adverse events	693	870	370
Subjects with adverse events	80 (94.1%)	84 (100.0%)	41 (95.3%)
Subjects with serious adverse events	20 (23.5%)	19 (22.6%)	5 (11.6%)
Subjects with severe adverse events	33 (38.8%)	40 (47.6%)	12 (27.9%)
Subjects with treatment related adverse events	63 (74.1%)	67 (79.8%)	34 (79.1%)
Subjects with treatment interrupted due to adverse event	26 (30.6%)	28 (33.3%)	5 (11.6%)
Subjects with treatment discontinued due to adverse event[1]	16 (18.8%)	17 (20.2%)	1 (2.3%)

Note: Except for the "Number of adverse events", subjects are counted only once in each row.
[1] Two additional subjects, C0406-308-003 in the pegloticase 8 mg/2 weeks group and C0406-319-004 in the pegloticase 8 mg/4 weeks group, had treatment discontinued due to infusion reactions. Their final dispositions are incorrectly noted in the clinical database and this table: the errors were revealed during comparison of subject narratives with data listings during CSR development.
month(s); N: number, SC: subcutaneous; wks: weeks

Adverse events

Table 30 Treatment-Emergent AEs in 4 or More Subjects by SOC and PT, Excluding Gout Flares and IRs (Pooled Data C0405/C0406)

	8 mg Pegloticase		Placebo
	Every 2 wks (N = 85)	Every 4 wks (N = 84)	(N = 43)
Number of AEs	428	479	266
Number (%) of Subjects with ≥ 1 AE	69 (81.2)	79 (94.0)	36 (83.7)
SOC/PT	n (%)	n (%)	n (%)
Infections and Infestations			
Upper Respiratory Tract Infection	4 (4.7)	4 (4.8)	9 (20.9)
Urinary Tract Infection	6 (7.1)	5 (6.0)	3 (7.0)
Nasopharyngitis	6 (7.1)	4 (4.8)	1 (2.3)
Localized Infection	2 (2.4)	5 (6.0)	3 (7.0)
Cellulitis	4 (4.7)	2 (2.4)	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	6 (7.1)	15 (17.9)	8 (18.6)
Back Pain	3 (3.5)	7 (8.3)	2 (4.7)
Muscle Spasms	3 (3.5)	5 (6.0)	4 (9.3)
Pain In Extremity	4 (4.7)	4 (4.8)	3 (7.0)
Musculoskeletal Pain	1 (1.2)	4 (4.8)	0
Joint Swelling	4 (4.7)	0	0
Gastrointestinal Disorders			
Diarrhoea	9 (10.6)	14 (16.7)	8 (18.6)
Nausea	10 (11.8)	6 (7.1)	1 (2.3)
Vomiting	4 (4.7)	5 (6.0)	1 (2.3)
Constipation	5 (5.9)	2 (2.4)	2 (4.7)
General Disorders and Administration Site Conditions			
Oedema Peripheral	10 (11.8)	11 (13.1)	6 (14.0)
Fatigue	5 (5.9)	6 (7.1)	4 (9.3)
Chest Pain	5 (5.9)	4 (4.8)	1 (2.3)
Pain	4 (4.7)	4 (4.8)	2 (4.7)
Pyrexia	2 (2.4)	5 (6.0)	1 (2.3)
Asthenia	2 (2.4)	4 (4.8)	0
Skin and Subcutaneous Tissue Disorders			
Pruritus	3 (3.5)	5 (6.0)	0
Nervous System Disorders			
Headache	8 (9.4)	9 (10.7)	4 (9.3)
Dizziness	3 (3.5)	7 (8.3)	4 (9.3)
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnoea	4 (4.7)	5 (6.0)	2 (4.7)
Pharyngolaryngeal Pain	4 (4.7)	2 (2.4)	0
Metabolism and Nutrition Disorders			
Dehydration	4 (4.7)	1 (1.2)	1 (2.3)
Hyperglycaemia	4 (4.7)	1 (1.2)	1 (2.3)
Injury, Poisoning and Procedural Complications			
Contusion	7 (8.2)	0	1 (2.3)
Investigations			
Blood Glucose Increased	4 (4.7)	2 (2.4)	1 (2.3)
Blood Pressure Increased	0	6 (7.1)	0
Psychiatric Disorders			
Insomnia	5 (5.9)	8 (9.5)	4 (9.3)
Depression	3 (3.5)	4 (4.8)	4 (9.3)
Vascular Disorders			
Hypertension	2 (2.4)	5 (6.0)	3 (7.0)
Blood and Lymphatic System Disorders			
Anaemia	7 (8.2)	4 (4.8)	4 (9.3)
Cardiac disorders			
Tachycardia	1 (1.2)	4 (4.8)	0

Source: 5.3.5.3 Pooled Data Analysis, Table 53
Note: If the same subject in a given treatment had more than one occurrence in the same PT event category, the subject was counted only once.

Adverse Events of Special Interest

Adverse events of special interest included those which pertained to renal safety, hepatic safety, hematological safety, central nervous system (CNS) safety, cardiac safety, and infusion site events.

Renal Safety

Table 31 AEs by PT, Pertaining to Renal Safety (Pooled Data C0405/C0406)

	8 mg Pegloticase		Placebo
Event PT	Every 2 wks (N = 85) n (%)	Every 4 wks (N = 84) n (%)	(N = 43) n (%)
Hyperkalaemia	3 (3.5)	2 (2.4)	0 (0.0)
Blood Creatinine Increased	2 (2.4)	2 (2.4)	0 (0.0)
Blood Urea Increased	2 (2.4)	2 (2.4)	0 (0.0)
Renal Failure Acute	2 (2.4)	1 (1.2)	1 (2.3)
Creatinine Renal Clearance Decreased	1 (1.2)	1 (1.2)	1 (2.3)
Haemoglobin Decreased	1 (1.2)	2 (2.4)	0 (0.0)
Proteinuria	1 (1.2)	2 (2.4)	0 (0.0)
Haematocrit Decreased	1 (1.2)	1 (1.2)	0 (0.0)
Hypocalcaemia	2 (2.4)	0 (0.0)	0 (0.0)
Renal Failure	0 (0.0)	1 (1.2)	0 (0.0)
Renal Failure Chronic	0 (0.0)	1 (1.2)	0 (0.0)
Renal Impairment	0 (0.0)	1 (1.2)	0 (0.0)
Nephrolithiasis	1 (1.2)	3 (3.6)	2 (4.7)
Haematuria	3 (3.5)	0	2 (4.7)
Flank Pain	0	1 (1.2)	2 (4.7)
Renal Colic	0	0	1 (2.3)
Dysuria	1 (1.2)	3 (3.6)	1 (2.3)
Pollakiuria	2 (2.4)	0	1 (2.3)
Chromaturia	1 (1.2)	1 (1.2)	0
Polyuria	0	1 (1.2)	0
Renal Cyst	0	0	1 (2.3)

Source: 5.3.5.3 Pooled Data Analysis, Table 64
Note: If the same subject in a given treatment had more than one occurrence in the same PT event category, the subject was counted only once.

Renal failure, renal failure chronic and renal impairment together was reported to have a frequency of 3.6% in the 8mg/4 weeks group versus 0% in the placebo group. Chromaturia is documented only for pegloticase Haematocrit and haemoglobin were decreased only in the pegloticase groups (total 3.6%) this is an AE and will be further monitored. In addition, hyperkaliaemia and Creatinine are increased (3.5% and 2.4% respectively).

In patients with renal insufficiency the incidence of severe AEs was increased versus placebo (placebo: 27%, 8mg/2 weeks: 38.5%, 8mg/4 weeks: 50%. However, there is no overall difference in safety across a variety of baseline renal function categories, from <30 mL/min, 30-50 mL/min, and >50 mL/min.

Hepatic Safety

Table 32 AEs by PT, Pertaining to Hepatic Safety (Pooled Data C0405/C0406)

Event PT	8 mg Pegloticase		Placebo
	Every 2 wks (N = 85) n (%)	Every 4 wks (N = 84) n (%)	(N = 43) n (%)
Cholecystitis	0 (0.0)	1 (1.2)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (1.2)	0 (0.0)
Hepatic Enzyme Abnormal	1 (1.2)	0 (0.0)	0 (0.0)
Hepatic Enzyme Increased	0 (0.0)	1 (1.2)	0 (0.0)
Hepatic Function Abnormal	0 (0.0)	1 (1.2)	0 (0.0)

Source: 5.3.5.3 Pooled Data Analysis, Table 65
Note: If the same subject in a given treatment had more than one occurrence in the same PT event category, the subject was counted only once.

Hepatic enzyme elevation has a total frequency of 2.4 % in the 8mg/4 weeks group versus 0% in the placebo group likewise cholelithiasis.

Haematological Safety

Table 33 AEs by PT, Pertaining to Hematological Safety (Pooled Data C0405/C0406)

Event PT	8 mg Pegloticase		Placebo
	Every 2 wks (N = 85) n (%)	Every 4 wks (N = 84) n (%)	(N = 43) n (%)
Anaemia	7 (8.2)	4 (4.8)	4 (9.3)
Neutropenia	1 (1.2)	0 (0.0)	1 (2.3)
Febrile Neutropenia	0 (0.0)	0 (0.0)	1 (2.3)
Haematocrit Increased	0 (0.0)	1 (1.2)	0 (0.0)
Leukocytosis	1 (1.2)	0 (0.0)	0 (0.0)
Leukopenia	1 (1.2)	0 (0.0)	0 (0.0)
Thrombocythaemia	0 (0.0)	1 (1.2)	0 (0.0)
Thrombocytopenia	1 (1.2)	0 (0.0)	0 (0.0)

Source: 5.3.5.3 Pooled Data Analysis, Table 66
Note: If the same subject in a given treatment had more than one occurrence in the same PT event category, the subject was counted only once.

In this table contradictory AEs are listed: haematocrit increased (see renal safety data) and anaemia (haematocrit and haemoglobin are decreased; see table with renal safety data).

Central Nervous System (CNS) Safety

Table 34 AEs by PT, Pertaining to CNS Safety (Pooled Data C0405/C0406)

Event PT	8 mg Pegloticase		Placebo
	Every 2 Weeks (N = 85) n (%)	Every 4 Weeks (N = 84) n (%)	(N = 43) n (%)
Syncope	1 (1.2)	2 (2.4)	1 (2.3)
Convulsion	0	1 (1.2)	0
Transient Ischaemic Attack	0	1 (1.2)	0

Source: 5.3.5.3 Pooled Data Analysis, Table 67
Note: If the same subject in a given treatment had more than one occurrence in the same PT event category, the subject was counted only once.

At present no specific increased risk could be indicated.

Infusion Site Events

There were in total 4 infusion events in C0405/C0406, 1 in Study C0405 (mild injection site erythema; pegloticase 8 mg/2 wks) and 3 in Study C0406 (infusion site irritation, pegloticase 8 mg/2 wks; infusion site erythema, pegloticase 8 mg/4 wks; injection site hemorrhage, placebo). All were reported as mild in severity.

Infections

Infections as AEs occurred in a greater percentage in the pegloticase 8mg/2wks group than the placebo group. The underlying mechanism for this is not clear.

Gout flares

Gout flare was the most common AE in the double-blind studies despite gout flare prophylaxis as seen with all effective urate lowering therapies. Most were mild to moderate in intensity, were generally tolerated by subjects but resulted in discontinuation of pegloticase therapy in 5 patients on pegloticase 8 mg/2 wks and 3 patients on pegloticase 8 mg/4 wks. Gout flares were especially frequent in the first 3 months of therapy (see efficacy section).

Infusion reactions

An infusion reaction (IR) was defined as an AE, or more typically, a cluster of AEs that occurred during or within 2 hours after the end of the study drug infusion. The prevalence and severity of IRs in the double-blind-trials is shown in the table below; more patients experienced an IR on the E4W regimen than on the E2W regimen. Likewise, the percentage of pegloticase infusions with an infusion reaction was much lower (5%; 43/852) in the E2W arm than in the E4W arm (65/430; 15%). Most patients developed only one or two IRs and most IRs were of moderate intensity.

Table 35 Prevalence and severity of IRs in the pooled analysis C0405/C0406

	Study 405/406			
	8 mg E2W	**8 mg E4W**	**both regimens**	**Placebo**
	n (%)	n (%)	n (%)	n (%)
N	85	84	169	43
Mild	7 (8.2)	4 (4.8)	11 (6.5)	0
Moderate	11 (12.9)	22 (26.2)	33 (19.5)	2 (4.7)
Severe	4 (4.7)	8 (9.5)	12 (7.1)	0
All	**22 (25.9)**	**34 (40.5)**	**56 (33.1)**	**2 (4.7)**

Anaphylactic and delayed hypersensitivity reactions

Applying the diagnostic criteria for anaphylaxis proposed by the NIAID/FAAN Joint Symposium on Anaphylaxis (Sampson et al. 2006) led to the detection of 14 cases (7 definite and 7 potential) out of the 273 patients of the entire pegloticase clinical study database (Studies C0402, C0403, C0405, C0406, and C0407), i.e. a prevalence of 5.1%. These reactions occurred during or within 2 hours of pegloticase infusion. Two cases occurred during the first infusion, including one in a patient that did not receive the full prophylaxis (missed fexofenadine and paracetamol); the remainder occurred between the third and sixth infusion. Symptoms of anaphylactic/anaphylactoid reaction included stridor, wheezing, perioral/lingual oedema, or hemodynamic instability, with or without rash or urticaria. Finally, 9/14 patients stopped treatment as a result of such reaction.

One case of possible delayed type hypersensitivity (angioneurotic oedema and urticaria occurring approximately 6 days after the third pegloticase dose was reported in the 8 mg/4 weeks group. It led to treatment discontinuation and fully resolved with corticosteroids and epinephrine.

A post-hoc analysis was carried out where various scenarios and simulations of stopping criteria based on SUA levels explored the effect of these stopping criteria on the response rates and IR rates simultaneously. Table 36 below presents the results of these scenarios in the 8 mg/2 weeks group, selecting different SUA cut-offs, 6 mg/dL, 7 mg/dL or 8 mg/dL as well as one or two consecutive measurements prior to stopping.

Table 36 Pegloticase Stopping Rule in the pooled analysis C0405/C0406 (N=85)

	IR rate	Response rate
No Stopping Criteria	22 (26%)	36 (42%)
One SUA >6 mg/dL	7 (8%)	31 (36%)
One SUA >7 mg/dL	7 (8%)	32 (38%)
One SUA >8 mg/dL	9 (11%)	33 (39%)
Two consecutive SUA >6 mg/dL	**12 (14%)**	**35 (41%)**
Two consecutive SUA >7 mg/dL	12 (14%)	35 (41%)
Two consecutive SUA >8 mg/dL	13 (15%)	36 (42%)

The results of these simulations demonstrated that if no stopping criterion were used (as was done during the phase III trials), the overall response rate would be 42% with an IR rate of 26% in the patients treated with the 8mg every two week regimen. The IR rate would be minimized when a single assessment of SUA with a cut-off of 6 mg/dL or 7 mg/dL were used. However, in such a scenario the efficacy would be reduced to 36%. Therefore, the applicant proposed that pegloticase should be stopped if SUA > 6 mg/dL in two consecutive tests, which according to the simulations reduced the IR rate substantially (14%) but maintained the efficacy almost at the same level (41%). This algorithm has been included in the SmPC as a risk mitigation measure.

Infusion related reactions in relation to BW

Infusion related reactions showed a tendency to occur in a greater proportion of patients in the higher weight group of >100kg since infusion reactions occurred in 53.7% for patients in the weight 70 to ≤100 kg weight group, 70.0% of the patients in the >100 to ≤120 weight group, and 75% of patients in the >120 kg weight group, respectively. Also the anti-pegloticase antibody titres showed higher levels of antibody in the higher weight groups. The statistically significant kg BW dose response relation suggests that patients over 100kg BW may not receive an optimal dose leading to a setting similar to an “interruption” of therapy.

Serious adverse events/ deaths/other significant events

Serious Adverse Events

Serious adverse events (SAEs), including IRs and gout flares, are summarized by system organ class and preferred term (for details see Table 37).

Table 37 SAEs, Including IRs and Gout Flares, by SOC and PT (Pooled Data C0405/C0406)

SOC/PT	8 mg Pegloticase		Placebo
	Every 2 wks (N=85)	Every 4 wks (N=84)	(N = 43)
Number of SAEs	34	30	14
Number (%) of Subjects with SAEs	20 (23.5)	19 (22.6)	5 (11.6)
	n (%)	n (%)	n (%)
General Disorders and Administration Site Conditions	7 (8.2)	7 (8.3)	0
Infusion Related Reaction	4 (4.7)	7 (8.3)	0
Chest Pain	1 (1.2)	0	0
Oedema Peripheral	1 (1.2)	0	0
Pyrexia	1 (1.2)	0	0
Infections and Infestations	3 (3.5)	5 (6.0)	4 (9.3)
Pneumonia	1 (1.2)	1 (1.2)	1 (2.3)
Cellulitis	1 (1.2)	1 (1.2)	0
Arthritis Bacterial	0	0	1 (2.3)
Cellulitis Staphylococcal	0	1 (1.2)	0
Herpes Zoster	0	0	1 (2.3)
Localized Infection	0	1 (1.2)	0
Necrotising Fasciitis	0	1 (1.2)	0
Perianal Abscess	0	0	1 (2.3)
Pyelonephritis	1 (1.2)	0	0
Sepsis	1 (1.2)	0	0
Staphylococcal Sepsis	1 (1.2)	0	0
Musculoskeletal and Connective Tissue Disorders	7 (8.2)	2 (2.4)	2 (4.7)
Gout	4 (4.7)	1 (1.2)	2 (4.7)
Fistula	0	1 (1.2)	0
Haemarthrosis	1 (1.2)	0	0
Myopathy Steroid	1 (1.2)	0	0
Osteoarthritis	1 (1.2)	0	0
Synovial Cyst	1 (1.2)	0	0
Cardiac Disorders	4 (4.7)	3 (3.6)	0

SOC/PT	8 mg Pegloticase		Placebo
	Every 2 wks (N=85)	Every 4 wks (N=84)	(N = 43)
Arrhythmia	2 (2.4)	0	0
Angina Pectoris	0	1 (1.2)	0
Cardiac Arrest	1 (1.2)	0	0
Cardiac Failure Congestive	1 (1.2)	0	0
Myocardial Infarction	0	1 (1.2)	0
Tachycardia	0	1 (1.2)	0
Gastrointestinal Disorders	3 (3.5)	1 (1.2)	2 (4.7)
Gastrooesophageal Reflux Disease	2 (2.4)	0	0
Pancreatitis	0	1 (1.2)	1 (2.3)
Barrett's Oesophagus	1 (1.2)	0	0
Gastritis Erosive	1 (1.2)	0	0
Inguinal Hernia, Obstructive	0	0	1 (2.3)
Number of Serious AEs	34	30	14
Number (%) of Subjects with Serious AEs	20 (23.5)	19 (22.6)	5 (11.6)
SOC/PT	**n (%)**	**n (%)**	**n (%)**
Renal and Urinary Disorders	0	2 (2.4)	2 (4.7)
Renal Failure Acute	0	1 (1.2)	1 (2.3)
Haematuria	0	0	1 (2.3)
Renal Failure	0	1 (1.2)	0
Metabolism and Nutrition Disorders	1 (1.2)	1 (1.2)	1 (2.3)
Hyperkalaemia	1 (1.2)	1 (1.2)	0
Hypoglycaemia	0	0	1 (2.3)
Nervous System Disorders	0	2 (2.4)	1 (2.3)
Convulsion	0	1 (1.2)	0
Syncope	0	0	1 (2.3)
Transient Ischaemic Attack	0	1 (1.2)	0
Injury, Poisoning and Procedural Complications	2 (2.4)	0	0
Facial Bones Fracture	1 (1.2)	0	0
Injury	1 (1.2)	0	0
Muscle Rupture	1 (1.2)	0	0
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	0	1 (1.2)	1 (2.3)
Chronic Lymphocytic Leukaemia Recurrent	0	0	1 (2.3)
Malignant Melanoma	0	1 (1.2) [1]	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (1.2)	1 (1.2)	0
Dyspnoea	1 (1.2)	0	0
Dyspnoea Exacerbated	0	1 (1.2)	0
Blood and Lymphatic System Disorders	0	0	1 (2.3)
Febrile Neutropenia	0	0	1 (2.3)
Hepatobiliary Disorders	0	1 (1.2)	0
Cholecystitis	0	1 (1.2)	0
Skin and Subcutaneous Tissue Disorders	0	1 (1.2)	0
Angioneurotic Oedema	0	1 (1.2)	0
Urticaria	0	1 (1.2)	0
Vascular Disorders	0	1 (1.2)	0

SOC/PT	8 mg Pegloticase		Placebo
	Every 2 wks (N=85)	Every 4 wks (N=84)	(N = 43)
Deep Vein Thrombosis	0	1 (1.2)	0

Source: 5.3.5.3 Pooled Data Analysis, Table 55
Note: If the same subject in a given treatment had more than one occurrence in the same PT event category, the subject was counted only once.
[1] Subject C0405-122-003 **reported an AE of "left ear skin lesion" on an unknown date in August 2006. This subject received their first dose of study medication on 03 August 2006.**

Forty-four (44) subjects experienced a total of 78 SAEs: 20 (23.5%) subjects were in the pegloticase 8 mg/2 wks group, 19 (22.6%) subjects were in the pegloticase 8 mg/4 wks group, and 5 (11.6%) subjects were in the placebo group. Serious AEs typically were experienced by single subjects, except for IRs which occurred in 4 (4.7%) subjects in the pegloticase 8 mg/2 wks group, 7 (8.3%) subjects in the pegloticase 8 mg/4 wks group, and 0 subjects in the placebo group. Other SAEs experienced by more than 1 subject in the pegloticase 8 mg/2 wks group included gout (4 subjects [4.7%]), arrhythmia (2 [2.4%]), and gastroesophageal reflux disease (2 [2.4%]). Gout was experienced by 2 (4.7%) subjects in the placebo group. No SAE was experienced by more than one subject in the pegloticase 8 mg/4 wks group. In comparisons between the pegloticase dose groups and placebo, no SAEs (by preferred term) were detected other than IRs that indicated a causal relationship to pegloticase dose administration.

Overall, the incidence of SAEs in the pegloticase groups was double in comparison to placebo (8mg/2 weeks: 23.5% vs 22.6% vs 11.6%).

It is recognised that incidences of serious AEs related to cardiac disorders were increased in comparison to placebo (0%) in the 8mg/2 weeks group, with a frequency of 4.7% and if chest pain is included 5.9%, and in the 8mg/4 weeks group with a frequency of 3.6%.

The incidence of severe infusion reactions (IR) was higher in the pegloticase 8 mg/4 wks group than in the pegloticase 8 mg/2 wks group: 9.5% vs. 4.7%, respectively. These IRs occurred very commonly and serious IRs were even common despite prior intensive prophylactic medication was applied to the patients. The frequency of IRs in the safety population being 100% of time on active treatment was 50% (38/76) in the pegloticase 8 mg/2 weeks group. The frequency of serious IRs in the safety population being 100% of time on active treatment was 13.2% (10/76) in the pegloticase 8 mg/2 weeks group. IRs are described to mostly occur within the first 4 months.

Deaths

Overall, there were 6 deaths. Five of them were in the pegloticase treatment arm. Subjects who were randomized in the two double-blind studies: 3 in the pegloticase every 2 wks group (C0405-203-001, cardiac arrest, unlikely to be related to study drug; C0406-301-003, *Staph. aureus* septicemia, unlikely to be related to study drug; C0406-315-005, sudden death attributed to cardiac arrhythmia, unlikely to be related to study drug); 2 in the pegloticase every 4 wks group (C0405-102-006, congestive heart failure, unlikely to be related to study drug; C0405-122-004, sepsis, unlikely to be related to study drug); and 1 in the placebo group (C0406-301-014, multi-system organ failure, not related to study drug).

Two of the 3 subjects in the pegloticase every 2 wks group who died had a most recent UA below 6 mg/dL. The one subject in the pegloticase every 4 wks group who died had a UA above 6 mg/dL. All subjects who died were older than 50 years of age and had multiple co-morbidities.

There were 2 additional deaths reported in subjects who received placebo in the double-blind studies, did not enroll in the OLE C0407 Study, and died approximately 4 months after participation in the

double-blind studies. None of the deaths appeared to be causally related to treatment, as judged by the Clinical Investigators and Savient Medical Monitors.

Laboratory findings

On the base of the submitted main clinically relevant laboratory findings (renal, liver, blood) no signal is apparent, however, no final conclusion could be made as the sample size is very small and most patients have several co-morbidities and co- medication.

Immunogenicity

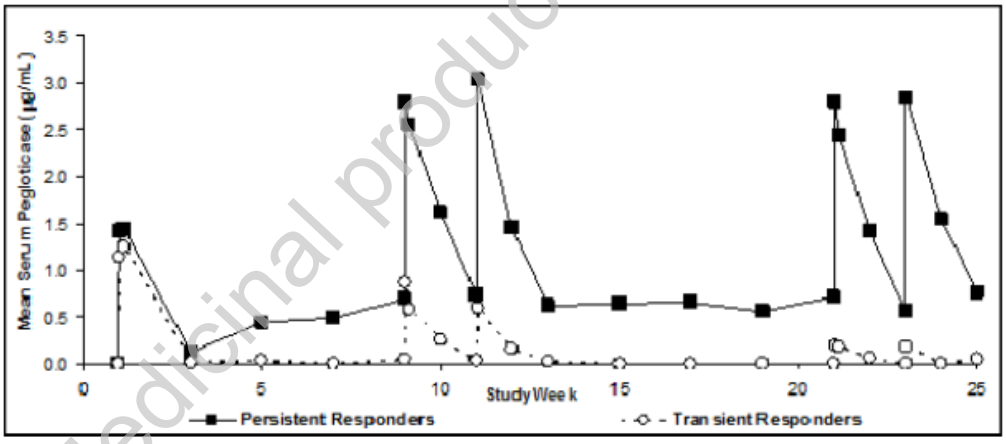
Anti-pegloticase antibodies were detected in 89% of subjects in the pegloticase 8 mg/2 weeks and pegloticase 8 mg/4 weeks treatment groups in the double-blind C0405 and C0406 Studies, and in 15% of the placebo group.

An increase in anti-pegloticase antibody titre was detected at week 3 following initiation of treatment with 8 mg pegloticase every two weeks. This relatively early onset suggested involvement of IgM antibodies in the immune response to treatment, which was confirmed by isotyping of all confirmed positive samples.

Impact on pharmacokinetics

The subjects in the pegloticase 8 mg/2 weeks treatment group with a transient response to pegloticase had a mean peak concentration of pegloticase that was approximately 70% lower (0.8 µg/mL) than for persistent responders at Week 9, attributable to more rapid clearance in the presence of higher levels of anti-pegloticase antibodies. The persistent responders in the pegloticase 8 mg every 2 week group had trough concentrations in the range of 0.5 to 0.7 µg/mL. See Figure 4.

Figure 4 Comparison of Mean Pegloticase Concentrations in Persistent and Transient Responders; Pegloticase 8mg/2 wks Group (Pooled Data C0405/C0406)

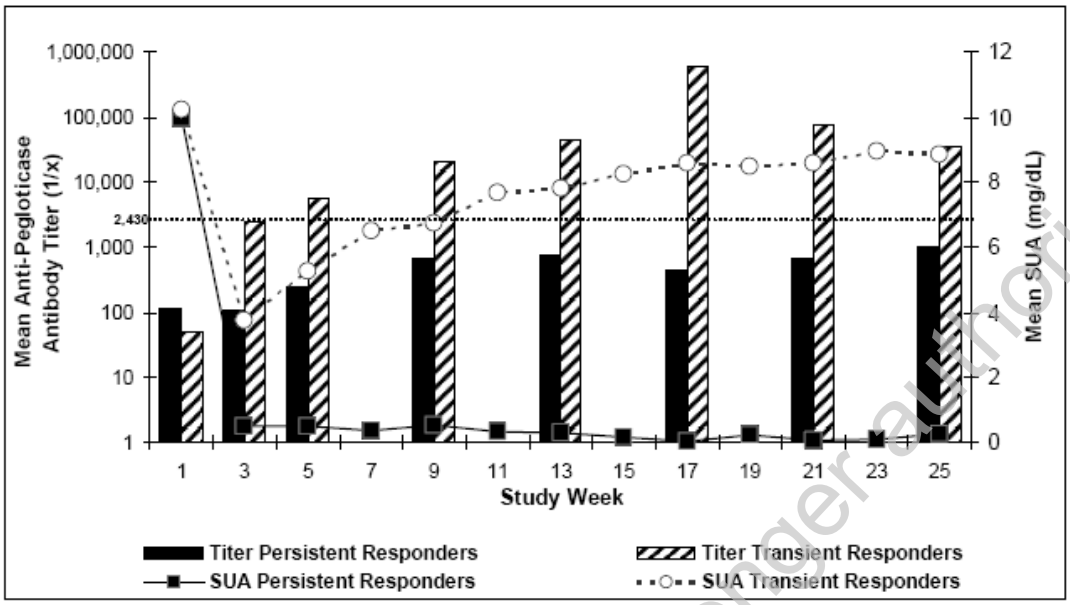


Source: 5.3.5.3 Pooled Data Analysis, Figure 15
Note: Peak concentrations of pegloticase following the 1st, 5th, 6th 11th and 12th infusions are shown as these were time points of more intense sampling. The remaining points are taken only at trough levels, i.e., immediately before study drug infusion.

Impact on efficacy

The detection of anti-pegloticase antibodies above a titre of 1:2430 was associated with a reduction in drug trough concentration and reduced therapeutic efficacy, as reflected in mean SUA levels exceeding the target of 6 mg/dL. In transient responders, SUA response was lost (defined as > 6 mg/dL) in 80% of subjects within the first few infusions and most (90%) within the first 9 weeks (see figure 5 below).

Figure 5 **Relationship between Anti-pegloticase Antibody Titer and SUA Comparing Persistent and Transient Responders; Pegloticase 8mg/2 wks Group (Pooled Data C0405/C0406)**



Loss of efficacy was not associated with detection of neutralising antibodies, as measured in an enzymatic assay.

Although the increased clearance of pegloticase with the resultant loss of SUA response is mediated by anti-pegloticase antibodies, there can be an apparent lag time between the onset of increased clearance and the presence of measurably increased antibodies in the serum. Therefore, measurement of anti-pegloticase antibody titres is not predictive of the loss of the SUA response, whereas monitoring SUA is a good surrogate for measuring the development of anti-pegloticase antibodies that cause increased clearance of administered pegloticase.

Impact on safety

There was a numerically higher rate of patients with IRs in the group of subjects who eventually manifested with high antibody titres (> 1:2430) (18/39; 46%) than in those whose titre remained low (4/46; 9%). No relationship was shown between antibody titres and severity of IRs.

The incidence of IR was lower in subjects who were responders to pegloticase and there were no severe infusion reactions in responders. In most pegloticase-treated subjects with IRs, loss of response to pegloticase (return to SUA > 6.0 mg/dL) preceded the time of the first IR. This observation points to the need for risk mitigation, i.e., monitoring serum uric acid with discontinuation of pegloticase when SUA > 6 mg/dL as indicated in the SmPC.

Safety in special populations

There are no safety studies in special populations.

Safety related to drug-drug interactions and other interactions

The CHMP considered acceptable that interaction studies were not conducted with pegloticase.

Discontinuation due to adverse events

A total of 34 subjects were reported in the clinical database as discontinued during the first 6 months of treatment due to an SAE, AE, IR, or gout flare. In the pegloticase 8 mg/2 wks group, 16 subjects were discontinued: 5 subjects discontinued due to gout flares and 7 subjects discontinued due to IRs. In the pegloticase 8 mg/4 wks group, 17 subjects were discontinued: 3 subjects discontinued due to gout flares and 10 subjects discontinued due to IRs. In the placebo group, 1 subject discontinued due to a gout flare and none discontinued due to IRs.

Post marketing experience

There have been no epidemiological studies and no post marketing studies with pegloticase.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

Infusion reaction

More patients experienced an IR on the E4W regimen than on the E2W regimen. Likewise, the percentage of pegloticase infusions with an infusion reaction was much lower (5%; 43/852) in the E2W arm than in the E4W arm (65/430; 15%). Most patients developed only one or two IRs and most IRs were of moderate intensity.

14 cases of anaphylaxis (7 definite and 7 potential) out of the 273 patients of the entire pegloticase clinical study database (Studies C0402, C0403, C0405, C0406, and C0407) were detected, i.e. a prevalence of 5.1%. These reactions occurred during or within 2 hours of pegloticase infusion. Symptoms of anaphylactic/anaphylactoid reaction included stridor, wheezing, perioral/lingual oedema, or hemodynamic instability, with or without rash or urticaria. Finally, 9/14 patients stopped treatment as a result of such reaction.

The applicant has proposed that pegloticase should be stopped if SUA > 6 mg/dL in two consecutive tests. A post-hoc analysis was carried out where various scenarios and simulations of stopping criteria based on SUA levels explored the effect of these stopping criteria on the response rates and IR rates simultaneously. According to the simulations the proposed SUA based algorithm will reduce the IR rate substantially (14%) but maintained the efficacy almost at the same level (41%). This algorithm has been included in the SmPC as a risk mitigation measure. Also, the ongoing (US) and planned (EU) observational studies are the only way to evaluate the effect of the proposed algorithm.

The statistically significant kg BW dose response relation suggests that patients over 100kg BW may not receive an optimal dose leading to a setting similar to an “interruption” of therapy. The applicant will further explore the optimal dose in patients with over 100kg BW, as documented in the risk management plan. Meanwhile the information above is reflected in the SmPC.

Serious cardiac events

An increased occurrence of cardiac adverse events in patients treated with Krystexxa has been observed, even if the data are limited. Because a preclinical signal has been detected for a cardiac risk (vacuoles) further preclinical studies were initiated and are ongoing to assess the impact of PEG on the heart.

Gout flares

Gout flare was the most common AE in the double-blind studies despite gout flare prophylaxis as seen with all effective urate lowering therapies. Most were mild to moderate in intensity, were generally tolerated by subjects but resulted in discontinuation of pegloticase therapy in 5 patients on pegloticase 8 mg/2 wks and 3 patients on pegloticase 8 mg/4 wks. Gout flares were especially frequent in the first 3 months of therapy (see efficacy section). A staggered dose escalation to achieve a more progressive PUA level reduction may reduce the frequency and severity of gout flares.

2.6.2. Conclusions on the clinical safety

IRs/anaphylaxis

Further data will be provided in a larger cohort of patients from the ongoing (US) and planned (EU) observational studies. Details of data collection are provided with the US study protocol and will be similar with the EU protocol and are considered the only way to evaluate the effect of the proposed algorithm.

Serious cardiac events

Preclinical studies are ongoing to assess the impact of PEG on the heart. Further data will be provided in a larger cohort of patients from the ongoing (US) and planned (EU) observational studies. Both data sets will be used to gain more information on the 'important potential risk' of worsening of congestive heart failure, other cardiac risks and long term cardiovascular safety.

Gout flares

The high incidence of gout flares is of concern, therefore, it should be investigated whether a staggered dose escalation may reduce the frequency and severity of gout flares. The applicant commits to conduct "Gout flare" interventional trial . Further data will be provided in a larger cohort of patients from the ongoing (US) and planned (EU) observational studies.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

In addition, the CHMP considered that the applicant should take the following minor points into consideration for future update to the Pharmacovigilance system:

- The flowchart should be expanded with more timelines for major processing steps.
- A summary of the information provided in the response document on the external safety committee should be included.
- The section on SOPs should be updated according to SOPs having been finalised by then.
- The description of the quality management system should be updated according to the comments in the clinical AR.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan

Table 38 Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important identified risks		
Acute effects on red blood cells due to G6PD deficiency	Routine PV with standardised acute onset anaemia follow-up questionnaire Proposed registry Internal safety committee oversight	SmPC section 4.3 will include a contraindication for Glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of haemolysis and methaemoglobinaemia. SmPC section 4.3 will include a recommendation that all patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) are screened for G6PD deficiency before starting KRYSTEXXA. SmPC section 4.4 will include: "If haemolysis and/or methaemoglobinaemia occur in patients receiving KRYSTEXXA, treatment should be immediately and permanently discontinued and appropriate measures initiated." SmPC section 4.8 will list haemolysis as an adverse reaction with not known incidence. Package leaflet section 2 will include an instruction to the patient not to use KRYSTEXXA if they have "6-phosphate dehydrogenase (G6PD) deficiency or favism." Package leaflet section 2 will include a precaution to inform his/her doctor if they have any inherited enzyme deficiencies which may lead to red blood cell destruction. Package leaflet section 4 will identify destruction of red blood cells as frequency not known.
Gout flare	Routine PV Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed 'Gout Flare' interventional trial Proposed registry	SmPC section 4.4 will include a sub-heading of Acute Gouty Attacks (Gout Flare) with a warning that an increase in gout flares is frequently observed upon initiation KRYSTEXXA as with other urate-lowering therapies, and inform that KRYSTEXXA does not need to be discontinued because of a gout flare. SmPC section 4.4 will include the following "To reduce the likelihood of gout flares after initiation of KRYSTEXXA prophylaxis with

	Internal safety committee oversight	colchicine or a non-steroidal anti-inflammatory drug (NSAID) is recommended. It is recommended that this start 1 week before initiation of KRYSTEXXA therapy and continued for at least 6 months, unless medically contraindicated or not tolerated". SmPC section 4.8 will include gout flares as a very common adverse reaction and include clinical trial data relating to gout flares Package leaflet section 2 will identify gout flares as common and include a warning that "An increase in gout flares is frequently observed when starting KRYSTEXXA." and note that "KRYSTEXXA does not need to be discontinued because of a gout flare." Package leaflet section 4 will identify gout flares as very common.
Severe infusion reaction	Routine PV with standardised allergic reaction follow-up questionnaire Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	SmPC section 4.2 will include the following "The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response." SmPC section 4.2 will include the following "Prior to infusions close monitoring of serum uric acid levels is required. KRYSTEXXA treatment should be discontinued if levels increase to above 360 µmol/l (6 mg/dl), particularly when 2 consecutive levels above 6 mg/dl are observed..." SmPC section 4.4 will include a sub-heading of Infusion-related Reactions and a warning that KRYSTEXXA can induce allergic responses. SmPC sections 4.2 & 4.4 will indicate that patients should receive pre-medication to minimize the risk of infusion-related reactions SmPC section 4.2 will indicate that KRYSTEXXA should infused over no less than 2 hours at a flow-rate of approximately 2ml/min SmPC section 4.2 & 4.4 will indicate that if an infusion-related reaction occurs the infusion may/can be slowed, or stopped and restarted at a slower rate, at the discretion of the physician SmPC section 4.2 will include a recommendation that patients are observed for approximately one hour post-infusion

		SmPC section 4.4 will include the following "Patients taking concomitant oral urate-lowering therapy may be at increased risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSTEXXA, patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA. There is the possibility that concomitant use of oral urate-lowering therapy may potentially mask the rise of SUA associated with the loss of response to KRYSTEXXA because of the development of anti pegloticase antibodies." SmPC section 4.4 will include a recommendation that patients are observed for an appropriate period of time after administration SmPC section 4.4 will state the following "Most infusion-related reactions have been observed when serum uric acid values were above 0.36 mmol/l (6 mg/dl). Therefore careful monitoring of serum uric acid values is recommended. Serum uric acid level should be measured prior to infusion. Discontinuation of treatment should be considered if levels increase to above 6 mg/dl, particularly in 2 consecutive treatment courses."
Severe infusion reaction *continued*		SmPC sections 4.2 & 4.4 will state the following "KRYSTEXXA should be administered in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and infusion reactions…" SmPC section 4.4 will include the following: "Very limited data are available from the clinical trials about re-treatment after interruption of therapy for one to six months. Because of the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of infusion reactions, including anaphylaxis. It is recommended that patients given repeat infusions of KRYSTEXXA after a treatment interruption be monitored carefully." SmPC section 4.8 will list infusion related reactions as a very common adverse reaction, list common signs and symptoms and include clinical trial data relating to infusion-related

		reactions. Package leaflet section 2 will include a warning that "If you stop taking KRYSTEXXA, and then are treated again, you may be at increased risk of infusion reactions, including anaphylaxis…" Package leaflet section 4 will identify severe allergic reactions as commonly reported, include symptoms of severe allergic reactions and instruct patients presenting with these to "tell your doctor or nurse IMMEDIATELY, since any of these may be signs of a serious allergic reaction." Package leaflet section 4 will identify that "…allergic reactions usually happen within 2 hours of the infusion, but may also happen at a later time."
Anaphylaxis	Routine PV with standardised allergic reaction follow-up questionnaire Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	SmPC section 4.2 will include the following "The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response." SmPC section 4.2 will include the following "Prior to infusions close monitoring of serum uric acid levels is required. KRYSTEXXA treatment should be discontinued if levels increase to above 360 µmol/l (6 mg/dl), particularly when 2 consecutive levels above 6 mg/dl are observed..." SmPC section 4.4 will include a sub-heading of Infusion-related Reactions and a warning that KRYSTEXXA can induce allergic responses. SmPC sections 4.2 & 4.4 will indicate that patients should receive pre-medication to minimize the risk of infusion-related reactions SmPC section 4.2 will indicate that KRYSTEXXA should infused over no less than 2 hours at a flow-rate of approximately 2ml/min SmPC section 4.2 & 4.4 will indicate that if an infusion-related reaction occurs the infusion may/can be slowed, or stopped and restarted at a slower rate, at the discretion of the physician SmPC section 4.2 will include a recommendation that patients are observed for

		approximately one hour post-infusion SmPC section 4.4 will include the following "Patients taking concomitant oral urate-lowering therapy may be at increased risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSTEXXA, patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA. There is the possibility that concomitant use of oral urate-lowering therapy may potentially mask the rise of SUA associated with the loss of response to KRYSTEXXA because of the development of anti pegloticase antibodies." SmPC section 4.4 will include a recommendation that patients are observed for an appropriate period of time after administration SmPC section 4.4 will state the following "Most infusion-related reactions have been observed when serum uric acid values were above 0.36 mmol/l (6 mg/dl). Therefore careful monitoring of serum uric acid values is recommended. Serum uric acid level should be measured prior to infusion. Discontinuation of treatment should be considered if levels increase to above 6 mg/dl, particularly in 2 consecutive treatment courses."
Anaphylaxis *continued*		SmPC sections 4.2 & 4.4 will state the following "KRYSTEXXA should be administered in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and infusion reactions…" SmPC section 4.4 will include the following: "Very limited data are available from the clinical trials about re-treatment after interruption of therapy for one to six months. Because of the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of infusion reactions, including anaphylaxis. It is recommended that patients given repeat infusions of KRYSTEXXA after a treatment interruption be monitored carefully." SmPC section 4.8 will list anaphylaxis as a common adverse reaction, list common signs

		and symptoms and include clinical trial data relating to anaphylaxis. Package leaflet section 2 will include a warning that "If you stop taking KRYSTEXXA, and then are treated again, you may be at increased risk of infusion reactions, including anaphylaxis…" Package leaflet section 4 will identify severe allergic reactions as commonly reported, include symptoms of severe allergic reactions and instruct patients presenting with these to "tell your doctor or nurse IMMEDIATELY, since any of these may be signs of a serious allergic reaction." Package leaflet section 4 will identify that "…allergic reactions usually happen within 2 hours of the infusion, but may also happen at a later time."
Antibody Development	Routine PV Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Internal safety committee oversight External safety committee oversight	SmPC section 4.4 will state the following "Most infusion-related reactions have been observed when serum uric acid values were above 0.36 mmol/l (6 mg/dl). Therefore careful monitoring of serum uric acid values is recommended. Serum uric acid level should be measured prior to infusion. Discontinuation of treatment should be considered if levels increase to above 6 mg/dl, particularly in 2 consecutive treatment courses." SmPC section 4.8 will list include clinical trial data relating to immunogenicity.
Concomitant use with oral urate lowering agents	Routine PV with standardised allergic reaction follow-up questionnaire Proposed registry Internal safety committee oversight	SmPC section 4.2 will include a recommendation that before starting KRYSTEXXA patients discontinue oral urate-lowering medication and do not institute therapy with oral urate-lowering medication whilst taking KRYSTEXXA. SmPC section 4.4 will include the following "Patients taking concomitant oral urate-lowering therapy may be at increased risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSTEXXA, patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA. There is the possibility that concomitant use of oral urate-lowering therapy may potentially mask the rise of SUA associated with the loss of

		response to KRYSTEXXA because of the development of anti pegloticase antibodies."
Worsening of congestive heart failure	Routine PV with standardised CHF follow-up questionnaire Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight External safety committee oversight	SmPC section 4.4 will contain the following "KRYSTEXXA has not been formally studied in patients with congestive heart failure, but a small number of patients with pre-existing cardiovascular conditions who were treated with pegloticase in the clinical trials had exacerbations of their congestive heart failure. Caution should be exercised when using KRYSTEXXA in patients who have congestive heart failure and patients should be monitored closely following infusion" SmPC section 4.8 will list worsening of congestive heart failure as an uncommon adverse reaction. Package leaflet section 2 will include a precaution to inform his/her doctor if they have any form of heart disease. Package leaflet section 4 will identify worsening of congestive heart failure as uncommon.
Important potential risks		
Delayed hypersensitivity reactions	Routine PV with standardised allergic reaction follow-up questionnaire Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	SmPC section 4.8 will include clinical trial data relating to infusion-related reactions, including an example of a delayed hypersensitivity reaction. Package leaflet section 4 will identify that "…allergic reactions usually happen within 2 hours of the infusion, but may also happen at a later time."
Re-administration of pegloticase to patients who have stopped pegloticase treatment for longer than four weeks	Routine PV including treatment history follow-up for serious cases Proposed registry Internal safety committee oversight	SmPC section 4.2 will include the following: "Limited data are available about retreatment after interruption of therapy for more than 4 weeks. It is therefore recommended that patients given repeat infusions of KRYSTEXXA after a treatment interruption be monitored carefully…" SmPC section 4.4 will include the following: "Very limited data are available from the clinical trials about re-treatment after interruption of therapy for one to six months. Because of the immunogenicity of KRYSTEXXA, patients

		receiving re-treatment may be at increased risk of infusion reactions, including anaphylaxis. It is recommended that patients given repeat infusions of KRYSTEXXA after a treatment interruption be monitored carefully." Package leaflet section 2 will include a warning that "If you stop taking KRYSTEXXA, and then are treated again, you may be at increased risk of infusion reactions, including anaphylaxis…"
Medication error	Routine PV Proposed registry Internal safety committee oversight	SmPC section 4.2 states "KRYSTEXXA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of severe refractory chronic gout." SmPC sections 6.6 & 4.2 detail the instructions for preparation and dosing/administration, respectively. Instructions for preparation are also provided in the package leaflet. SmPC section 4.9 states "No case of overdose with KRYSTEXXA has been reported during clinical development. The maximum dose that has been administered as a single intravenous dose during clinical studies was 12 mg. A post-marketing report documented administration of the contents of 2 vials (16 mg) without any adverse reaction related to KRYSTEXXA administration. It is recommended that patients suspected of receiving an overdose be monitored, and general supportive measures be initiated as no specific antidote has been identified."
Off-label use	Routine PV Proposed registry Internal safety committee oversight	SmPC section 4.1 states the indicated use as "…treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated.." Package leaflet section 1 indicates that: "Pegloticase is used to treat severe long-term gout in adult patients who also have one or more painful deposits of uric acid crystals under the skin that cause difficulty in carrying out daily activities and who do not respond or cannot take other anti-gout medicines."

Interaction of anti-pegloticase antibodies and pegylated products	Routine PV Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Internal safety committee oversight External safety committee oversight	SmPC section 4.5 will contain the following "As anti-pegloticase antibodies can bind to the PEG moiety of KRYSTEXXA, there may be potential for binding to other PEGylated products. This has not been studied to date; it is currently unknown whether the development of anti-PEG antibodies may reduce the efficacy of other PEGylated medicinal products" SmPC section 4.8 will list include a section of clinical trial data relating to immunogenicity Package leaflet section 2 will include a precaution to "Tell your doctor if you are taking, have recently taken or might take any other medicines. It is especially important to tell your doctor if you are currently taking other urate lowering medicines or medicines containing polyethylene glycol (PEG)."
Cardiac Arrhythmias and Ischemic Events	Routine PV Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	In the absence of specific safety signals relating to cardiac arrhythmias or ischemic events, the Applicant does not propose any risk minimisation activities at this time.
Cellulitis	Routine PV with standardised infection follow-up questionnaire for serious cases Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	SmPC section 4.8 will list cellulitis as an uncommon adverse reaction. Package leaflet section 4 will identify skin infection as uncommon.
Sepsis	Routine PV with standardised infection follow-up questionnaire for serious cases Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study)	In the absence of specific safety signals relating to sepsis, the Applicant does not propose any risk minimisation activities at this time.

	Proposed registry Internal safety committee oversight	
Serious Infections	Routine PV with standardised infection follow-up questionnaire for serious cases Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	In the absence of specific safety signals relating to serious infections, the Applicant does not propose any risk minimisation activities at this time.
Important missing information		
Long-term exposure	Routine PV including treatment history follow-up for serious cases Two observational studies (Proposed M0402 EU observational study and M0401 USA observational study) Proposed registry Internal safety committee oversight	SmPC section 4.4 will include: "The database for long term treatment from controlled clinical studies with Krystexxa is limited. This should be considered when the decision is made for a therapy longer than 6 months."
Use in patients <18 years	Routine PV including age follow-up for all cases Proposed registry Internal safety committee oversight	SmPC section 4.2 will identify that there are no available on the safety and efficacy of KRYSTEXXA in children below the age of 18 years. SmPC section 5.2 will include: "The pharmacokinetics of KRYSTEXXA has not been studied in children and adolescents" Package leaflet section 2 will include a warning that KRYSTEXXA has not been studied in children or adolescents under 18 years of age. Therefore, this medicine is not recommended in this age group.
Use in patients with a history of hyposplenism or splenectomy	Routine PV including medical history follow-up for serious cases Two observational studies (Proposed M0402 EU observational study and M0401	In the absence of specific safety signals relating to use in patients with a history of hyposplenism or splenectomy, the Applicant does not propose any risk minimisation activities at this time.

	USA observational study) Proposed registry Internal safety committee oversight	
Use in patients with a history of organ transplant	Routine PV including medical history follow-up for serious cases Proposed registry Internal safety committee oversight	In the absence of specific safety signals relating to use in patients with a history of organ transplant, the Applicant does not propose any risk minimisation activities at this time.
Use in patients with severe renal impairment	Routine PV including medical history follow-up for serious cases Proposed registry Internal safety committee oversight	SmPC section 4.2 will include "Based on similar efficacy and safety profiles of pegloticase in patients with creatinine clearance < and ≥ 50 ml/min, no dose adjustment is required for patients with renal impairment…" SmPC section 5.2 will identify that there have been no formal studies conducted to examine the effects of renal insufficiency on KRYSTEXXA pharmacokinetics.
Use in patients with severe hepatic impairment	Routine PV including medical history follow-up for serious cases Proposed registry Internal safety committee oversight	SmPC section 5.2 will identify that there have been no formal studies to examine the effects of hepatic impairment.
Use in pregnant women	Routine PV with standardised use during pregnancy follow-up questionnaire Proposed registry Internal safety committee oversight	SmPC section 4.6 will contain the following "There are no or limited amount of data from the use of KRYSTEXXA in pregnant women. Embryofetal development studies in rats do not indicate direct or indirect harmful effects with respect to reproductive toxicity…" "KRYSTEXXA is not recommended during pregnancy." Package leaflet section 2 will include "If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. It is recommended not to use KRYSTEXXA during pregnancy and breast-feeding."
Use in breastfeeding women	Routine PV with standardised use during breastfeeding follow-up questionnaire	SmPC section 4.6 will include the following "It is unknown whether KRYSTEXXA/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

	Proposed registry Internal safety committee oversight	Therefore, KRYSTEXXA should not be used during breast-feeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant." Package leaflet section 2 will include "If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. It is recommended not to use KRYSTEXXA during pregnancy and breast-feeding."

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

Description	Due date
M0402: EU Pegloticase post-marketing Observational Study Safety data of pegloticase use in adult hyperuricemic patients with severe debilitating chronic tophaceous gout and efficacy and safety data in re-exposed patients.	Study protocol within 2 months after Commission Decision
M0401: USA Pegloticase post-marketing Observational Study Safety data of pegloticase use in adult hyperuricemic patients with severe debilitating chronic tophaceous gout. The study is ongoing.	Study report due in December 2015.
"Gout flare" interventional trial A staggered dose escalation study to investigate if it may reduce the frequency and severity of gout flares.	Study protocol within 6 months after Commission Decision. Study report due in March 2016.
Registry / Drug Utilisation study Off-label use, medication error and re-administration of pegloticase to patients who have stopped pegloticase treatment for longer than four weeks will be addressed in the Drug Utilisation study that will provide a registry to cover all important identified and potential risks and missing information.	Study protocol within 6 months after Commission Decision

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

2.8. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

The beneficial effect of peglotiocase is its ability to effectively reduce uric acid level in patients who have failed to respond to conventional urate-lowering therapy. In the two main studies the primary endpoint achieved statistical significance and clinically relevant superiority versus placebo showing that the percentage of subjects achieving and maintaining plasma uric acid (PUA) levels <6 mg/dL for at least 80% of the time during Months 3 and 6 was 42.4% for pegloticase (8mg/2weeks) versus 0% for placebo (ITT-population, pooled data studies C0405 and C0406/6). In patients receiving pegloticase 8 mg/4weeks the difference was also significant but less pronounced.

The secondary endpoints showed for the intended therapeutic dose (8 mg/2 weeks) that the continuous lowering of plasma uric acid under the threshold of crystallisation induces a clinical improvement. For clinically relevant parameters as function, pain or tender and swollen joints a clinically meaningful improvement for the intended therapeutic dose could be shown compared to placebo at week 25. The marked decrease of PUA is mainly maintained over time so that uric acid can be mobilized from the tissue which is documented in gout tophi dissolving as from 3-5 month of treatment.

Uncertainty in the knowledge about the beneficial effects

Dose subgroup analyses indicate that PUA responses might be influenced by absolute bodyweight (BW) and might be modified in the elderly and in patients with renal impairment. This is supported by data from population pharmacokinetic analysis revealing an influence of the BSA and of the patient's creatinine clearance on the clearance of pegloticase. This might have an impact on dose selection for patients with renal impairment and different weight. However, as no obvious unexpected safety signals have been seen in the elderly and in patients with impaired renal function, a dose adjustment in these patients seems not justified. This is reflected in the SmPC. With regard to the efficacy in patients over 100kg BW, the SmPC indicates the lower response rates that were observed in these patients but also clarifying that the available data is not conclusive. The CHMP has recommended and the applicant has agreed to further explore the optimal dose in patients with over 100 kg BW in a dedicated study. This together with this information in the SmPC is considered adequate.

Long-term data are obtained from a very small (33 patients on stable dose of 8mg/2 weeks over a treatment duration of one year) and heterogeneous population with different co-medications. In principle, continuous PUA decrease is likely, however with a potential for patients to drop out because of loss of effect due to antibody formation. Furthermore, the optimal treatment duration with pegloticase has not been established. In light of these limitations, the benefit risk relation of a treatment should be re-assessed on an ongoing basis by the physician considering tophus resolution but also the increased risk and the initially increased burden for the patient. However, it is not considered justified to recommend stopping therapy after 6 months in those patients that maintain a

response with an acceptable tolerance. Therefore, the duration of treatment should be based upon maintenance of response (serum uric acid levels < 6 mg/dl) and clinical judgment, as stated in the SmPC. More data from long-term treatment will be provided by the ongoing (US) and planned (EU) observational studies as well as the registry, as specified in the risk management plan.

Risks

Infusion reactions (IRs) are very common (25.9%) in treatment with pegloticase (8mg/2 weeks) (pooled analyses C0405/06). These events potentially occur as anaphylaxis despite potent prophylactic measure. IRs are described to mostly occur within the first 4 months. To manage this identified risk a serum uric acid based algorithm has been developed and implemented in the SmPC. On the basis of a post hoc analysis of the two pivotal trials it seems that the incidence of IRs could be reduced to a calculated frequency of approximately 14% with this algorithm. The presented data also indicate that the 8mg/2 week regimen has the better risk profile and in contrary to the 8mg/4 week regimen the chance to reduce the IRs by means of the proposed algorithm. It should however be noted that in the first US post-marketing reports half the reactions occurred during the 2nd infusion. Since the proposed algorithm requires 2 consecutive pre-infusion levels > 6 mg/dl, only reactions potentially occurring after the 2nd infusion can be avoided using this algorithm. The potential of this algorithm to manage this risk needs therefore further data from post-marketing experience, and such data is considered key to the benefit risk of the product. An observational study will be conducted in the EU, and is a condition to the authorisation. The data from this study together with data from other sources identified in the risk management plan will be the basis for the evaluation of the effect of the proposed algorithm.

An increased occurrence of cardiac adverse events has been observed, even if the database is too small to detect a clear cardiac safety signal. Because a preclinical signal has been detected for a cardiac risk (vacuoles) further preclinical studies are ongoing to assess the impact of PEG on the heart. Additionally, further data will be provided in a larger cohort of patients from the ongoing (US) and planned (EU) observational studies. In the US study cardiovascular events are not a primary endpoint but it is understood that they are included in secondary endpoints in Serious Adverse Events. In the proposal for the EU Post Authorization Observational Study cardiovascular adverse events were included amongst others as primary endpoints; therefore the data from this study is considered key to the benefit risk. Both the US based observational study and the EU observational study will be used to gain more information on the worsening of congestive heart failure, other cardiac risks and long term cardiovascular safety.

Upon treatment initiation with pegloticase, gout flare frequency is distinctly increased at the beginning. To reduce the likelihood of gout flares prophylaxis with colchicine or a non-steroidal anti-inflammatory drug (NSAID) is recommended; this recommendation is included in the SmPC. Based on available data it is expected that continuous treatment with pegloticase decreases frequency and intensity of gout flares hence treatment does not need to be interrupted because of a gout flare, which should be managed concurrently as appropriate for the individual patient. Additional data on this identified risk will be obtained in a larger cohort of patients from the ongoing (US) and planned (EU) observational studies. Furthermore, the risk management specifies the conduct of a gout flare interventional study, which will investigate whether a staggered dose escalation may reduce the frequency and severity of gout flares at the initiation of treatment.

Uncertainty in the knowledge about the unfavourable effects

Overall the size of the safety data base is small with 208 patients having received at least one infusion of 8 mg pegloticase in the pivotal trials, half of them at the recommended E2W dosing regimen. However, this is considered reflecting the restricted indication for treatment of patients who have failed

to respond to conventional urate-lowering therapy. Also data on re-exposure is limited. Additional data including long-term data will be generated through the post authorisation safety study in the EU, which is a condition to the marketing authorisation.

Infusion related reactions show a tendency to occur in a greater proportion of patients in the higher weight group of >100kg since infusion reactions occurred in 53.7% for patients in the weight 70 to ≤100 kg weight group, and 70.0% of the patients in the >100 to ≤120 weight group, and 75% of patients in the >120 kg weight group, respectively. Also the anti-pegloticase antibody titers show higher levels of antibody in the higher weight groups. This information is reflected in the SmPC. The post-marketing authorisation study will enrich the data in this population.

Benefit-risk balance

Importance of favourable and unfavourable effects

Chronic gout is a debilitating disease, which may be associated with chronic pain or recurrent flares, joint deformities and/or joint destruction, disfiguring tophi, and renal impairment. Chronic gout results in activity limitations, reduction in quality of life. If a patient fails to respond to conventional urate-lowering therapy (xanthine oxidase inhibitors or uricosuric agents) or is unable to tolerate them, there is no alternative option currently available. Therefore, there is clearly an unmet medical need that pegloticase can address.

Pegloticase provides a very potent means to reduce serum uric acid to undetectable level, which translates in very important clinical benefit to the patient.

Three safety signals (infusion reactions/anaphylactic reactions, serious cardiac events, and gout flares) have been identified. The risk minimisation activities are considered adequate to manage these risks in this specific patient population. Additional data will be generated particularly through a post-authorisation safety study to be conducted in the EU, which is considered key to the benefit risk of the product.

Benefit-risk balance

The benefit risk balance for Krystexxa is positive for a very restricted group of severely affected patients, i.e. adult patients with severe debilitating chronic tophaceous gout who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated.

Discussion on the benefit-risk balance

The indication describes a very restricted group of severely affected patients with tophaceous gout which is the consequence of the chronic inability to eliminate urate as rapidly as it is produced. It is considered that for these patients the potential benefits of treatment with KRYSTEXXA outweigh the potential safety concerns, also considering the risk minimisation activities.

The ongoing (US) and planned (EU) observational studies will better characterise the long-term safety profile of the product, evaluate the effect of the recommended algorithm and, and evaluate the efficacy and safety with re-exposure to pegloticase after a treatment-free interval. Furthermore, to address the fact that during initial treatment with Krystexxa gout flare frequency is distinctly increased, likely due to a particularly effective reduction of SUA levels, a dedicated study to evaluate a dose titration approach to potentially mitigate gout flares when initiating pegloticase treatment will be performed.

Preclinical studies are ongoing to assess the impact of PEG on the heart and further data will be provided in a larger cohort of patients from the ongoing/planned observational studies to evaluate the cardiac risk with pegloticase. Additional data will be generated regarding the optimal dose in patients with over 100 kg BW.

The overall B/R of KRYSTEXXA is positive with the condition to perform the post-authorisation safety study in the EU as it is deemed key to the benefit risk.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Krystexxa in the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalize serum uric acid with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated (see Section 4.4) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical restricted prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

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

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

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

In addition, an updated RMP should be submitted:

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

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

Not applicable

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
M0402: EU Pegloticase post-marketing Observational Study The applicant should conduct a long-term EU observational study to end December 2018 on safety data of pegloticase use in adult hyperuricemic patients with severe debilitating chronic tophaceous gout and efficacy and safety data in re-exposed patients. The applicant should submit a yearly interim report.	Study protocol within 2 months after approval Commission Decision

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Pegloticase is qualified as a new active substance.