Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alpha-1 proteinase inhibitor

Proprietary Product Name: Prolastin-C

Sponsor: Grifols Australia Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
AAT	alpha1-antitrypsin (synonym for alpha$_1$ proteinase inhibitor)
AE	adverse event
Alpha$_1$ MP	Alpha$_1$-Proteinase Inhibitor (Human) Modified Process (Prolastin-C)
Alpha$_1$-PI	Alpha$_1$ Proteinase Inhibitor
ANCOVA	Analysis of covariance
ANOVA	analysis of variance
AUC	area under the curve
$AUC_{0\text{-}7\ days}$	AUC from Day 0 to Day7
$AUC_{0\text{-}last,\ wk8}$	AUC from start of infusion to the last sampling time during Week 8
$AUC_{0\text{-}10days,\ wk16}$	AUC from Day 0 to Day 10 during the 16 week double blind crossover phase
BALF	bronchial alveolar lavage fluid
BORG	Borg rating of perceived exertion scale
ChAMP	Study of pharmacokinetic comparability of Alpha-1 MP (11816)
CHMP	The committee for medicinal products for human use (EMA)
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
COPD	Chronic obstructive pulmonary disease
CT	computed tomography
DLCO	pulmonary diffusing capacity for co
ELF	anti-neutrophil elastase capacity in the lung fluid
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Meaning
FEV1	Change in forced expired volume in 1 second
FRC	functional residual capacity
GCP	Good clinical practice
GLP	Good laboratory practice
ICH	International Committee on Harmonisation
ITT	intent-to-treat
KCO	transfer factor of carbon monoxide
NE	Neutrophil elastase
PBS	phosphate buffered saline
PD	pharmacodynamic(s)
PI	Product information
PK	pharmacokinetic(s)
PSUR	Periodic safety update report
SGRQ	St George's Respiratory Questionnaire
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	14 October 2016
Date of entry onto ARTG	10 November 2016
Active ingredient:	Alpha-1-proteinase inhibitor (human)
Product name:	Prolastin-C
Sponsor's name and address:	Grifols Australia Pty Ltd Unit 5/80 Fairbank Road Clayton South VIC 3169
Dose form:	Powder for injection with diluent vial
Strengths:	1,000 mg
Containers:	vials
Pack size:	1 vial with diluent vial and two needles
Approved therapeutic use:	*Prolastin-C is an alpha-1-proteinase inhibitor (human, Alpha1-PI) indicated to increase serum Alpha1-PI levels in adults with congenital deficiency of alpha-1 antitrypsin and with clinically significant emphysema (FEV1 < 80%).* *The data for clinical efficacy of Prolastin-C is derived from changes in the biomarkers alpha-1 anti-protease level and CT lung density. Efficacy on FEV1 or patient relevant endpoints such as quality of life or pulmonary exacerbations has not been established in randomised clinical trials.* *Clinical trials have only included patients who were not smoking.*
Route of administration:	Intravenous infusion
Dosage:	The recommended dose of Prolastin-C is 60 mg/kg body weight administered intravenously once weekly. For further details see the Product Information.
ARTG number:	234553

Product background

This AusPAR describes the application by Grifols Australia Pty Ltd (the sponsor) to register Prolastin-C, alpha$_1$-proteinase inhibitor 1,000 mg powder for injection with diluent vial for the following indication;

> *Prolastin-C is indicated for chronic augmentation therapy of individuals with congenital deficiency of alpha PI (alpha 1 antitrypsin deficiency) with clinically demonstrable emphysema.*

Alpha-1 proteinase inhibitor ($alpha_1$-PI) (also referred to as alpha-1 antitrypsin (AAT)) is a protease inhibitor of the enzyme elastase, and also other enzymes including trypsin, chymotrypsin, C-1 inhibitor and thrombin.

$Alpha_1$-PI deficiency (also referred to as alpha-1-antitrypsin deficiency, AATD) is inherited as an autosomal co-dominant disorder. Affected individuals have inherited an abnormal AAT gene from each parent. Only some alleles are associated with clinically apparent AATD. Approximately 95% of all severely $alpha_1$-PI deficient patients are homozygous for the PiZ allele. Individuals with the PiZZ variant typically have serum $alpha_1$-PI levels less than 35% of the average normal level. Individuals with the Pi (null)(null) variant have undetectable $alpha_1$-PI protein in their serum. Individuals with these low serum $alpha_1$-PI levels that is, less than 11 µM, have a markedly increased risk for developing emphysema over their lifetimes. The lung disease in AATD is associated with too much elastase (for example, from exposure to pollutants, smoking, or, infection) and of insufficient protease inhibitor. A small proportion of patients with chronic obstructive pulmonary disease (COPD) have AATD.

In healthy individuals, $alpha_1$-PI is mainly produced in the liver and reaches the lungs by diffusion from the circulation and by local production in macrophages and bronchial epithelial cells. $Alpha_1$-PI provides over 90% of the defence against the elastolytic burden in the lower airways posed by neutrophil elastase.

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with $alpha_1$-PI deficiency. The intended goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease inhibitors. The maintenance of blood serum levels of $alpha_1$-PI above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection. Individuals with severe $alpha_1$-PI deficiency have been shown to have increased neutrophil and neutrophil elastase concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with $alpha_1$-PI less than 11 µM have emphysema attributed to $alpha_1$-PI deficiency.

Prolastin-C is a human plasma derived $alpha_1$-PI. Prolastin–C differs from the earlier versions of Prolastin in that the production process has been refined and incorporates additional steps such as cation exchange chromatography and nanofiltration. The modified process has the following advantages: increased quantity of $alpha_1$-PI that can be extracted per mL of plasma (therefore more efficient use of a scarce resource), and a higher concentration of solution (50 mg/mL) therefore lower fluid volume and infusion time.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 10 November 2016.

Overseas registration of Prolastin in the 1980s was based on showing that plasma concentrations of $alpha_1$-PI rose to at least 11 µM/L. A registry for patients with AATD was established in North America to gather clinical data. Other $alpha_1$-PI products (Zemaira, Aralast, Glassia) were registered in the US based on bioequivalence to Prolastin.

Overseas registration of Prolastin-C was based on bio-equivalence to Prolastin.

Prolastin-C is approved in the USA, Canada, Chile and Turkey.

In June 2015, the EMA approved the marketing of Zemaira (Respreeza) alpha$_1$-PI based on the results of the RAPID study (Phase III RCT with the primary endpoint of decline of computed tomography (CT) measured lung density).

At the time the TGA considered this application, a similar application had been approved in: USA, 2009; Argentina 2011; Canada 2010; Chile 2015; Columbia 2011; Puerto Rico 2009, Turkey 2014;) was under consideration in (Brazil, Uruguay).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

Structure

Human alpha$_1$-PI is a glycoprotein containing 394 amino acid residues. It is a typical member of the family of proteins that are serine protease inhibitors. Alpha$_1$-PI has a molecular weight of approximately 51,000 Daltons, and functions by forming a tight complex with target proteases.

Drug substance (active ingredient)

The drug substance is manufactured from human plasma by plasma fractionation and the final protein is purified from fraction IV-1 by several steps including PEG precipitation, depth filtration, solvent detergent incubation, anion and cation exchange chromatography and nano-filtration.

The issue of abbreviated drug substance specification has been put to the sponsor. Grifols agrees that in the absence of expansion of the testing listed in specification of the drug substance all future variations involving changes to any aspect of the manufacturing process in which data evaluation is required must be accompanied by characterization down to the product level and the specification (both release and shelf life) must meet the approved drug product specification. This is standard practice for Grifols any time a process change is made. This commitment has been recommended to the Delegate as part of the conditions of registration for this product.

Drug product

The drug product is formulated to a concentration of not less than 44 mg/mL with a specific activity of not less than 0.8 mg/mg. The drug product specification is considered adequate.

The proposed shelf life for this product is 36 months at not more than 25°C.

For reconstituted product, the proposal is to 'administer within 3 hours of reconstitution'. The proposed drug product shelf life is supported by the data provided.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Prolastin-C alpha-1-proteinase inhibitor (human) 1,000 mg, powder for reconstitution for injection.

Proposed Conditions of Registration

1. It is a condition of registration that all batches of Prolastin-C alpha-1-proteinase inhibitor (Human) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Prolastin-C alpha-1-proteinase inhibitor (Human) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

III. Nonclinical findings

Introduction

The submitted nonclinical dossier was substantially smaller than would be expected for an new chemical entity submission; a single pharmacology study was submitted to support efficacy, there was only a basic set of pharmacokinetic and toxicity studies, and no reproductive studies were submitted. Furthermore, the quality of the submitted studies was generally low. Overall, the submitted dossier was not generally compliant with the relevant guideline,[1] (the principles of which can be applied to plasma derived products), and is considered inadequate.

No data were provided to indicate how the batches of $alpha_1$-PI used in the animal studies compared with batches proposed for marketing. Many of the studies were old (for example, from the 1980s and 1990s) and changes in the manufacturing process over the course of the products' development have occurred. In any case, the absence of this information is not considered to be a major concern, given other more serious limitations with the submitted data.

Pharmacology

Primary pharmacology

A deficiency in $alpha_1$-PI (AATD) is an autosomal, co-dominant condition that is a known genetic risk factor for the development of COPD.[2] Several studies have indicated that elastases of both neutrophils and macrophages have been implicated in lung disease initiation and progression.[3] $Alpha_1$-PI, the major anti-protease in the lower respiratory tract, is considered to have a major role in protecting normal tissues from elastolytic effects. In the absence of $alpha_1$-PI (or with reduced levels) increased levels of neutrophils (for example, as a result of exposure to cigarette smoke) leads to increased damage to

[1] ICH S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals
[2] Chotirmall, S.H. et al. (2015) Alpha-1 proteinase inhibitors for the treatment of alpha-1 antitrypsin deficiency: safety, tolerability, and patient outcomes. *Ther. Clin. Risk Manag.* 2015 11: 143–151.
[3] Sandhaus, R.A. and G. Turino. (2013) Neutrophil elastase-mediated lung disease. *COPD* 2013; 10(S1): 60–63.

pulmonary tissues.[4] Treatment with exogenous alpha$_1$-PI in individuals with an alpha$_1$-PI deficiency and emphysema is suggested to alleviate the severity of emphysema.

In vitro, alpha$_1$-PI inhibited neutrophil elastase activity with picomolar potency (Ec_{50}, 22 to 99 pM). No studies were submitted demonstrating efficacy in an appropriate animal model. In a published study retrieved independently by the evaluator[5], treatment of transgenic CD-1 mice (expressing very low levels of human alpha$_1$-PI) with Prolastin (alpha$_1$-PI; 20 mg IP/mouse every 2 days), reduced neutrophil levels and lavage macrophages, increased airspace size and abolished the increase in tumour necrosis factor-alpha (TNF-α) levels seen following exposure to smoke. Together, the data generally support the proposed use of exogenous alpha$_1$-PI to augment the clinical signs of emphysema occurring as a result of a severe deficiency of alpha$_1$-PI. No comment can be made, however, on the appropriateness of the proposed clinical dose.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacology studies were submitted. Alpha$_1$-PI is a serine protease inhibitor that has the potential to inhibit other enzymes. Inhibitory potency against other proteases should have been examined.

Specialised safety pharmacology studies assessed effects on the cardiovascular system (male rats, female dogs and cynomolgus monkeys [both sexes]) and on haematology/coagulation parameters (male rats, male rabbits and cynomolgus monkeys [both sexes]). The pivotal cardiovascular studies in dogs and monkeys were good laboratory practice (GLP) compliant and adequately conducted. The age of the remaining studies influenced the quality of the study reports and design quality of the studies themselves. Nonetheless, no adverse effects were seen on cardiovascular function in rats (at 100 mg/kg IV), dogs and monkeys (at ≤ 240 mg/kg IV). The doses in the most relevant species (dogs and monkeys) were 4 times the clinical dose on a mg/kg basis. Although the dose ratios are modest, given the molecular weight of alpha$_1$-PI, it is not expected to interact with ion channels in the heart[6]. Altogether, alpha$_1$-PI may be considered to have a low risk of adverse effects on cardiovascular function.

Haematology and coagulation parameters were unaffected by treatment in rats (approximately 100 mg/kg IV), rabbits (100 mg/kg IV) and cynomolgus monkeys (240 mg/kg IV). Maximum doses were 4 times the clinical dose on a mg/kg basis.

In the submitted repeat dose toxicity study, there were no clinical signs of central nervous system (CNS) effects in rabbits that received IV doses of 288 mg/kg (approximately 5 times the clinical dose on a mg/kg basis). It is unclear if clinical signs were adequately monitored in the acute toxicity studies, as the reporting in these studies was extremely limited and do not meet the standard currently expected for a toxicity study report.

Blood gases were unaffected in rabbits that received 100 mg/kg IV alpha$_1$-PI, suggesting no overt effects on the respiratory system in this species. However, the dose tested is low (1.7 times the clinical dose on a mg/kg basis) and a clinically relevant acute effect on respiratory function cannot be definitively ruled out. Based on the anticipated pharmacology of alpha$_1$-PI, improved lung function may be expected with alpha$_1$-PI treatment to patients.

[4] Turino, G.M. (2002) The origins of a concept: the protease:antiprotase imbalance hypothesis. *Chest* 2002; 122: 1058–1060.
[5] Churg, A., et al (2003) α_1-Antitrypsin ameliorates cigarette smoke-induced emphysema in the mouse. *Am. J. Respir. Crit. Care Med.* 2003; 168: 199–207.
[6] Vargas, HM. et al. (2008) Scientific review and recommendations on preclinical cardiovascular safety evaluation of biologics. *J. Pharmacol. Toxicol. Methods 2008;* 58**:** 72–76.

Pharmacokinetics

The pharmacokinetics of alpha$_1$-PI was generally typical for this type of compound. Following IV administration, the elimination half-life was long in rabbits and human subjects (approximately60 h and 146 h, respectively). The volume of distribution was low in rabbits (less than total body water). Consistent with this, tissue distribution of radioactivity in rabbits after IV administration of radiolabelled alpha$_1$-PI was limited, with levels generally below blood levels. Following IV administration significant levels of alpha$_1$-PI were seen in bronchial alveolar lavage fluid (BALF) of cynomolgus monkeys, suggesting some localisation of the protein to the lungs, the intended site of pharmacological action.

No metabolism or excretion studies were submitted, which is considered acceptable given the protein nature of the drug.

Overall, the pharmacokinetic profile of alpha$_1$-PI in rabbits and humans was qualitatively similar, thus supporting the use of the chosen animal species in the toxicity study (based on pharmacokinetic parameters only).

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were submitted. Given the protein nature of alpha$_1$-PI, pharmacokinetic drug interactions involving cytochrome P450 (CYP450) enzymes are not expected.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice, rats and rabbits. The clinical route (IV) was used in all species. The observation period (14 days) was adequate. Given the plasma half-life of the test item (approximately 60 h in rabbits), animals are still likely to have had circulating alpha$_1$-PI at the end of the study. The study reports were of poor quality, with the details of clinical signs, body weight and necropsy findings not fully documented or tabulated. As a result of the limited reporting, target organs for toxicity could not be determined from these studies. The doses tested were extremely high, exceeding the limit dose in rodents. Only males were examined; normally both sexes should be examined. In fact, only males were used in all submitted toxicity studies. Maximum non-lethal doses were 2,500 mg/kg IV in mice and 517.5 mg/kg IV in rabbits (42 and 9 times the clinical dose, respectively, on a mg/kg basis). A maximum non-lethal dose was not determined in rats (deaths were observed at the lowest tested dose of 2,500 mg/kg IV), but the LD50 was determined to be approximately 3,625 mg/kg IV in this species (60 times the clinical dose on a mg/kg basis), indicating that alpha$_1$-PI has a low order of acute toxicity by the IV route.

Deaths were seen in mice at ≥ 3,125 mg/kg IV and rats at ≥ 2,500 mg/kg IV; no rabbits died prematurely (maximum tested dose, 517.5 mg/kg IV). These deaths generally occurred soon after dosing and may be associated with the injection process (large volumes of liquid containing protein) rather than an actual drug related effect. One rat that received the vehicle only (phosphate buffered saline (PBS)) also died immediately after dosing. The vehicle chosen was possibly not the best control article to use. Perhaps a control article containing an equivalent amount of another relatively innocuous protein (such as albumin) may have been a more appropriate control. The maximum dose volumes used in rodents (156 mL/kg to mice and 125 mL/kg to rats) exceed the maximum recommended volumes for IV administration in these species (25 mL/kg and 20 mL/kg,

respectively;[7] dosing is estimated to have occurred over no more than 5 minutes), further lending support to the suggestion the deaths are an artefact of the dose volumes used rather than a direct drug related effect.

Repeat dose toxicity

Only one repeat dose toxicity study was submitted; a 5 day repeat dose toxicity study in rabbits with a 4 week recovery period. Findings with two lots of alpha$_1$-PI were compared. Only one species was used. Normally toxicity in two species (including a rodent species) would be examined. The rationale for the choice of species is unclear. Rabbits are an atypical animal species to be used in general toxicity studies. It is unknown if alpha$_1$-PI is pharmacologically active in this species, therefore, it is unknown if this is a relevant species to test the toxicity of alpha$_1$-PI. Only males were assessed (aside from a single female animal that was sexed incorrectly); both sexes would normally be used in a pivotal repeat dose toxicity study. The toxicity of alpha$_1$-PI has not been investigated in females. The dosing period of the study was only 5 days, which is too short in duration for any chronic toxicities to manifest. For a biotechnology product intended for chronic use, a 6 month repeat dose toxicity study would normally be expected, unless an adequate explanation is provided to justify a study of shorter duration[8]. No such justification was provided. Group sizes were too small (5/group; main and recovery groups, with two animals dying during the course of the study and one animal sexed incorrectly). The observations and examinations performed were inadequate; organ weights were not assessed and only a limited set of tissues was examined histopathologically. Only one dose level was assessed. Normally multiple doses would be expected to assess the relationship of findings to dose.[8,9] However, the magnitude of the dose tested (288 mg/kg; 5 times the clinical dose on a mg/kg basis) may be considered acceptable given the volume of liquid injected; larger volumes would not have been appropriate on animal ethics grounds. The clinical route of administration (IV) was used, and dosing was more frequent than that proposed clinically (daily compared with weekly in patients).

There were no adverse effects on bodyweight gain, haematology or clinical chemistry parameters. The only notable effect observed during post-mortem analyses was a minimal mild chronic interstitial nephritis observed in 3/5 rabbits that received one lot of alpha$_1$-PI. This finding has an uncertain relationship with treatment.

The absence of any other findings should be interpreted with caution given the numerous serious limitations of the repeat dose toxicity programme.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were submitted as is usual for most biotechnology derived pharmaceuticals (ICH S6). Based on its chemical nature, alpha$_1$-PI is not expected to interact directly with DNA and therefore has a low potential for genotoxic effects.

Reproductive toxicity

No reproductive toxicity studies were submitted. The tissue distribution study did not examine localisation to reproductive tissues and the only submitted repeat dose toxicity study did not examine effects on reproductive tissues, hormones, oestrous cycling or sperm parameters. (As well, the study was not of sufficient length nor in an appropriate

[7] Derelanko, M.J. and M.A. Hollinger. Eds. CRC Handbook of Toxicology. CRC Press Inc, Florida, USA.
[8] ICH S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals.
[9] Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1)

species to do this; furthermore females were not used). Therefore, no comment can be made regarding possible effects of treatment on fertility.

It is unknown if alpha$_1$-PI crosses the placenta. Effects on the developing embryo/fetus are unknown.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2[10]. This category is considered appropriate as it is for drugs in which animal studies examining embryofetal development effects are lacking.

Local tolerance

One study made detailed examinations of injection sites following IV administration to rabbits. A minimal inflammatory reaction (lymphohistiocytic infiltrates) was seen at a number of injection sites. Injection site reactions may be seen in patients.

Paediatric use

Alpha$_1$-PI is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- In vitro, alpha$_1$-PI inhibited neutrophil elastase activity with picomolar potency. Reduced pulmonary neutrophil levels were seen following IP administration of alpha$_1$-PI in a mouse model of emphysema associated with reduced alpha$_1$-PI levels. These pharmacology studies lend some support to the proposed clinical use of alpha$_1$-PI.
- No secondary pharmacology studies were submitted.
- There were no adverse effects on cardiovascular function in dogs and monkeys or haematology and coagulation parameters in monkeys with single IV administration at 4 times the clinical dose.
- The pharmacokinetics of alpha$_1$-PI were generally typical for this type of compound, characterised by a long half-life, low volume of distribution and limited tissue distribution following IV administration to rabbits. Significant levels of alpha$_1$-PI were seen in BALF of cynomolgus monkeys following IV administration, suggesting some localisation of the protein to the lungs, the intended site of pharmacological action.
- Alpha$_1$-PI had a low order of acute IV toxicity in mice, rats and rabbits.
- The repeat dose toxicity programme for alpha$_1$-PI was very limited. Only one repeat dose toxicity study was submitted; a 5 day study in rabbits with a 4 week recovery period. This study had many design flaws which affects the utility of this study for regulatory purposes. The only notable effect observed during post-mortem analyses was a minimal mild chronic interstitial nephritis observed in 3/5 rabbits that received one lot of alpha$_1$-PI. This finding has an uncertain relationship with treatment. The absence of any other findings should be interpreted with caution. There was no investigation of repeat dose toxicity in a second species.

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

- No metabolism, excretion, pharmacokinetic drug interaction, genotoxicity or carcinogenicity studies were submitted, which is considered acceptable given the protein nature of the drug.
- No reproductive toxicity studies were submitted.
- No clinically relevant toxicity findings were identified in the submitted nonclinical dossier. However, the overall quality of the nonclinical data set was low and the scope extremely limited. Due to numerous serious deficiencies in the repeat dose toxicity programme, evidence of safety has not been properly demonstrated in laboratory animal species, and potential toxicity neither identified nor well characterised. Registration should only proceed if the clinical data are sufficient to allay these concerns.
- The nonclinical evaluator also made other comments on the safety specification of the risk management plan and PI but presentation of these is beyond the scope of the AusPAR.

IV. Clinical findings

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

Introduction

Clinical rationale

The clinical activity of Prolastin-C is related to the ability of the alpha$_1$-PI molecule to inhibit tissue proteinases, especially neutrophil elastase. An excess of neutrophil elastase is an important etiologic agent in the development of the lung tissue damage observed in patients with panacinar emphysema due to congenital alpha$_1$-PI deficiency. The augmentation of alpha$_1$-PI in the lower lung of congenital alpha$_1$-PI deficient patients could thus potentially reduce panacinar damage. Thus to support intravenous alpha$_1$-PI therapy, first it has to be proven that intravenously administered alpha$_1$-PI penetrates to the lower lung and that it exerts its inhibitory action on elastase secreted by lung neutrophils (using activity assays in bronchoalveolar lavage fluid (BALF)). Then it needs to be shown that the presence of alpha$_1$-PI in the lung is correlated with improvement in lung function, quality of life and survival. The submission presents data to show the first part of this hypothesis. Data on changes in imaging surrogates in one trial and other published manuscripts are used to examine the effect of Prolastin on lung function. There was no information on patient related endpoints such as quality of life or survival.

Contents of the clinical dossier

The submission contained the following clinical information;

- Three literature searches; two in Scopus and one in Cochrane database.
- Clinical study reports (Reports of human Pharmacokinetic studies, Patient pharmacokinetic and initial tolerability studies, Reports of human pharmacodynamic (PD) studies
- Study reports of controlled clinical studies (Study report number: 100533/EudraCT No: 0010/0251)
- Study reports of uncontrolled clinical studies,

- Reports of post-marketing experience, literature references.
- Individual patient data pertaining to this study are stated to be available electronically, listing and narratives of adverse events, serious adverse events, discontinuations and deaths were provided.
  - STAMP: Safety and Tolerability of Alpha-1 MP (Prolastin–C): Study 11815; multi-centre, open label trial to evaluate the safety and tolerability of Alpha-1 MP in subject with AATD.
  - ChAMP: Pharmacokinetic Comparability of Alpha-1 MP (Prolastin-C): Study 11816; multi-centre, randomized, double blind, crossover trial to evaluate the pharmacokinetic comparability of Alpha- 1 MP to Prolastin in subjects with AATD.
  - EXACTLE: The EXAcerbations and Computed Tomography scan as Lung Endpoints: Study 100533; multi-centre, randomized trial with IV Prolastin to evaluate frequency of exacerbations and progression of emphysema by means of multi-slice computed tomography (CT) scans in patients with congenital AATD. Data from this study was pooled with similar data to examine effects of Prolastin on CT guided change in lung function (published as Stockley 2010[11]).

Paediatric data

The submission did not include paediatric data and is not requesting use in a paediatric population. Specifically, the sponsor has not submitted data to the US Food and Drug Administration for any of the four paediatric age ranges for the use(s) in this application to TGA. There is no agreed Paediatric Investigation Plan (PIP) in Europe and no waiver to submit a PIP has been sought.

Good clinical practice

All trials were stated to be in compliance with good clinical practice (GCP) and International Conference on Harmonisation (ICH) recommendations, as well as applicable local, state, and federal regulations and guidelines regarding the conduct of clinical trials.

Pharmacokinetics

Studies providing pharmacokinetic data

The absence of biopharmaceutic and bioavailability data was justified by the sponsor because the active ingredient of Prolastin-C is a human plasma protein and it has not been modified during the manufacturing process. The bioavailability of the product and of the natural protein is the same.

A single pharmacokinetic (PK) study (ChAMP) was provided in addition to 4 PK published studies.

For the full details of the evaluation of this study please see Attachment 2, extract from the clinical evaluation report.

[11] Stockley RA et al 2010 Therapeutic efficacy of alpha-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry. *Respiratory Research* 2010; 11:136-144

Evaluator's conclusions on pharmacokinetics

The ChAMP study has shown that when administered at a dose of 60 mg/kg alpha$_1$-PI per potency or functional activity assay, alpha-1 MP (Prolastin-C) has PK comparability to Prolastin based on the primary endpoint ($AUC_{0\text{-}7\ days}$ of plasma alpha$_1$-PI measured by potency or functional activity assay; 155.9 mg.h/mL for Prolastin-C and 152.4 mg.h/mL for Prolastin, point estimate and 90% confidence interval of 1.03 and 0.97 to 1.09, respectively). The point estimate and 90% confidence interval of the geometric least-squares mean ratio, Prolastin-C versus Prolastin, for $AUC_{0\text{-}7\ days}$ by the content assay, were also calculated at 0.98 and 0.95 to 1.02, respectively.

Alpha-1 MP (Prolastin-C) and Prolastin administered at the same dose of 60 mg/kg alpha$_1$-PI per potency assay produced comparable mean trough concentrations of plasma alpha$_1$-PI, 16.9 and 16.7 µM, respectively, as measured by the antigenic content assay.

The published literature showed some inconsistencies with this data. The Hubbard study supported the findings; here after a single 250 mg/kg dose, serum alpha$_1$-PI concentrations remained above the 80 mg/dL level for 21 days and the concentration above the pre-infusion alpha$_1$-PI concentration for 28 days. Anti-neutrophil elastase capacity in the lung fluid (ELF) levels was elevated at 7, 14 and 28 days after each monthly infusion. ELF alpha$_1$-PI was more than 10 fold higher than the pre-infusion ELF alpha$_1$-PI level. The ELF alpha$_1$-PI levels 28 days post infusion of 2.35 µmol were nearly 7 fold higher than the pre-infusion level and higher than the theoretical 'threshold' of 1.3 µmol. The infusion was well tolerated and no new adverse events (AEs) were noted in the chronic study of 12 months. However it was noted that despite the increase in ELF alpha$_1$-PI, pulmonary status did not change.

In another study (Wewers 1987)[12], there was a 4 fold increase in serum alpha$_1$-PI concentrations and a 2 fold increase in capacity of the lung to inhibit neutrophil elastase capacity over the 5 to 6 months with both serum concentrations of serum alpha$_1$-PI and serum anti-neutrophil elastase activity elevated during LT (up to 6 months) use in 21 patients.

However in another study (Barker)[13], 23 patients given 120 mg/kg IV infusion every 2 weeks did not maintain a nadir concentration above 70 to 80 mg/dL for most patients. The serum alpha$_1$-PI and neutralizing elastase levels correlated but did not correlate with lung BALF alpha$_1$-PI or neutralizing elastase levels (measured in 5 people). AEs did occur; there was one discontinuation after the first infusion and almost all had AEs judged probably or possibly related to study drug. Further, despite the infusions, the FEV1 did not change and the FVC declined 0.17L.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 1: Studies providing pharmacokinetic data

PD	PH-30125 Gottlieb, D. J. 2000	5.3.4.1, Vol. 7 5.4, p. 559	- Desmosine / Isodesmosin excretion - Connective tissue degradation-	multicenter, prospective, open-labeled, uncontrolled	Prolastin; 60 mg/kg; weekly I.V.	12	Patients with PiZZ, PiZ Null, PiNull Null	8 weeks	Complete; Full
PD / PK	PH-30567 Stockley, R. A. 2002	5.3.4.2, Vol. 8 5.4, p. 523	Biochemical and clinical effects	single center, open-labeled	Prolastin; 60 mg/kg; weekly I.V.	12	Patients with PiZZ	4 weeks	Complete; Full

[12] Wewers, MD et al 1987 Replacement therapy for Alpha1-antitrypsin deficiency associated with emphysema. *N Engl J Med* 1987; 316: 1055-1062

[13] Barker AF et al 1997 Pharmacokinetic study of α1-Antitrypsin Deficiency. *Chest* 1997; 112: 607-613.

- Study PH30125[14]
- Stockley 2002; BAYX5747 200034 – PH 30567/1 Report 2001[15]

Evaluator's conclusions on pharmacodynamics

Study PH30125 showed that using a biochemical assay or urinary excretion of desmosine, baseline levels of desmosine in this population group with AATD were very high but that 8 weeks of IV alpha$_1$-PI therapy did not change this. It raises issues as to whether the protective levels of alpha$_1$-PI are insufficient or if elastin degradation is dependent on other pathways. It is likely that Prolastin is not be having even an acute effect on these excretion parameters as evidenced by the lack of difference in peak and trough values.

BAYX5747 200034 – PH 30567/1 Report 2001 similarly showed that although the alpha$_1$-PI concentration increased post infusion, that there were no beneficial effects on PD parameters or BORG score[16] seen. Infusion AEs were reported.

Dosage selection for the pivotal studies

The dosage selected for the single pivotal study is N/A as there was no pivotal study. PK data suggested the dosage requested in the indication of 60 mg/kg weekly is reasonable.

Efficacy

For evaluation of the studies which provided evidence of efficacy please see Attachment 2, extract of the clinical evaluation report.

Evaluator's conclusions on efficacy

In the comparative study disease progression was demonstrated in both treatment groups using CT densitometry to assess emphysema severity. There was no difference in the primary endpoint.

There was a treatment difference in the rate of lung density progression (unadjusted 15th percentile of lung density) between the Prolastin and placebo groups of 1.472 (95% confidence interval: 0.009 to 2.935), p = 0.049. But when adjusted for total lung capacity (TLC) this was no longer significant. There was a non-significant trend evident in the four analysis methods used for primary efficacy endpoint analysis perhaps suggesting a slight deceleration of lung density decline in the Prolastin group.

Prolastin was associated with significantly less severe exacerbations but it did not have a significant effect on duration or number of exacerbations.

Prolastin did not have an effect on FEV1 or transfer factor of carbon monoxide (KCO) and pulmonary diffusing capacity for CO (DLCO) indicated any advantage of the Prolastin treatment. All of these parameters consistently reflected a deterioration of lung function. As to be expected, the speed of deterioration was not markedly different under Prolastin treatment when compared to placebo treatment (all p values > 0.1; random coefficient regression model). These results were further in accordance with the results referring to other lung function parameters.

[14] Gottlieb, D.J., et al. 2000 Short-term supplementation therapy does not affect elastin degradation in severe alpha1-antitrypsin deficiency". The American-Italian AATD Study Group. *Am J Respir Crit Care Med*, 2000. 162: 2069-2072.
[15] Stockley, R.A., et al. (2002) The effect of augmentation therapy on bronchial inflammation in alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med*, 2002; 165: 1494-1498.
[16] The Borg Rating of Perceived Exertion (RPE) is a way of measuring physical activity intensity level

The interpretation of the pooled dataset (Stockley[17]) is unclear as is the clinical significance of a difference in lung density of 1.01 g/L over 2.5 years which not discussed.

Overall, Prolastin may have minor effects on lung decline; however these are likely to be small and clinically insignificant. There is no effect on quality of life.

Safety

Studies providing safety data

For evaluation of the studies providing safety data and other safety aspects please see Attachment 2, extract of the clinical evaluation report.

Evaluator's conclusions on safety

STAMP Study; functional Alpha-1 MP (Prolastin–C) administered at a dose of 60 mg/kg for 20 weeks was safe and well tolerated in naïve and non- naïve adult subjects with AATD. Overall, the adverse event (AE) profile of $alpha_1$-PI as Prolastin-C in both naïve and non-naïve subjects was consistent with the known AE profile of $alpha_1$-PI as Prolastin. There was no treatment emergent safety concerns with regard to clinical laboratory assessments, including immunogenicity test results and vital signs, and there were no viral seroconversions for Hepatitis B, Hepatitis C, Human Immunodeficiency Virus, or Parvovirus B19.

Other studies show 'immune' like reactions such as rash, urticaria, chest tightness, which is well known to occur with this medicine, occurred infrequently. There were no new concerns in the studies and no new concerns highlighted by the periodic safety update report (PSUR).

First Round Benefit-Risk Assessment

First round assessment of benefits

The sponsor's application in favour of registration is in the biochemical efficacy of augmentation therapy for the treatment of alpha-1 antitrypsin deficiency. These studies are found in the clinical module. The literature review was provided to support clinical efficacy of alpha-1-PI as augmentation therapy in patients with severe AATD and clinically evident emphysemas.

It is the opinion of the evaluator that Prolastin-C increases lung $alpha_1$-PI concentration. Further that Prolastin-C is effective on the inhibitory actions on lung elastase.

The literature review did not clearly demonstrate a benefit of biochemical improvement on clinical outcome.

The literature review did not clearly demonstrate a clear relationship of surrogate marker such as CT measurements to clinical outcomes in this patient group. Further the effects of Prolastin on clinically relevant surrogates of lung disease in this submission were not consistent. There was variable discussion in the literature provided regarding the most appropriate surrogate in lung imaging for this endpoint in this particular condition.

[17] Stockley RA et al 2010 Therapeutic efficacy of alpha-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis of 2 randomised clinical trials using computed tomography densitometry. *Respiratory Research* 2010; 11:136-144

Thus the benefit of Prolastin-C in the proposed usage is thus to increase concentrations of lung alpha$_1$-PI concentrations and inhibitory effects of neutrophil elastase function.

There were two additional potential clinical efficacy benefits seen in the placebo controlled study. The applied analysis of covariance (ANCOVA) model demonstrated a treatment difference in the rate of lung density progression between the Prolastin and placebo groups of 1.472 (95% confidence interval (CI): 0.009 to 2.935), p = 0.049. But note that when TLC adjusted this was not significant.

Further, one of the secondary endpoints, analysis of the lung sub-regions, was significantly different between the two groups. Here a significant change in unadjusted lung density using slope analysis was seen when comparing the decrease in lung density in the basal third of the lung; between Prolastin and placebo. Comparison of the slopes of the decrease in lung density in the middle and apical thirds did not identify a significant difference however. Further, the mean lung volume values remained nearly unchanged from baseline to endpoint in both treatment groups and were not significant.

There was no improvement in quality of life raising the issue of uncertainty in benefit.

Clinical trial data on clinical benefits of this drug including morbidity and mortality will be presented in the near future. SPARTA is one such Phase III study with comparative and clinical endpoint data. This is a three year randomised, placebo controlled trial that is currently recruiting. It aims to assess the efficacy and safety of two separate doses of Prolastin-C (60 and 120 mg/kg) administered weekly over 3 years in patients aged 18 to 70 years with a diagnosis of AATD and clinical evidence of pulmonary emphysema. The primary measure of efficacy is a change from baseline whole lung 15th percentile lung density (PD15). Secondary efficacy variables will be the evaluation of severe chronic obstructive pulmonary disease exacerbations and PD15 of the basal lung region using CT densitometry. The study will also examine the evidence for the justification of the surrogate endpoints.

Overall it is the evaluator's opinion that the biochemical improvement noted with Prolastin has not been demonstrated to result in a clinically relevant translation of those results as may be seen with increased density of lung, improved lung capacity or improved quality of life.

First round assessment of risks

Adverse events are reported with this therapy. These are relatively minor and uncommon and consist predominantly of allergic/urticarial symptoms. Psoriasis is a reported event, the incidence of which should be monitored.

The infusion has been used for 30 years.

First round assessment of benefit-risk balance

Prolastin-C is accepted as being bioequivalent to Prolastin; however data on clinical benefits (including quality of life) of this therapy is needed.

The benefits to date are in the improvement of the concentrations of alpha$_1$-PI, which per se are suggestive but not yet proven as improving patient outcomes. The latter has not been demonstrated in current data, in the literature review provided nor any such randomised controlled clinical trials.

There are minor side effects with the therapy and potential effects on quality of life regarding need (cost/time) for infusions.

This assessment is thus negative; predominantly because of the lack of documented clinical benefit (notwithstanding the biochemical benefit). The risk of assuming a clinical

benefit from a biochemical benefit of Prolastin-C in the proposed usage is that increasing levels of protein may not be related to improved disease status that is the effect of alpha$_1$-PI therapy on pulmonary exacerbations, quality of life, morbidity and mortality (including the progression of emphysema in AATD). There are several reasons why this may be the case including a lack of knowledge around the disease process (for example other pathways or processes to damage respiratory tissue) or a need for concentrations to be consistently above a 'threshold' rather than just the maximum concentration (C_{max}).

First Round Recommendation Regarding Authorisation

Reject because of lack of convincing evidence of efficacy on patient relevant/patient important endpoints. The safety is well understood and well characterised. The product (or its bioequivalent precursor, Prolastin) has been marketed in high income countries with sophisticated systems for post-marketing surveillance (similar to those in Australia) for nearly 30 years. Recommend respiratory physician input.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The responses to questions were complete. There were no new matters arising or matters or error in the clinical evaluation report. A correction was made by the sponsor in regards to the expected adverse event of psoriasis with Prolastin; this event was reported to regulatory agencies. There were responses to errors and omissions which highlighted that all but one of the manuscripts had been evaluated.

There were also two expert reviews which whilst stating that low CT volumes correlated with mortality were not able to reference any study that showed that a gain of the amount seen in the pivotal study made a difference to outcome (there being a difference in a low concentration of an agent versus the benefit when the concentration of the agent increases with this therapy).

It is assumed the trial data from SPARTA will help in this regard however this will not be reporting until 2022.

After consideration of the responses to clinical questions, the benefits of Prolastin in the proposed usage are unchanged from the first round evaluation.

Second round assessment of risks

No new clinical information was submitted in response to questions except the reported psoriasis was in a patient with a family history of this disease. The possibility of Prolastin precipitating the development of such an immunological event remains.

Second round assessment of benefit-risk balance

The benefit-risk balance of Prolastin-C, given the proposed usage is unfavourable. It is noted that there is a single relatively high volume user of this drug via special access scheme (SAS) in Australia.

Second round recommendation regarding authorisation

Reject, based on unclear clinical benefit despite biochemical improvements.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan for Prolastin-C alpha$_1$-proteinase inhibitor (human) 1,000 mg powder for intravenous infusion vial EU-RMP (Version: 1.1, dated 19 May 2015) with an Australian Specific Annex (ASA) as Annex 13 (undated) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 2.

Table 2: Summary on ongoing safety concerns

Summary of safety concerns	
Important identified risks	Anaphylactic and hypersensitivity reactions
Important potential risks	Theoretical risk of pathogen infection
Important missing information	Use in women who are pregnant or lactating Use in children

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities for all the specified safety concerns and missing information are sufficient.

Routine risk minimisation activities will comprise labelling, including contraindications, precautionary statements and/or notification of undesirable effects for all the specified safety concerns and missing information.

Reconciliation of issues outlined in the RMP report

Table 3 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 3: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
The sponsor should apply appropriate document control (for example version and date) to the ASA.	The sponsor states: "A revised RMP is provided, which addresses the recommendations made in the RMP Evaluation Report".	Appropriate document control has now been applied to the ASA. This is acceptable.
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor does not appear to have directly addressed the Clinical Evaluator's comment that "psoriasis is a possible side effect of Prolastin, which might need to be included in the RMP".	The sponsor should include 'Psoriasis' as an ongoing safety concern giving due consideration to proposing appropriate pharmacovigilance and risk minimisation activities for this potential risk, which need only be reflected in a revised ASA preferably before this application is approved. Alternatively the sponsor should provide to the TGA for review compelling justification for the omission of the important potential risk: 'Psoriasis' from the RMP.
The proposed Australian PI states: "Clinical studies with Prolastin-C did not contain sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects". Consequently for completeness it is recommended that the sponsor include the missing information: 'Use in adults aged 65 years and older' as a new safety concern. The ASA should be amended accordingly noting that routine pharmacovigilance and risk minimisation activities are considered appropriate for this new safety concern.	The sponsor states: "A revised RMP is provided, which addresses the recommendations made in the RMP Evaluation Report".	The missing information: 'Use in adults aged 65 years and older' has been added to the RMP with the application of routine pharmacovigilance and routine risk minimisation proposed. This is acceptable.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The sponsor was asked to respond to safety considerations raised by the nonclinical and clinical evaluators, in the context of relevance to the RMP. However, the sponsor does not appear to have directly addressed the clinical evaluator's comment that "*psoriasis is a possible side effect of Prolastin, which might need to be included in the RMP*" (see below). Consequently the sponsor should include 'Psoriasis' as an ongoing safety concern giving due consideration to proposing appropriate pharmacovigilance and risk minimisation activities for this potential risk, which need only be reflected in a revised ASA preferably before this application is approved. Alternatively the sponsor should provide to the TGA for review compelling justification for the omission of the important potential risk: 'Psoriasis' from the RMP.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA requests for information the sponsor provided an updated EU-RMP (Version 1.2, dated 16 October 2015) with an updated ASA (Version 1.1, dated 16 October 2015). Key changes from the versions evaluated at Round 1 are summarised in Table 4 below.

Table 4: Key changes to the updated RMP

Key changes to the updated RMP	
EU-RMP	Part VI.2.7: 'Summary of changes to the Risk Management Plan over time' states: "Not applicable". Nevertheless the missing information: 'Use in adults aged 65 years and older' has been added with the application of routine pharmacovigilance and routine risk minimisation proposed.
ASA	The table titled: 'How risk minimisation activities will be implemented in Australia" and the table in Section 4: 'Summary of the RMP' have been updated to incorporate the above change in the EU-RMP.

Suggested wording for conditions of registration

RMP:

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were a number of critical issues identified in the initial evaluation.

1. There is no validated control in place for alpha$_1$-PI glycosylation patterns, contents and limits in the drug substance or drug product specification. Alpha$_1$-PI contains approximately 12% carbohydrate and is a highly heterogeneous protein due to variably trimmed glycosylation. Without information on its glycosylation pattern and content following manufacture, it is impossible to determine the impact of future process changes on glycosylation of alpha$_1$-PI with potential consequential effects on potency, stability and efficacy.
2. A number of process related and plasma protein impurities were identified during evaluation whose level appeared not to be monitored or whose concentration increased during purification. These include PEG, polysorbate 20, TNBP, alpha – acid glycoprotein, haptoglobin and IgA (the sponsor has disputed this)
3. The drug company provided only two parameters in the drug substance specification list (potency and sterility)
4. The sterile water for injections proposed for this product has been prepared with USP as the standard. This does not meet the requirements of TGO 89 (Standard for water for Injections for Parenteral Medicines) which mandates that "water for injections must comply with the monograph for water for injections in the British Pharmacopoeia or the European Pharmacopoeia"

These issues have all since been addressed with the by sponsor.

Nonclinical

- The submitted nonclinical dossier was substantially smaller than would be expected for a new chemical entity submission and the overall quality of the submitted studies was generally low.

"Overall, the submitted dossier was not generally compliant with the relevant guideline, ICH S6: Preclinical safety evaluation of biotechnology derived pharmaceuticals (the principles of which can be applied to plasma derived products), and is considered inadequate."

- In vitro, alpha$_1$-PI inhibited neutrophil elastase activity with picomolar potency. Reduced pulmonary neutrophil levels were seen following IP administration of alpha$_1$-PI in a mouse model of emphysema associated with reduced alpha$_1$-PI levels. These pharmacology studies lend some support to the proposed clinical use of alpha$_1$-PI.
- No secondary pharmacology studies were submitted.
- There were no adverse effects on cardiovascular function in dogs and monkeys or haematology and coagulation parameters in monkeys with single IV administration at 4 times the clinical dose.
- The pharmacokinetics of alpha$_1$-PI were generally typical for this type of compound, characterised by a long half-life, low volume of distribution and limited tissue distribution following IV administration to rabbits. Significant levels of alpha$_1$-PIwere seen in BALF of cynomolgus monkeys following IV administration, suggesting some localisation of the protein to the lungs, the intended site of pharmacological action.
- alpha$_1$-PI had a low order of acute IV toxicity in mice, rats and rabbits.
- The repeat dose toxicity programme for alpha$_1$-PI was very limited. Only one repeat dose toxicity study was submitted; a 5 day study in rabbits with a 4 week recovery

period. This study had many design flaws which affects the utility of this study for regulatory purposes. The only notable effect observed during post-mortem analyses was a minimal mild chronic interstitial nephritis observed in 3/5 rabbits that received one lot of alpha$_1$-PI. This finding has an uncertain relationship with treatment. The absence of any other findings should be interpreted with caution. There was no investigation of repeat dose toxicity in a second species.

- No metabolism, excretion, pharmacokinetic-drug interaction, genotoxicity or carcinogenicity studies were submitted, which is considered acceptable given the protein nature of the drug.
- No reproductive toxicity studies were submitted.
- No clinically-relevant toxicity findings were identified in the submitted nonclincial dossier. However, the overall quality of the nonclinical data set was low and the scope extremely limited. Due to numerous serious deficiencies in the repeat dose toxicity programme, evidence of safety has not been properly demonstrated in laboratory animal species, and potential toxicity neither identified nor well characterised. Registration should only proceed if the clinical data are sufficient to allay these concerns.

Clinical

Scope of clinical dossier

The dossier submitted included a PK study CHAMP 11816, clinical study 10053(EXACTLE), safety study STAMP 11815, as well as a number of literature references.

Pharmacokinetics

The absence of biopharmaceutic and bioavailability data in the dossier was justified because the active ingredient of Prolastin-C is a human plasma protein that has not been modified during the manufacturing process. The bioavailability of the product and natural protein is thought to be the same.

Note: The 11 μM threshold for AAT is based upon a historical publication that showed individuals with AAAT level < 11 μM were at increased risk of emphysema.

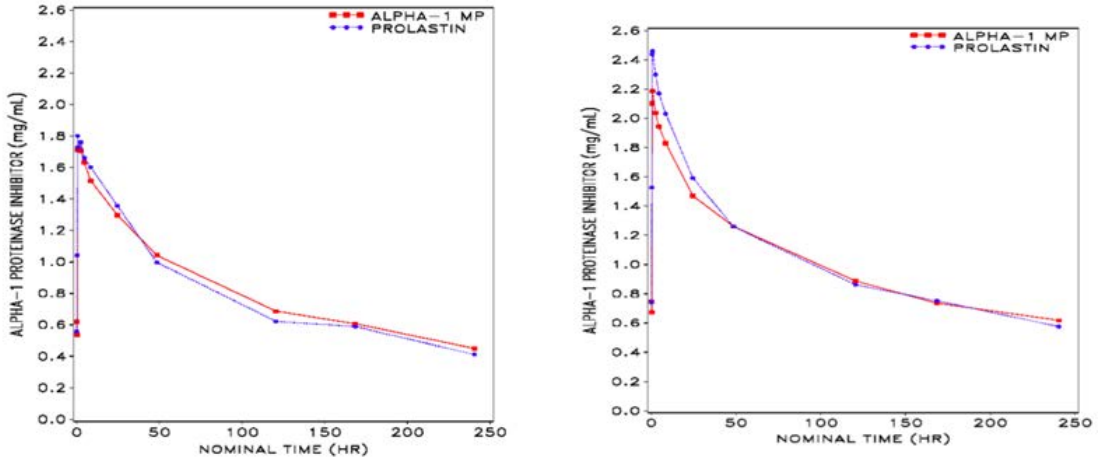
PK Study 11816

Study 11816 was a pharmacokinetic comparability study of alpha$_1$-PI MP (Prolastin-C) versus Prolastin.

Multi-centred, randomised, double blind cross over trial to evaluate the PK comparability of Prolastin-C to Prolastin in 24 adults with AATD.

There were 24 subjects, 100% white, PI*ZZ in 23, at risk SZ in 1 subject. Age 40 to 72, mean age 57.7 years .A bioassay and immunoassay were performed.

Figure 1: Mean Plasma Alpha1-PI post Alpha-1 MP or Prolastin; Potency Assay (left) and Content Assay (right)



Primary PK Endpoint: The $AUC_{0\text{-}7days}$ by the bioassay assay was 155.9 mg.h/mL for Prolastin-C and 152.4 mg.h/mL for Prolastin. Analysis of variance (ANOVA) analysis showed that the geometric least-squares mean ratio for the bioassay of $AUC_{0\text{-}7days}$ had a point estimate and 90% confidence interval (CI) of 1.03 and 0.97-1.09, respectively. The 90% CI falls within the limit of 0.80- 1.25 that is "bioequivalent". The point estimate and 90% confidence interval of the geometric least-squares mean ratio for $AUC_{0\text{-}7days}$ by the immunoassay assay, were also calculated at 0.98 and 0.95-1.02, respectively

Table 5: PK Studies submitted as literature references and relevant to the submission

Study	Objective	Intervention	Population	Duration	Outcome
Wewers 1987[12]	Feasibility, safety and biochemical efficacy	60mg/kg $alpha_1$ antitrypsin weekly	5 subjects	6 months	After steady state had been reached, the group had serum trough levels of $alpha_1$-PI of 126 ± 1 mg/dL (compared with 30 ± 1 mg/dL before treatment). Serum anti-neutrophil elastase levels were 13.3 ± 0.1 µM (compared with pre-treatment 5.4 ± 1 µM. The $alpha_1$-PI and ant neutrophil elastase capacities in the lung also improved. There was no change in lung function or X ray changes.
Campos 2013[18]	PK and safety	Randomised trial of 120mg/kg weekly versus 60mg/kg	30 subjects	Cross over trial- 8 weeks each arm	Mean steady state and trough concentrations higher and more physiological after higher dose. Less adverse events

[18] Campos MA et al (2013) Safety and Pharmacokinetics of 120 mg/kg versus 60 mg/kg weekly intravenous infusions of Alpha-1 proteinase inhibitor in Alpha-1 antitrypsin deficiency: a multicenter randomized double-blind crossover study (SPARK). *COPD* 2013; 10: 687-695.

Study	Objective	Intervention	Population	Duration	Outcome
		weekly			due to COPD exacerbations in high dose group

Pharmacodynamics

Gottleib 2000: Urinary markers of elastin degradation[14]

The study involved 12 patients with AATD and FEV1 < 80% predicted. The rate of elastin degradation by urinary elastin degradation was high at baseline and did not change significantly with Prolastin therapy. The negative finding may be due to either lack of validity of the endpoint or lack of efficacy.

Stockley 2002[15]

This was a Phase II, open label, prospective study of Prolastin 60mg/kg weekly over 4 weeks. Main outcomes were alpha$_1$-PI level, neutrophil elastase activity, neutrophil elastase inhibitory ability and other. Sputum and serum alpha$_1$-PI levels were clinically and significantly raised after 4 weeks. There was a trend to reduction in sputum elastase, IL-8, Leukotrine B4 (LTB4), sputum elastase inhibitory capacity and myeloperoxidase (MPO). There were no clinically significant changes in lung function, BORG dyspnoea score or sputum bacteriology.

Efficacy

Morbidity

NHLBI Registry- uncontrolled

Initiated in 1988, following registration in US, includes 36 centres in the US and 1 in Canada. Some 1,129 subjects with severe AATD were enrolled over 4 years. Eligibility criteria included age > 18 years, alpha$_1$-PI < 11 µM/L, PI*ZZ phenotype. The registry included patients on augmentation therapy and not. The differences in mortality used internal comparisons.

Mean baseline FEV1 was 46.7% and age 48 ± 10 years. More than 20% of subjects were receiving augmentation therapy at enrolment, the proportion increased to 46% within 3 months. Approximately 58% of subjects with FEV1 < 30% received augmentation therapy, compared to 54% of those with FEV1 30 to 50% predicted. Significant reduction in mortality in patients who received augmentation (relative risk (RR) 0.64, 95% CI 0.43-0.95 p = 0.02).The greatest clinical benefit was in patients with FEV1 35 to 49% of predicted (RR = 0.21, 95% CI 0.09-0.5 p < 0.01). No significant difference were seen in patients with FEV1 < 35% or > 50%.

German registry (Seersholm 1997)[19]

198 subjects who received Prolastin were compared to 97 from a Danish registry with no therapy. The patients in the German registry included patients with alpha$_1$-PI levels < 35% normal, FEV1 < 65% or annual decline in FEV1 of > 120mL and not smoking at the time of enrolment. All received 60 mL/kg Prolastin weekly. The Danish registry was established in 1978, and included patients with PI*ZZ or PI*ZO and alpha$_1$-PI levels < 12 µM.

There was a significant slower decline in FEV1 in the treatment group. The decline in FEV1 in the treatment group was 52 mL/year (95% CI 48 to 598) compared with 75 mL/year in

[19] Seersholm, N., et al. (1997) Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. *Eur Respir J,* 1997; 10: p. 2260-2263.

the non-treatment group (95% CI 63 to 87 ml/year) p = 0.02. However, when the results were corrected for initial FEV1, the difference only remained significant in the group with FEV1 31 to 65% predicted.

Table 6: Demographic data for the treated German group and the untreated Danish group

	Groups		
	Treated (German)	Untreated (Danish)	p-value
Patients n	198	97	
Sex M/F	142/56	55/42	0.01
Initial FEV_1 % pred	37 (14)	42 (10)	0.02
Age at entry yrs	46 (8)	45 (10)	NS
Follow-up yrs	3.2 (1.6)	5.8 (3.4)	<0.01

Data are presented as absolute value, or mean and SD in parenthesis. M: male; F: female; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; NS: non-significant.

Table 7: Annual change FEV1 for the treated German group and the untreated Danish group stratified by initial FEV1% predicted

	Groups					
	Treated (German)			Untreated (Danish)		
	Pts n	ΔFEV_1 $mL \cdot yr^{-1}$		Pts n	ΔFEV_1 $mL \cdot yr^{-1}$	p-value
Initial FEV_1						
≤30% pred	75	24.2	(23.6)	27	30.9 (36.3)	0.6
31–65% pred	112	61.8	(25.3)	58	82.8 (49.3)	0.04
>65% pred	11	162.0	(28.7)	12	140.0 (83.2)	0.7
Total	198	53.0	(37.6)	97	74.5 (59.6)	0.02

Data are presented as absolute number (of patients), and as mean and SD in parenthesis. ΔFEV_1: decline in forced expiratory volume in one second.

EXACTLE (randomised data)

100533/EudraCT multicentre, randomised trial with intravenous Prolastin to evaluate the frequency of exacerbation and progression of emphysema by means of multi-slice CT scans in patients with congenital AATD.

Phase II, multicentre, double blind randomised controlled trial, to assess the utility of CT scans to measure the progression of emphysema and the potential efficacy of Prolastin administered weekly by IV infusion at 60 mg/kg in patients with progressive emphysema with severe $alpha_1$-PI deficiency from November 2003 and December 2006.

Efficacy endpoint was the 15th percentile of lung parenchyma tissue loss, calculated by analysis of CT lung histograms and exacerbations as clinical endpoints for the progression of emphysema.

The study population was 77 adult Caucasians aged 35 to 74 years. Subjects had severe congenital AATD with phenotype PiZ, serum $alpha_1$-PI < 11 µM, FEV1 < 80% and FEV1/VC < 70%.

After 24 months, there was a numerically slower rate of loss of tissue density in the Prolastin group (-1.38) than the placebo group (2.24), but this was not statistically significant.

Table 8: Changes in TLC adjusted 15th percentile of lung density (g/L) from baseline to endpoint (mITT population) with exclusion of data at Months 3 and 21

Statistic	Prolastin		Placebo	
Baseline [mean ± SD]	(n = 36)	54.554 ± 17.371	(n = 35)	53.898 ± 15.968
Endpoint [mean ± SD]	(n = 36)	51.167 ± 17.175	(n = 35)	49.076 ± 15.926
Change from baseline [mean ± SD]	(n = 36)	-3.387 ± 4.621	(n = 35)	-4.822 ± 3.813
[median]		-3.669		-5.126
[range]		(-10.19; 7.15)		(-12.54; 3.61)
Random coefficient regression model [a]:				
Mean slope [95% CI]	-1.384 [-2.023; -0.745]		-2.241 [-2.905; -1.577]	
Estimated difference between mean slopes [b] [95% CI]	0.857 [-0.065; 1.778]			
P value for the difference between mean slopes	0.068			

The applied ANCOVA model demonstrated a treatment difference in the rate of lung density progression between the Prolastin and placebo groups of 1.472 (95% confidence interval: 0.009 to 2.935), p = 0.049.

Comparison of the slopes of the decrease in lung density in the basal third of the lung showed a difference between Prolastin (mean slope: -0.850 ± 0.2767) and placebo (mean slope: -1.747 ± 0.2880) of 0.897 ± 0.3994, 95% CI 0.100 to 1.694, p = 0.028. Comparison of the slopes of the decrease in lung density in the middle and apical thirds did not identify a significant difference.

Prolastin shortened the duration of the exacerbation in the Prolastin group by about 10% compared to placebo group (not statistically significant). There were less severe exacerbations in the Prolastin group (6.7% versus 13.5% under placebo treatment; p = 0.013; Cochran–Mantel–Haenszel (CMH) test). The annual exacerbation rate was not significantly different.

There was no significant change in the carbon monoxide transfer or pulmonary diffusing capacity for CO (DLCO).

Stockley 2010[11]

Stockley 2010 pooled data from two randomised, double blind, placebo controlled trials that had investigated the efficacy of IV alpha$_1$-PI augmentation therapy on emphysema progression using CT densitometry. These two similar trials were; the two centre Danish-Dutch study (n = 54) and the EXACTLE study described above. The PD endpoint of interest was the change in 15th percentile of lung density measured by CT scan was obtained from both trials.

Mean follow-up was approximately 2.5 years. The mean change in lung density from baseline to last CT scan was -4.082 g/L for alpha$_1$-PI and -6.379 g/L for placebo with a treatment difference of 2.297 (95% CI, 0.669 to 3.926; p = 0.006). The corresponding annual declines were - 1.73 and -2.74 g/L/year, respectively.

Using pooled data there was a statistically significant reduction in the reduction in lung density over 2.5 years of 2.3 g/L in a combined alpha$_1$-PI/Prolastin group.

RAPID Trial

RAPID Trial; not included in the dossier. Intravenous augmentation treatment and lung density in severe AATD (RAPID): a randomised, double blind, placebo controlled trial.[20]

Methods

This was a multicentre, double blind, randomised, parallel group, placebo controlled trial of alpha$_1$-PI (Zemaira) in patients with AATD. Non-smokers aged 18 to 65 years were

[20] Chapman, KR et al. 2015 Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial *Lancet* 2015; 386: 360-368.

recruited if they had severe AATD (< 11 μM) and FEV1 35 to 70% predicted. Patients received 60 mg/kg alpha$_1$-PI for 24 months or placebo. The primary end point was CT lung density at total lung capacity (TLC) and functional residual capacity (FRC) at 0, 3, 12, 21 and 24 months.

Results

93 patients were randomised to alpha$_1$-PI, 87 to placebo. The annual rate of lung density loss at TLC was significantly less in patients treated with alpha$_1$-PI, -1.45g/L (standard error (SE) 0.23) per year compared with -2.19 g/L in the placebo group (SE 0.25), (placebo – subtracted) difference 0.74 g/L per year (95% CI 0.06-1.42) p = 0.03. The loss of lung tissue was not significantly different at FRC, -1.54g/L per year compared with -2.02g/L difference 0.48 g/L (95% CI -0.22 to 1.18). Treatment emergent adverse events were similar in the two groups. There was no significant change in FEV1, St George's Respiratory Questionnaire (SGRQ) score, or exacerbations.

FEV1 rate of progression

FEV1 data from 1,509 patients; derived from 4 non randomised trials and 1 RCT combined using random effects. The decline in lung function was slower by 23% with augmentation. No significant effect where FEV1 < 30% or > 65%.

Cochrane review 2010[21]

Two trials were included (total 140 patients) that ran for two to three years. All patients were ex- or never-smokers and had genetic variants that carried a very high risk of developing chronic obstructive pulmonary disease. Mortality data were not reported. Annual number of exacerbations and quality of life were similar in the two groups. FEV1 deteriorated more in the active group than in the placebo group (difference was -20 mL per year; 95% confidence interval -41 to 1; p = 0.06). Lung density measured by CT scan deteriorated a little less in the active group than in the placebo group (difference 1.14 g/L; 95% confidence interval 0.14 to 2.14; p = 0.03).

Safety

The most serious adverse reaction in clinical trials was a rash; consistent with hypersensitivity. The most common drug related adverse events observed in > 1% of patients were chills, malaise, headache, rash, hot flush and pruritis; consistent with an infusion reaction to a therapeutic protein.

In Study 100533/EurdraCT, one patient in the Prolastin group developed psoriasis. The sponsor did not consider this as a treatment related event; however the clinical evaluator has disagreed. In this study, overall there were similar amounts of AE and TEA in the treatment and placebo groups.

In the STAMP study, 38 subjects received open label treatment with alpha$_1$-PI for 20 weeks. Of these, 19 were treatment naïve. There were 752 treatment infusions, of these interruptions occurred in 10 subjects (IV infiltration in 3, infusion reactions in 2).

Two PSUR were submitted from 2013 and 2014. No new safety concerns were identified. In 2013 the estimated exposure was 4 948 patients per year.

Unknown safety concerns

- Antibodies and immunogenicity: There were no immunogenicity data from clinical trials. In the STAMP and CHAMP a total of 4 patients developed antibodies detected by ELISA; none of these were neutralising

[21] Gotzsce PC and , Johansen HK . Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *The Cochrane Library* 2010 Issue 7

- Effect on other proteins

Clinical evaluator's recommendation

Reject because of lack of convincing evidence of efficacy on patient relevant/ patient important endpoints.

The safety is well understood and well characterised. The product (or its bioequivalent precursor, Prolastin) has been marketed in high income countries with sophisticated systems for post-marketing surveillance (similar to those in Australia) for nearly 30 years.

Recommend respiratory physician input.

Other clinical input

Results of EU Working Group regarding use of CT Lung density

Minutes of Ad hoc experts group meeting, January 14, 2015

"…lung density measurement by CT scan have been used since the 1980s and is the most sensitive to change endpoint in [alpha$_1$-PI deficiency] emphysema and uniquely suitable as a clinical study endpoint due to its direct and validated representation and quantification of the anatomical changes underlying this condition."

EU Evaluation report from Repreeza (Zemaira) WC 500193167

The primary efficacy variable was the lung volume adjusted lung density (Adjusted P15) estimated by the 15th percentile of the frequency histogram of the lung pixels. Lung loss is measured via whole lung CT densitometry; that is the 15th percentile point, is a physiological endpoint used in clinical alpha$_1$-PI augmentation therapy studies. CT densitometry has previously been accepted by the CHMP[22] as an acceptable method to detect progression of emphysema in patients with alpha$_1$-PI deficiency. It is agreed the "TLC" inspirations state is the most suitable endpoint to use in studies since it has the best possibility to detect small differences in lung density. Thus, lung density measured at the "TLC" inspiration state is a relevant parameter to use as it measures the physiological change in the organ which is affected of the disease.

Expert Opinions

Expert opinions were sought in view of the negative opinion from the clinical evaluator.

Sponsor's Expert Opinions

Expert 1 Dr [Information redacted]

Dr [Information redacted] stated 'Unfortunately, robust data that would directly correlate lung density (as measured by CT densitometry) to patient-reported outcomes (symptom-based) do not exist. However, a growing body of evidence links the extent of emphysema (derived by CT-techniques) to mortality.' Some data were presented showing a relationship between CT volumes on outcomes; it is assumed that by increasing CT volumes (or slowing the decline) there will be a benefit on mortality.

CT morphology is stated to be the clinical marker most closely related to clinical endpoints.

Commenting on registry data, 'In my point of view, the body of evidence is not suited to answer the question on symptom-based patient-relevant endpoints. None of the present studies has been powered adequately to do so. Also, registry data (at least in the given quality, present at the moment) are most likely not suited to answer the question.

[22] The Committee for Medicinal Products for Human Use (CHMP) European Medicines Agency

However, based on the evidence about lung density and mortality, it may be assumed that a disease modifying effect (that is very likely) would result in a life-prolonging effect that certainly is important for patients. It is not suitable to apply the same strict rules about approval in a rare disease like AATD as in a frequent disease like COPD in general'.

Adverse events are considered minor in clinical practice.

Expert 2 Dr [Information redacted]

To the question of whether the small treatment differences identified on lung CT clinically meaningful, Dr [Information redacted] states: 'Yes these studies indicated that loss of lung is reduced. This is indirect evidence that AAT replacement therapy decrease the loss of lung tissue characteristic of alpha-1-antitrypsin deficiency.' It thus remains unclear if the Expert believed this small numerical change was clinically relevant.

The totality of data from registries and RCLs indicated that AAT therapy decreases lung loss.

Therefore there appears to be a consistent belief that this therapy improves AAT concentrations; that CT volumes are better than FEV1 as a predictor of clinical endpoints, and that symptom related data is not available. There is disagreement with the evaluator on the statements that the noted changes on CT are not clinically relevant however evidence to refute this was not given.

Risk management plan

A revised RMP with ASA is required prior to registration.

Routine pharmacovigilance and risk minimisation is proposed.

Risk-benefit analysis

Delegate's considerations

There were a number of deficiencies in the data provided

1. Concerns regarding quality; lack of well characterised glycosylation, poorly characterised product specifications, concerns about water for injection; these have been resolved
2. Lack of toxicology data
3. Poor quality evidence for efficacy- based on raising PK endpoint, PD data, surrogate markers and registry studies
4. Poorly described safety in terms of immunogenicity.

Efficacy

In other jurisdictions such as the USA, Prolastin C was registered on the basis of an increase in the level of deficient protein above the level considered to cause emphysema (11 μM/L). This level is the level below which patients are likely to develop emphysema (which is below the lower limit of the normal adult level of 20 μM). Although raising the level of a deficient enzyme or substrate is considered to be a relevant marker of efficacy in small populations for a disease associated with a deficiency, there are several concerns in this case. Firstly, not all patients with a deficiency develop emphysema thus other factors are also involved. There is a lack of correlation between raising the levels of $alpha_1$-PI and clinical markers such as FEV1, symptoms and quality of life.

In recent studies, a small reduction in the loss of CT lung density has been demonstrated. This is considered to be a valid clinical endpoint by experts in Europe.

Registry studies support an effect on improvements in mortality.

Safety

The main safety concerns relate to infusion reactions, risk of anaphylaxis and a theoretical risk of transmission of infectious disease. This product is given intravenously, thus it comes with the risk of repeated vascular access.

Risk-benefit balance

This product has been approved for use in other first world countries and appears relatively safe. It has efficacy on a PK and surrogate endpoint, but the evidence for significant changes in clinical endpoints is minimal. The lack of good clinical data to support the efficacy is surprising given the long history of the product.

Indications

The following could be considered based on the wording from other jurisdictions:

- use in in conjunction with other therapy for emphysema
- specifying genotype
- specifying severity; clinical trials have shown it is most beneficial where FEV1 is between 35 and 70% (would we then recommend stopping Prolastin-C when FEV1 < 35%?)

RMP

This needs to be updated.

Unknown

- Is a higher dose more efficacious?
- Is targeting alpha$_1$-PI levels helpful?

PI/CMI

The need to not smoke needs to be highlighted.

Conditions of registration

1. Satisfactory RMP
2. Submit the final study report of trial GTi1201: A randomised double blind placebo controlled study to assess the efficacy and safety of two dose regimen (60 mg/kg and 120 mg/kg) of weekly IV alpha$_1$-PI in subjects with pulmonary emphysema due to AATD.
3. All future variations involving changes to any aspect of the manufacturing process in which data evaluation is required (Category 3 submission) must be accompanied by characterization data down to the product level and the specification (both release and shelf life) must meet the approved drug product specification.
4. Batch Release Testing and Compliance with Certified Product Details.

Summary

1. Prolastin –C is an orphan drug for rare disease
2. No similar product is available on the Australian market
3. Prolastin has been approved for use in USA for over 25 years. Regulatory approval was based upon raising alpha$_1$-PI levels

4. The evidence for efficacy in the pivotal clinical trial is based on a surrogate endpoint (lung density on CT). For another alpha$_1$-PI, this endpoint was evaluated by an expert working group of the EMA and accepted as a regulatory endpoint
5. For Prolastin/Prolastin-C, there is supportive evidence from long term registries on mortality
6. No major safety concerns have been identified over the past 25 years of use.

Proposed action

The Delegate had no reason to say, at this time, that the application for Prolastin-C should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

1. *The non-clinical evaluation which requires comment from the sponsor in its pre-ACPM response is regarding the overall quality of the nonclinical data set was low and the scope was extremely limited. Due to the numerous serious deficiencies in the repeat dose toxicity programme evidence of safety has not been properly demonstrated in laboratory animal species, and potential toxicity neither identified nor well characterized. In addition comments were made regarding the lack of toxicology data.*

Grifols recognizes that the data submitted in the nonclinical dossier was not generally compliant with ICH S6. The ICH S6 guideline was finalized in July 1997. The precursor product, Prolastin, was originally licensed in 1987. Therefore, most of the studies conducted pre-date the ICH guideline. The change to Prolastin-C in 2008 involved a modification to the manufacturing process. Until that time, Prolastin had been used clinically in humans for over 25 years. Pre-clinical studies conducted for Prolastin-C were designed to focus on the process change, as alpha$_1$-PI was not considered a new product. Prolastin-C manufactured with the modified process has now been used clinically in humans for over 8 years. Safety of the product is well characterized and well understood as demonstrated by controlled clinical studies and long term clinical use. Prolastin-C and its bioequivalent precursor, Prolastin, have been marketed in countries with sophisticated systems for post marketing surveillance for nearly 30 years.

It should also be noted that additional data was added to the submission during the pre-evaluation responses which provided more information. The nonclinical data have also been addressed in the RMP Part II SII.

2. *Comments concerning the efficacy of the product based on raising PK endpoint, PD data, surrogate markers and registry studies.*

Efficacy has been demonstrated for Prolastin-C in the bioequivalence study performed using a comparison of Prolastin to Prolastin-C in the ChAMP PK study previously provided. As Prolastin has a history as a safe and efficacious product in the US and Canada, the bioequivalence study demonstrates that the process change for Prolastin-C continues to provide a safe and efficacious product. In addition, there are three additional alpha$_1$-PI products marketed in the US (Aralast, Zemaira and Glassia) that achieved licensure by way of comparative PK studies where Prolastin was used as the control article. Please refer to the responses previously provided that includes the clinical responses that were submitted in January 2014. Both products, Prolastin and Prolastin-C have more than 25 years of treatment with a good safety profile.

3. *Comments concerning the safety of the product in addition to the safety in terms of immunogenicity.*

As discussed (during the teleconference with the TGA), immunogenicity testing was performed during clinical trials and confirmed no positive neutralizing antibody responses. The clinical Study 11816-ChAMP and Study 11815-STAMP as well as the integrated summary of safety provided all of the immunogenicity results. In addition characterization testing will be performed twice per year and Grifols will add an evaluation of glycosylation profiles to this testing. Isoelectric focus testing of the drug product will continue to be performed when a process change is made as part of the characterization.

It is important to note that this product has been licensed for approximately 8 years using the current process and more than 25 years for the precursor product.

4. *Comments concerning the risk/benefit balance. This product has been approved for use in other first world countries and appears relatively safe. It has efficacy on a PK and surrogate endpoint, but the evidence for significant changes in clinical endpoints is minimal. The lack of good clinical data to support the efficacy is surprising given the long history of the product.*

Please see the response to comment 2 concerning the efficacy of the product. Since the international birthdate (December 1987), Grifols alpha$_1$-PI (Prolastin and Prolastin-C) has continued to demonstrate a favourable benefit risk ratio. To date, post marketing data has not identified a safety issue that would alter the benefit risk ratio. Given the overall quantity and quality of information, the favourable product safety profile remains consistent with cumulative experience and the reference safety information as reflected in the product labelling.

Prolastin was initially licensed based on its ability to raise lung and serum levels of alpha$_1$-PI. At the time, non-invasive monitoring of emphysema was conducted using pulmonary function tests, in particular the rate of decline of FEV1. However, FEV1 is a measure of both airway wall thickening and collapse of the small airways due to loss of elastic recoil in the lung lobes, whereas lung density is a more specific reflection of airspace enlargement by alveolar destruction present in emphysema.

Therefore, FEV1 fails to characterize all aspects of COPD, most notably emphysema and even chronic bronchitis. It has been estimated that hundreds of subjects over a 3 to 5 year period would be needed to detect differences in FEV1 decline. Therefore, it was considered to be infeasible to conduct an efficacy study (not only by Grifols, but also other companies in conjunction with regulatory bodies such as FDA and EMEA) with FEV1 as a primary measure of efficacy with alpha$_1$-PI in the treatment of AATD, particularly as AATD is rare (orphan). This has led to the development of CT lung densitometry because it is a minimally invasive tool for identifying destructive changes in the lung, which can provide objective quantification of parenchymal changes.

More recently, a number of other studies in AATD patients have shown that CT densitometry is an appropriate clinical endpoint and correlates cross sectionally with lung function (including FEV1 and the carbon monoxide transfer coefficient (KCO)), health status, exercise capacity, and mortality. In addition, the US Food and Drug Administration (FDA) recently accepted serial lung density measurements by CT scan as an appropriate clinically meaningful endpoint to assess the efficacy of augmentation therapy with IV alpha$_1$-PI products.

There are now three placebo controlled clinical trials using CT densitometry as the primary efficacy endpoint. These studies have all demonstrated the efficacy of alpha$_1$-PI products in slowing the progression of lung density loss over time and confirmed that it is possible to quantify the extent of emphysema and measure the progressive lung density

loss with CT lung densitometry over a relatively short period of time compared to FEV1. As TGA notes, CT densitometry is 'considered to be a valid clinical endpoint by experts in Europe.'

5. *Comments concerning the indications which could be considered based on the wording from other jurisdictions:*

Use in conjunction with other therapy for emphysema

Grifols does not currently have this terminology included in the US Package Insert. If TGA feels this information is necessary to include this clarification then Grifols agrees to do so.

Specifying genotype

Grifols would prefer to not include the phenotype information in the indication section. There is the potential that a patient could be excluded from using the product if the information is too specific.

Specifying severity; clinical trials have shown it is most beneficial where FEV1 is between 35 and 70% (would we then recommend stopping Prolastin-C when FEV1 < 35%?)

Grifols is concerned that the inclusion of stopping rules in the labelling will prevent patients from therapy that may still derive benefit. Therefore, Grifols prefers to include the language in the recommendations for amendments to the PI to state for the indication… "clinically significant emphysema (FEV1 < 80%)".

6. *Comments concerning the RMP*

An updated risk management plan was provided to TGA as part of the October 2015 responses and now complies with the format requested. Based on the document previously provided, Grifols considers that the RMP meets the requests of the TGA. The RMP includes reference to the European SmPC Version 6.1.1, March 2014. Since Prolastin-C is not registered in Europe, the 'Prolastin' SmPC is included in Foreign PI under European SmPC.

7. *Comments concerning the unknown such as:*

Is a higher dose more efficacious?

Currently, Grifols has a clinical trial ongoing (Gti1201-SPARTA) which compares two different doses of alpha$_1$-PI. Augmentation therapy with weekly IV infusions of 60 mg/kg alpha$_1$-PI may be sufficient to slow progression of lung density decline in AATD patients; however, whether higher doses are able to provide better protection is currently unknown. There are data indicating that severe AATD patients have increased concentrations of neutrophils and neutrophil elastase (NE) in their lungs; therefore, increased serum alpha$_1$-PI concentrations may help to combat this increase and provide additional benefit in patients with AATD.

Is targeting alpha$_1$-PI levels helpful?

Based on the discussion above regarding the dosing information of alpha$_1$-PI, the approved dosing of 60 mg/kg of alpha$_1$-PI slows the progression of emphysema in AATD patients. This shows that targeting 60 mg/kg weekly is clinically meaningful for patients.

The RAPID trial identified the need to explore potential benefits associated with a higher dose/optimal dose for severe AATD patients. The post-hoc pharmacometrics analysis showed that patients with the highest trough serum concentration tended to have the slowest annual rates of lung density loss. The RAPID publication references the SPARK study as data supporting higher dose therapy. As demonstrated in SPARK, the 120 mg/kg alpha$_1$-PI weekly dose was considered to be safe and well tolerated as well as provided a favourable physiologic alpha$_1$-PI serum level than the currently recommended 60 mg/kg dose. Grifols SPARTA trial will use CT lung densitometry measured at TLC as a primary

endpoint, to assess the degree of lung tissue preservation over time. In addition, SPARTA will be the first trial to evaluate the efficacy of Prolastin-C at the higher dose of 120 mg/kg weekly and the standard 60 mg/kg dose vs placebo. This will allow further assessment of the potential impact of the 120 mg/kg dose on increasing serum levels to within the normal range, and slowing the annual rate of lung function decline.

8. Comments concerning the PI and CMI as provided in the Delegates overview report and the provided attachment.

Grifols has evaluated the TGA requests and an updated PI is provided. The updated PI addresses all of the comments provided by the TGA. In addition, the CMI has been updated to address the need to highlight that the patient does not need to smoke. An updated annotated CMI is provided.

9. Comments concerning the conditions of registration that has been provided by TGA.

Satisfactory RMP: See the response 6 above.

Submit the final study report of trial GTi1201: Grifols commits to providing the final study report of clinical trial GTi1201.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the efficacy of Prolastin-C Powder for solution for injection, vials containing 1000 mg of Alpha-1-proteinase inhibitor for the following indication:

> *Prolastin-C is indicated for chronic augmentation therapy of individuals with congenital deficiency of alpha PI (alpha 1 antitrypsin deficiency) with clinically demonstrable emphysema.*

The ACPM taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered this product to have an overall negative benefit–risk profile.

In making this recommendation the ACPM

- took a negative view of approval due to the lack of convincing evidence of efficacy on patient-relevant and patient-important endpoints.
- noted that there was some evidence demonstrating a statistically significant reduction in rates of lung density loss, however this evidence was very limited and the impact on lung density considered to be underwhelming.
- noted that regarding secondary endpoints, shortening duration of exacerbations and differences in annual exacerbation rates were non-significant, no benefit was shown through lung function testing and gas exchange, speed of deterioration was not markedly different and overall quality of life (SGRQ scoring) was unchanged.
- noted that the overall benefit-risk assessment was negative. Although the risks associated with Prolastin-C were considered to be relatively minor and uncommon, consisting predominantly of allergic/urticarial type symptoms, the benefits of such treatment have not been proved with biochemical improvement not having been demonstrated to result in a clinically relevant translation of those results into physiological or clinically meaningful outcomes such as increased lung density, improved lung capacity or improved quality of life.

Advice sought from the Delegate included:

1. Is efficacy adequately established?

The ACPM did not consider that efficacy was adequately established based on the reasons described above.

2. Are amendments to the indications required?

This issue was not addressed given the ACPM were of the opinion that the product should not be approved for registration.

Delegate's evaluation of sponsor's post ACPM response

The Sponsor was given the opportunity to respond to the ACPM's advice.

Conclusions

The sponsor has clarified the use of CT lung density as an endpoint in studies of alpha$_1$-PI replacement therapy.

Taken together, the results from:

- serum alpha$_1$-PI levels from PK studies
- the EXACTLE randomised study
- the non-randomised registry studies

provide support for the efficacy of Prolastin-C for the proposed usage.

It is accepted that these efficacy results are subject to uncertainty. However, this is not unusual for rare diseases. Regulators (globally and in Australia) have set a precedent, for other medicines, of being more tolerant of uncertainty around efficacy for rare diseases.

The ACPM's concerns could be addressed by communicating the uncertainty around efficacy to prescribers and patients; via relevant statements in the PI and CMI.

Safety is well characterised following several years of post-approval use in the USA and Canada. Both counties have sophisticated systems for post-approval surveillance.

The sponsor's update on the ongoing SPARTA trial is also noted. This trial is comparing the efficacy and safety of two doses of Prolastin-C (60 mg/kg and 120 mg/kg) versus placebo. The primary endpoint is lung CT density. The planned sample size is 113 patients per arm or 339 in all; planned follow-up is 3 years. The first patient was recruited in April 2014. As of August 2016, 135 patients had been randomised and 128 were on treatment (24 in Australia).

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Prolastin-C alpha-1-proteinase inhibitor (human) 1000 mg powder for injection vial (with diluent vial), indicated for:

> *Prolastin-C is an alpha-1-proteinase inhibitor (human, Alpha1-PI) indicated to increase serum Alpha1-PI levels in adults with congenital deficiency of alpha-1 antitrypsin and with clinically significant emphysema (FEV1 < 80%).*
>
> *The data for clinical efficacy of Prolastin-C is derived from changes in the biomarkers alpha-1 anti-protease level and CT lung density. Efficacy on FEV1 or patient relevant endpoints such as quality of life or pulmonary exacerbations has not been established in randomised clinical trials.*
>
> *Clinical trials have only included patients who were not smoking.*

Specific conditions of registration applying to these goods

- The Prolastin-C (alpha-1-proteinase inhibitor (human)) EU Risk Management Plan (RMP), version 1.2, dated 16 October 2015, data lock point (DLP) 31 December 2014 with Australian Specific Annex version 1.2, dated 22 December 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Submit the final study report of trial GTi1201: A randomised double blind placebo controlled study to assess the efficacy and safety of two dose regimen (60 mg/kg and 120 mg/kg) of weekly IV alpha$_1$-PI in subjects with pulmonary emphysema due to AATD.
- All future variations involving changes to any aspect of the manufacturing process in which data evaluation is required (Category 3 submission) must be accompanied by characterisation data down to the product level and the specification (both release and shelf life) must meet the approved drug product specification.
- Batch Release Testing

  All batches of Prolastin-C alpha-1-proteinase inhibitor (human) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  Each batch of Prolastin C alpha-1-proteinase inhibitor (human) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. [further details were not included]

Attachment 1. Product Information

The PI for Prolastin-C approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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