Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sebelipase alfa

Proprietary Product Name: Kanuma

Sponsor: Alexion Pharmaceuticals Australia Pty Ltd

June 2018

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
ASCVD	Atherosclerotic cardiovascular disease
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
$AUC_{0\text{-last}}$	Area under the concentration time curve from the start of the infusion to the time of the last quantifiable concentration
AUC_{ss}	Area under the concentration time curve at the steady state
BSA	Body surface area
CL	Total body clearance
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
CPD	Certified Product Details
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HDL-c	High density lipoprotein cholesterol
HSA	Human serum albumin
HSCT	Haematopoietic stem cell transplant
INR	International normalised ratio

Abbreviation	Meaning
IV	Intravenous
λz	Apparent terminal rate constant
LAL	Lysosomal acid lipase
LAL-D	Liposomal acid lipase deficiency
LDL	Low density lipoprotein
LDL-c	Low density lipoprotein cholesterol
LLMs	Lipid lowering medications
LLN	Lower limit of normal
LSD	Lysosomal storage disorder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PSUR	Periodic Safety Update Report
qw	Once weekly
qow	Every other week
rhLAL	Recombinant human lysosomal acid lipase
SAE	Serious adverse event
SBC-102	Sebelipase alfa
t½	Apparent terminal half-life
TBil	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed serum concentration
ULN	Upper limit of normal
UK	United Kingdom

Abbreviation	Meaning
US	United States
V_c	Volume of distribution central compartment
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	17 May 2017
Date of entry onto ARTG	18 May 2017
Active ingredient:	Sebelipase alfa
Product name:	Kanuma
Sponsor's name and address:	Alexion Pharmaceuticals Australia Pty Ltd Suite 401 Level 4 Building A 20 Rodborough Road Frenches Forest NSW 2086
Dose form:	Injection, intravenous infusion
Strength:	2 mg/mL
Container:	vial
Pack size:	1 vial
Approved therapeutic use:	*Kanuma; sebelipase alfa (rce) is indicated for long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D)*
Route of administration:	intravenous
Dosage:	For infants < 6 months of age) presenting with LAL-D 1 mg/kg administered as an IV infusion once weekly with dose escalation considered based on clinical response. For children and adults presenting with LAL-D 1 mg/kg administered fortnightly as an IV infusion. For the full details of dosage please see the Product Information (Attachment 1).
ARTG number:	274498

Product background

This AusPAR describes the application by Alexion Pharmaceuticals Australasia Pty Ltd (the sponsor) to register Kanuma sebelipase alfa 2 mg/mL solution for intravenous (IV) infusion for the following indication:

> *Kanuma (sebelipase alfa) is indicated for long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).*

This is a submission to register the new biological entity sebelipase alfa as enzyme replacement therapy for the long term treatment of patients of all ages with lysosomal acid lipase deficiency. Sebelipase alfa (SBC-102) is a first in class recombinant human lysosomal acid lipase.

Liposomal acid lipase deficiency (LAL-D) is a very rare, life threatening autosomal recessive lysosomal storage disorder caused by mutations affecting a single gene. It is associated with significant morbidity and mortality affecting individuals from infancy through to adulthood. LAL-D presenting in infants is a medical emergency with rapid disease progression over a period of weeks that is typically fatal within the first 6 months of life.

Deficient lysosomal acid lipase (LAL) enzyme activity results in progressive complications due to the lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the liver, spleen, intestine and the walls of blood vessels.

Current treatment options for infants with LAL-D are limited to supportive therapies, including nutritional support, blood transfusions and albumin in an attempt to mitigate some of the effects of this rapidly fatal disease. Treatment for children or adults presenting with LAL-D is limited to liver transplant as liver function deteriorates, and attempts to manage dyslipidaemia through diet and the use of lipid lowering medications.

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalised into lysosomes. Sebelipase alfa catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

Proposed dosage:

Infants (< 6 months of age) presenting with LAL-D:

> *The recommended starting dose in infants < 6 months of age presenting with rapidly progressive LAL-D is 1 mg/kg administered as an intravenous (IV) infusion once weekly. Dose escalation to 3 mg/kg once weekly should be considered based on clinical response.*

Children and adults presenting with LAL-D:

> *The recommended dose in children and adults presenting with LAL-D is 1 mg/kg administered fortnightly as an IV infusion.*

Orphan drug status

Sebelipase alfa was designated an orphan drug in Australia for the treatment of LAL-D in November 2015. Sebelipase alfa was granted orphan designation in the US, Europe, and Japan, and was subsequently approved in the US (December 2015), Europe (August 2015), and Japan (March 2016). The prevalence of LAL-D in Australia is estimated to be 142 to 297 individuals.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 18 May 2017.

At the time the TGA considered this application; similar applications had been approved in the countries or regions on the dates as follows:

- US indication (approved 8 December 2015): Kanuma is indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency.
- European indication (approved 28 August 2015): Kanuma is indicated for long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.
- Japan: approved on 28 March 2016
- South Korea: approved on 21 March 2016

In addition, similar applications were under consideration in Canada, Switzerland, Singapore and New Zealand.

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. Registration timeline

Table 1: Registration timeline for Submission PM-2016-01313-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2016
First round evaluation completed	31 October 2016
Sponsor provides responses on questions raised in first round evaluation	29 November 2016
Second round evaluation completed	30 January 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	Dated 17 May 2017
Sponsor's pre-Advisory Committee response	No response required
Advisory Committee meeting	This submission was not presented to ACM.
Registration decision (Outcome)	17 May 2017
Completion of administrative activities and registration on ARTG	18 May 2017

Description	Date
Number of working days from submission dossier acceptance to registration decision*	220

*Statutory timeframe is 255 working days

III. Quality findings

Introduction

Sebelipase alfa has been developed as an ERT intended for long term treatment of patients with LAL-D, a very rare autosomal recessive monogenic disorder in which patients are deficient for a key lysosomal enzyme, lysosomal acid lipase, leading to the lysosomal accumulation of cholesteryl esters and triglycerides in various tissues and cell types throughout the body.[1]

LAL-D is a progressive multisystem disease which frequently manifests early in life leading to serious complications. In infants, these complications include failure to thrive with progressive liver injury, rapid development of liver fibrosis, and early death. In children and adults, chronic liver injury with liver fibrosis leading to such complications as variceal bleeding due to cirrhosis, and marked disturbances of lipid metabolism leading to dyslipidaemia increasing the risk of premature atherosclerosis, are seen. Currently there are no safe or effective therapies for this life threatening disease.

Sebelipase alfa is the first ERT to be developed for LAL-D and treatment is intended to directly address the root cause of disease by replacement of the missing or deficient enzyme which leads to reduction of the accumulated substrates and restoration of normal lipid metabolism. Enzyme replacement therapy in patients with LAL-D is a rational approach given the demonstrated medical value and long term safety of ERTs for other lysosomal storage disorders (LSDs), including Gaucher disease, Pompe disease, Fabry disease, and the mucopolysaccharidoses.[2,3,4,5,6,7,8]

Based on clinical experience with sebelipase alfa in a broad spectrum of patients with LAL-D, the recommended dose is 1 mg/kg administered as an intravenous infusion once every other week. In patients presenting with rapidly progressive LAL-D in infancy, the

[1] Grabowski GA, et al. Lysosomal acid lipase deficiencies: The Wolman disease / cholesteryl ester storage disease spectrum. In: Valle D, et al, eds. The Online Metabolic and Molecular Basis of Inherited Disease. New York City, NY: McGraw Hill Inc. Updated March 2012. Available from: http://www.ommbid.com/OMMBID/. Accessed 02 December 2013.
[2] Barton NW, et al. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher disease. *Proc. Natl. Acad. Sci. U S A*. 1990;87: 1913-1916.
[3] Barton NW, et al. Replacement therapy for inherited enzyme deficiency-macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med.* 1991;324: 1464-1470.
[4] Kishnani PS, et al. Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology.* 2007; 68: 99-109.
[5] van der Ploeg AT, et al. A randomised study of alglucosidase alfa in late onset Pompe's disease. *N Engl. J Med*. 2010; 362: 1396-1406
[6] Wilcox, WR, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am. J. Hum. Genet*. 2004; 75: 65-74.
[7] Wraith JE, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomised, double-blinded, placebo controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr*. 2004; 144: 581-588.
[8] Muenzer J, et al. A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). *Mol. Genet. Metab*. 2007; 90: 329-37

recommended starting dose is 1 mg/kg administered as an intravenous infusion once weekly. In clinical studies, these patients were dose escalated to 3 mg/kg once weekly.

Drug substance (active ingredient)

Sebelipase alfa is a lysosomal acid lipase (LAL) glycoprotein. The average molecular weight of the glycosylated protein is 55 kDa; following de-glycosylation it is 43 kDa. Its primary amino acid sequence contains 378 amino acids and is identical to the Genbank reference sequence for human LAL and is preceded by an amino acid leader sequence.

Liquid chromatography, tandem mass spectroscopy, 100% peptide mapping, and amino acid analysis of sebelipase alfa confirmed 100% homology between the natural human amino acid sequence and the recombinant hLAL gene.

Physical and chemical properties

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic *Gallus gallus*, with the same amino acid sequence as the native human enzyme. Purified sebelipase alfa is a glycoprotein with a molecular weight of approximately 55 kD with 6 N-linked glycosylation sites. Structural and compositional analyses demonstrate that sebelipase alfa glycans consist of predominately N-acetyl-glucosamine (GlcNAc) and mannose terminated N-linked structures, as well as mannose-6-phosphate moieties. These glycans target uptake via receptors expressed on a number of cell types including Kupffer cells and hepatocytes in which substrate accumulation leads to disease pathogenesis. The described N-glycan structures are common to those found in human proteins and have been shown to facilitate protein uptake into cells via the macrophage mannose or mannose-6-phosphate receptors.[9,10] N-acetyl-galactosamine (GalNAc) was not detected in the monosaccharide analysis, indicating that O-linked glycans are not present.

LAL has been shown to catalyse the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. The specific activity of sebelipase alfa is approximately 260 U/mg protein (one unit is defined as the amount of activity that results in the hydrolysis of 1 µmol of a synthetic substrate, 4-methylumbelliferyl oleate (4-MUO), per minute under the assay conditions).

Manufacturing steps include clarification, precipitation and low pH viral inactivation, chromatography, nano filtration, ultrafiltration and diafiltration followed by formulation. The formulated product includes human serum albumin (HSA) as a stabiliser. All manufacturing steps are validated.

Specification testing for the drug substance includes testing for residual egg white proteins, concentration of HSA, and verification of sebelipase alfa purity and identity and enzyme activity. All assays are validated.

Drug product

After sterilising filtration of the formulated drug substance vials are filled prior to final visual inspection for control of visible defects.

[9] Stahl, PD et al 1978, Evidence for receptor-mediated binding of glycoproteins, glycoconjugates, and lysosomal glycosidases by alveolar macrophages *Proc. Natl. Acad. Sci. USA*; 1978; 75: 1309-1403.
[10] Coutinho, MF et al, Mannose-6-phosphate pathway: A review on its role in lysosomal function and dysfunction *Mol Genet Metab* 2012 105 542–550

The product specification testing includes appearance, pH, concentration of sebelipase alfa, identity, purity, endotoxin and bioburden testing. All assays are validated.

Stability of sebelipase alfa drug product is evaluated consistent with International Conference on Harmonisation (ICH) guidelines.[11,12] Long term and accelerated stability data are provided for drug product lots stored at conditions of 5 ± 3°C and 25 ± 2°C (60 ± 5% relative humidity), respectively. The data from these studies support an expiration period of 24 months for sebelipase alfa drug product when stored at 5 ± 3°C.

The stability studies also demonstrated that diluted sebelipase alfa at concentrations of 0.1 mg/mL and 1.0 mg/mL in a syringe are stable for up to 72 hours at 2 to 8°C plus an additional 24 hour equilibration to room temperature followed by administration through a 0.2 µm filter.

The data demonstrate that sebelipase alfa diluted in 0.9% sodium chloride for injection USP/EP, within a concentration range of 0.1 mg/mL to 1.5 mg/mL may be stored for up to 24 hours at 2 to 8°C or 8 hours at 25 ± 2°C with minimal change to the product attributes.

With respect to quality matters, the PI, CMI and labels as detailed in the table above are acceptable.

Quality summary and conclusions

Assuming completion of TGA GMP certification there are no further objections on quality grounds to the approval of Kanuma (sebelipase alfa) 2 mg/mL solution for IV infusion.

Proposed conditions of registration

Batch release testing and compliance with certified product details (CPD)

1. It is a condition of registration that all batches of Kanuma (sebelipase alfa) 2 mg/mL solution for IV infusion imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
2. It is a condition of registration that each batch of Kanuma (sebelipase alfa) 2 mg/mL solution for IV infusion 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.
3. The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

[11] Q1A (R2): Stability Testing of New Drug Substances and Products
[12] Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products. Long term and accelerated stability data

IV. Nonclinical findings

Introduction

The nonclinical dossier included extensive primary pharmacology studies (in vitro and in vivo), three repeat dose toxicity studies (up to 6 months) in two species, reproductive toxicity studies in two species, and anti-drug antibody testing. All pivotal safety related studies were good laboratory practice (GLP) compliant. The dossier was therefore considered to be comprehensive for a biotechnology derived product, in accordance with the ICH guideline;[13] and adequate to evaluate the safety of this first in class medicine.

Pharmacology

Primary pharmacology

Endogenous LAL is localised to lysosomes where it catalyses the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. LAL substrates accumulate in multiple organs in LAL-D patients, particularly in those that play a major role in lipid metabolism and disposal, leading to organomegaly and organ dysfunction, a failure to thrive, and decreased survival. It is intended that sebelipase alfa administered IV to LAL-D patients is sequestered from the circulation into cells via receptor mediated endocytosis and targeted to lysosomes, thereby restoring LAL activity and alleviating the LAL-D phenotype.

In vitro, sebelipase alfa was shown to be taken up by cultured rat alveolar macrophages and to localise to lysosomes within them. Cellular uptake was receptor mediated, as it was inhibited in a concentration dependent manner by an oligosaccharide competitor, mannan.[14] Treatment with sebelipase alfa increased LAL activity in normal human fibroblasts and, in LAL-deficient fibroblasts from patients, was able to fully and rapidly restore activity to normal endogenous levels. These findings indicate that sebelipase alfa is capable of functionally restoring LAL activity in LAL-deficient patient cells by restoring its missing endogenous counterpart.

A battery of studies was conducted in LAL-knockout rats, a model of human LAL-D, to examine the in vivo pharmacodynamics of sebelipase alfa administered IV. Consistent with in vitro studies, a single 5 mg/kg dose of sebelipase alfa led to a rapid and marked increase (as soon as 1 hour post dose) in hepatic LAL activity that exceeded that in control (LAL proficient) livers by up to 21 fold and persisted for up to approximately 72 hours post dose. Several repeat dose studies of at least 4 weeks treatment duration were conducted to assess the effect of a variety of parameters on disease phenotype including treatment duration, dose, dosing frequency, rat age (and thus disease severity) at the commencement of treatment, and treatment withdrawal. These studies showed:

- The levels of LAL substrates in the major organs in which they are normally hydrolysed; the liver, spleen and intestine; were dramatically reduced in a dose and frequency dependent manner by sebelipase alfa, reaching the levels in control animals at the maximum dose and frequency (5 mg/kg weekly).
- Corresponding improvements to liver and intestine histopathology and function (as reflected in serum chemistry and lipid profiles) and body weight relative organ weights were generally dose and frequency dependent. All or most parameters

[13] ICH guideline S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals
[14] Mannan oligosachcharide is a glucomanno protein complex derived from the inner cell wall of fungi.

roughly normalised (equivalent to control animals) by approximately 3 to 5 mg/kg weekly dosing (3 mg/kg weekly being the maximum proposed clinical dose).

- Untreated LAL-D rats failed to gain weight from approximately 8 weeks of age. In contrast, dose dependent increases in weight were observed in sebelipase alfa treated rats, attaining the level in control rats with ≥ 3 mg/kg weekly doses. Survival at 19 weeks of age was increased from 0 to 100%.
- Whereas fortnightly treatment with ≥ 3 mg/kg was generally sufficient to significantly reverse most LAL-D-associated pathology, monthly dosing only led to moderate improvements to histopathology and to fluctuations in body weight, although all animals survived. Accordingly, from 4 weeks after the cessation of treatment (in a 13 week recovery period), all physiological parameters significantly deteriorated towards the untreated state.

In summary, the LAL-D phenotype in rats was substantially reversed by a sebelipase alfa dosing regimen (approximately 3 to 5 mg/kg/week) that was highly similar to that proposed clinically (maximum 3 mg/kg/week) and which elicited serum exposure in rats comparable to that observed clinically (see Pharmacokinetics, below).

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic effects of sebelipase alfa were not examined. This is acceptable given that the amino acid sequence of sebelipase alfa is identical to that of the endogenous human enzyme it is designed to restore in LAL-D patients, and sebelipase alfa was shown in vitro and in vivo to be rapidly taken up by cells and to localise to the appropriate organelle, the lysosome.

Safety pharmacology studies covered the core battery of systems. In a study on the rat respiratory system, small increases in respiratory rate and minute volume (approximately ≤ 1.2 fold) were observed at ≥ 6.7 fold peak clinical exposure (maximum observed serum concentration (C_{max}) = 8 µg/mL in rats (male and female average) at dose of 20 mg/kg compared with C_{max} = 0.96 µg/mL in patients). These effects do not raise particular safety concerns as they were moderate and reversible, were observed only during IV infusion, and were only statistically significant (in the case of minute volume) at the mid, but not high, dose. These effects might be linked to the dose dependent hypersensitivity reactions in rats during infusion that were observed in repeat dose toxicity studies (and which are attributed to the administration of foreign (human) proteins).

Safety pharmacology studies on the rat central nervous and monkey cardiovascular systems did not show any significant drug related effects at doses up to 50 mg/kg at which the estimated peak exposure was 98 and 163 fold (in rats and monkeys, respectively) that in humans.[15]

Based on the safety margins and minor transient nature of effects in the above mentioned studies, no significant clinical safety concerns are raised for the central nervous, cardiovascular or respiratory systems.

Pharmacokinetics

In Sprague Dawley rats and monkeys, peak (C_{max}) and overall area under the concentration time curve (AUC) exposure were shown to be supra proportional to dose from 1 to 50 mg/kg, suggesting clearance from the circulation was saturable over this dose range. In adult patients, these parameters were similarly supra proportional to dose from 1 to 3 mg/kg, but were roughly proportional up to 1 mg/kg in adults and children and 3 mg/kg

[15] Calculated as the C_{max} (average of male and female) of 94 µg/mL and 156 µg/mL for rats and monkeys, respectively, compared to steady state C_{max} of 0.96 µg/mL in adult patients.

in infants (the maximum clinical dose). Serum concentration and exposure generally did not increase with repeat dosing for up to 4 weeks in rats and monkeys and up to 6 months in humans, but were increased by repeat dosing for 6 months in monkeys. Although sex differences in serum kinetics were evident for rats, this was not the case for monkeys and humans, and the half-life was very short in all species examined (maximum apparent terminal half-life ($t_{½}$) of 20 minutes, 69 minutes and 84 minutes in rats, monkeys and humans). Volume of distribution was limited (approximately 11%, < 31% and approximately 16% of total body water in rats, monkeys and humans) and plasma clearance was low to moderate in monkeys and humans (< 8% and < 60% hepatic blood flow, respectively).

Specific distribution studies were not conducted. The low volume of distribution estimated from single and repeat dose serum kinetics indicates that the distribution of sebelipase alfa into tissues was limited, as anticipated for a large recombinant protein. However, broad tissue uptake is anticipated since the N-glycans present on sebelipase alfa (which are intended to promote its endocytosis) bind to cognate receptors that are expressed throughout the body in vertebrates. Accordingly, pharmacodynamic studies showed that the uptake of sebelipase alfa by cells in culture was receptor mediated (including via the broadly expressed mannose-6-phosphate receptor). Further, in LAL-D rats in vivo, sebelipase alfa reversed the pathology in a variety of organs which cause the disease phenotype.

No metabolism and excretion studies were performed and this is acceptable based on the ICH guideline.[13] Once sebelipase alfa has been taken up by cells, these processes are anticipated to parallel those of endogenous LAL.

Together these data show that the pharmacokinetic properties of sebelipase alfa in rats and monkeys are sufficiently similar to those in humans to allow the laboratory animal species to serve as appropriate models for assessing the toxicity profile of sebelipase alfa.

Pharmacokinetic drug interactions

No drug interaction studies were performed. This is acceptable given the nature of the drug.

Toxicology

Acute toxicity

A single dose of sebelipase alfa was administered to two cynomolgus monkeys by IV infusion (the clinical route of administration) in a non GLP compliant study. Considerable detail on the conduct of the study was lacking. At the maximum dose of 40 mg/kg (13 fold the maximum clinical dose and estimated to elicit an exposure > 500 fold that observed clinically; Study SBC102-T006) there were no mortalities, nor significant treatment related effects.

In repeat dose studies, the maximum non-lethal dose was 50 mg/kg in both rats and monkeys.

Taken together, these data indicate that sebelipase alfa administered by IV infusion has low acute toxicity.

Repeat dose toxicity

The repeat dose toxicity of sebelipase alfa was evaluated in studies of 4 weeks duration in Sprague Dawley rats and up to 6 months in cynomolgus monkeys. The choice of species (rat as the rodent and monkey as the non-rodent) is acceptable on the basis of pharmacodynamic and pharmacokinetic considerations and the degree of similarity in lysosomal function and LAL amino acid sequence between these species and humans. The

species used, group sizes and use of both sexes were consistent with ICH guideline,[13] as was the duration, particularly considering the presence of anti-drug antibodies in the sera of most animals after repeat dosing for 4 weeks. The duration of the pivotal (6 month) study in monkeys is consistent with the intended long term clinical use of sebelipase alfa. Doses were administered weekly by IV infusion, the clinical frequency and route of administration, and the dose selection was appropriate. Animals were monitored appropriately in all studies.

Relative exposure

Exposure ratios have been calculated based on animal and human serum AUC values (shown in Table 2, below). The AUC data used for animals is the mean of male and female values on the last sampling occasion. Human reference values are for exposure after 23 weeks repeat dosing according to the proposed clinical dosing regimen (and maximum recommended dose in each patient group) and were derived by population pharmacokinetics (PK) modelling.

The exposure in rats and monkeys relative to humans was high (at least 300 fold), despite exposure differing markedly according to patient group.

Table 2: Relative exposure in repeat dose toxicity studies

Species	Study duration/type [Study ID]	Dose (mg/kg)	Dosing freq. (/ftn)	AUC^ (µg·h/mL)	Exposure ratio#		
					Adults	Children	Infants
Rat (SD)	4 weeks [Study SBC102-T002]	5	2	2.4	2.5	5.3	2.0
		20		42	44	93	35
		50		370	390	822	308
Monkey (cynomolgus)	4 weeks [Study SBC102-T001]	5	2	4.8	5.1	10.7	4.0
		20		79	83	176	66
		50		431	454	958	359
	6 months [Pivotal; Study SBC102-T006]	3	2	6.1	6.4	13.6	5.1
		10		105	111	233	88
		30		1063	1119	2362	886
Human (LAL-D patients)							
Adults (≥ 18 years)	Population PK Study [Study SYN201301]	1	1	1.9	–	–	–
Children (4 to 11 years)				0.9	–	–	–
Infants (< 1 year)		3	2	1.2	–	–	–

^ = animal data are for the sexes combined at the last sampling occasion and $AUC_{0\text{-last}}$ [16]and AUC_{ss} [17]values are presented for animal and human studies, respectively. # = animal serum $AUC_{0\text{-last}}$: human serum AUC_{ss} exposure ratios were normalised for dosing frequency by multiplying each AUC value by the respective dosing frequencies shown.

Major findings

There were no significant toxicity findings due to sebelipase alfa in either rats or monkeys.

The most prominent finding was a transient hypersensitivity type ('anaphylactoid') reaction during dosing of both control and drug treated animals. This effect was most prevalent and pronounced in rats, in which it was characterised by redness of the skin and swelling of the paws, was dose dependent and was alleviated by treatment with diphenhydramine. The effect may reasonably be attributed to the exposure of the animals to foreign proteins (sebelipase alfa and human serum albumin present in the vehicle) and is common in nonclinical studies with recombinant human proteins. These findings are not considered to raise significant concerns for the use of sebelipase alfa in humans.

[16] $AUC_{0\text{-last}}$ = area under the concentration-time curve from the start of the infusion to the time of the last quantifiable concentration
[17] AUC_{ss} = area under the concentration time curve at the steady state

Minimal cellular infiltration in a variety of tissues was a recurrent observation in monkeys in both the 4 week and the 6 month (pivotal) study and appeared to occur more frequently in drug treated animals. However, the incidence was generally low in all groups and there were no statistically significant differences between dose groups. In the brain and heart, the incidence of infiltrating immune cells or inflammation appeared to be obviously higher in monkeys dosed for 4 weeks with 20 or 50 mg/kg/week sebelipase alfa compared to controls. However, the incidence of these findings in the pivotal study was not dose related and there were no clinical signs or electrocardiogram (ECG) changes suggestive of abnormal central nervous system (CNS) or heart function.

After 4 weeks of repeat dosing, the sera of most or all animals from all dose groups and studies contained anti-drug antibodies, including neutralising antibodies. However, the presence of antibodies was not correlated with exposure and thus is not considered to present a concern for the interpretation of the repeat dose toxicity data.

Genotoxicity

Genotoxicity studies were not performed and are not required under ICH guideline.[13] As a large molecular weight protein which localises to the lysosome once taken up by cells (in the primary pharmacology Study SBC102-P001), sebelipase alfa is not anticipated to interact with deoxyribonucleic acid (DNA).

Carcinogenicity

Carcinogenicity studies were not performed. This is considered to be acceptable given the nature of the drug and it's, in vitro and in vivo pharmacodynamics, and to be in accordance with ICH guideline.[13]

Reproductive toxicity

The effects of sebelipase alfa on male and female fertility, early embryonic development, and pre/post-natal development, were examined in rats. Embryofetal development toxicity was examined in both rats and rabbits. All of the main studies for each stage of development and species were fully GLP compliant. The choice of species, group sizes, timing, dosages and duration of treatment are considered appropriate. Doses were administered by IV infusion (the clinical route of administration) twice weekly, more frequent than the clinical dosing frequency (weekly or fortnightly). The observations and measurements performed were comprehensive.

Relative exposure

Table 3: Relative exposure in reproductive toxicity studies

Species	Study [Study ID]	Dose (mg/kg)	Dosing freq. (/ftn)	C_{max} (µg/mL)	AUC^ (µg·h/mL)	Exposure ratio#	
						(C_{max})	(AUC)
Rat (SD)	Fertility§	6	4	1.4†	5.0†	1.3	11
		20		11	42	10	88
		60		116‡	470‡	106	1009
	Embryofetal [Study SBC102-T011] and pre-/post-natal development	6	5	0.6	2.2	0.5	5.8
		20		5	12	5	32
		60		58	227	53	597
Rabbit (NZW)	Embryofetal development [Study SBC102-T008]	3	5	1.1	4	1	11
		10		6	23	5.5	61
		25		59	237	54	624
		50		146	653	133	1718
Human (Adult LAL-D patients, ≥ 18 years)	Population PK Study [Study SYN201301]	1	1	1.1	1.9	–	–

§ = exposure in fertility studies (SBC102-T009 and –T010) based on C_{max} and AUC (average male and female) from repeat dose study SBC102-T002: †, estimate based on linear interpolation from line-of-best fit of PK parameters at 5 and 20 µg/mL doses; ‡ = estimate based on linear extrapolation from line-of-best fit of PK parameters at 20 and 50 µg/mL doses. ^ = $AUC_{0\text{-last}}$ and $AUC_{steady\ state}$ values are presented for animal and human studies, respectively. # = animal: human ratios of serum C_{max} or AUC; exposure ratios based on AUC were normalised for dosing frequency by multiplying the AUC values by the respective dosing frequencies shown.

Animal: human exposure ratios have been calculated based on maximum serum concentration and AUC (see Table 3, above). Toxicokinetics were examined as part the embryofetal development studies in rats and rabbits provided by the sponsor. These data are considered to provide an acceptable estimate of the exposure in the pre-/post-natal development study in rats also, since the dose amounts, frequency and duration were the same. Toxicokinetic data from the 4 week repeat dose toxicity study in rats were used to estimate the exposure in the fertility and early embryonic development studies.

In all studies, the relative exposure based on AUC was high; reaching at least approximately 600 fold the clinical exposure. The exposure ratio based on C_{max} was also high, reaching at least 53 fold. Exposure was generally supra proportional to dose and similar (relative to dose) to that observed in repeat dose toxicity studies (see Table 2, above). The serum half-life was short.

Placental transfer and excretion into milk were not studied and are not anticipated for a large recombinant protein.

There were no noteworthy effects of sebelipase alfa on male or female fertility or early embryonic development in rats. Minor gross abnormalities in the liver and thymus (principally discolouration) of male rats were neither dose dependent, present in the corresponding cohort of female rats, nor observed in repeat dose toxicity studies in rats. Clinical signs consistent with a hypersensitivity reaction, and treatment related minor tissue pathology at the infusion site, mirrored the findings from repeat dose toxicity studies. The no observed adverse effect level (NOAEL) for both male and female fertility was 60 mg/kg twice weekly.

Embryofetal development studies in rats and rabbits showed no significant toxicity of sebelipase alfa. Increases in the incidence of incomplete hyoid and/or supra occipital bone ossification (both species) and bilateral thirteenth ribs (rabbits) occurred at high relative exposures (> 53 fold), lacked dose proportionality and/or did not exceed historical control data from the testing facility. In rabbits, the apparent increase in pre-implantation loss and decreases in mean implantations and live fetuses were minimal, not statistically significant, and occurred only at a high relative exposure (> 130 and 1700 fold, based on C_{max} and AUC, respectively). The stated NOAEL was 60 mg/kg and 50 mg/kg twice weekly for rats and rabbits, respectively.

In the study of pre- and post-natal development in rats, no noteworthy toxicity due to sebelipase alfa was evident. Both the maternal and neonate NOAEL were 60 mg/kg twice weekly.

Based on these findings, sebelipase alfa is not considered to raise any concerns for reproductive toxicity from a nonclinical perspective.

Pregnancy classification

The sponsor has proposed Australian Pregnancy Category B2.[18] Since the animal reproductive toxicity studies were adequate and raised no significant concerns, Australian Pregnancy Category B1 is warranted.[19]

Local tolerance

The local tolerance to the IV infusion of sebelipase alfa was examined as part of repeat dose toxicity and reproductive toxicity studies in rats, rabbits and monkeys which were fitted with implanted catheters. In all species, a low to moderate incidence of perivascular inflammation, fibrosis, intimal proliferation, thrombi and thickening were observed at the catheter entrance and/or tip in both control and sebelipase alfa treated groups. These changes are considered to be due to catheterisation and are not of toxicological concern.

[18] Australian Pregnancy Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
[19] Australian Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Paediatric use

Sebelipase alfa is intended for use in patients of all ages with LAL-D. Although specific studies in juvenile animals were not provided, the 4 week and 6 month repeat dose toxicity studies in monkeys were conducted in juvenile animals (2 to 3 years of age). Neither the results of the comprehensive safety and general repeat dose toxicity studies, nor the pharmacology of sebelipase alfa, raise any specific concerns for toxicity towards developing systems and use in paediatric populations. It is considered acceptable and consistent with the guideline;[20] that studies in juvenile animals were not performed.

Comments on the nonclinical safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for sebelipase alfa detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The nonclinical dossier was adequate and the set of studies was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines.[13] The overall quality of the nonclinical dossier was high. All pivotal safety related studies were GLP compliant.
- In vitro, sebelipase alfa was shown to be taken up by cells, localise to lysosomes, and restore LAL enzyme activity in LAL-D patient cells. In vivo in a rat model of LAL-D, doses of sebelipase alfa equivalent to that proposed clinically (based on mg/kg) were shown to increase hepatic LAL activity and reverse the hallmark pathology of LAL-D including organomegaly and tissue LAL substrate accumulation, dyslipidaemia, and a failure to thrive. In vitro and in vivo results were consistent with broad tissue uptake. These data support the proposed clinical indication.
- Safety pharmacology studies of the effects of sebelipase alfa on the monkey cardiovascular system and rat respiratory and central nervous systems did not raise any safety concerns.
- In laboratory animal species (rats, rabbits and cynomolgus monkeys), as in humans, sebelipase alfa exposure was supra proportional to dose above approximately 1 mg/kg (the proposed dose in adults and children) and was generally not increased by repeat dosing (dosing for 6 months in monkeys being the exception). Sebelipase alfa exhibited a short serum half-life and was rapidly cleared from the circulation after the completion of IV infusion. The volume of distribution in all species was limited, as anticipated for a drug of this nature.
- The repeat dose toxicity of sebelipase alfa administered by IV infusion was assessed in studies of up to 4 weeks duration in rats and 6 months in monkeys and maximum exposures (AUC) were high. There were no findings considered to be of toxicological concern. Transient dose dependent hypersensitivity reactions were frequently observed in both vehicle and drug treated rats during or immediately following dosing; a common finding in rats administered foreign recombinant proteins; but infrequently in monkeys. Infusion associated hypersensitivity reactions were observed in some patients in the clinical studies and corresponding statements are included in the PI and RMP. No concerns were raised for local toxic effects of sebelipase alfa at the site of IV infusion.

[20] EMEA/CHMP/SWP/169215/2005 Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications. 24 January 2008.

- Anti-drug antibodies were present in the sera of most rats and monkeys after repeat dosing with sebelipase alfa, yet were not correlated with exposure, toxicity, or the pharmacodynamics of sebelipase alfa in a rat model of LAL-D. Monkeys dosed repeatedly for 6 months tested positive for anti-ovalbumin antibodies, consistent with sebelipase alfa being produced from chicken egg whites, which may have implications for patients with egg allergies.
- Consistent with the ICH guideline no genotoxicity or carcinogenicity studies were conducted.[13]
- In comprehensive reproductive toxicity studies in rats and rabbits, sebelipase alfa exposure was high and no concerns were raised for reproductive safety from a nonclinical perspective. Pregnancy Category B1 is warranted, rather than the sponsor's proposal for Category B2.[18,19]
- Based on the data provided and evaluated in this report, there are no nonclinical objections to the registration of Kanuma sebelipase alfa.
- The nonclinical evaluator also raised issues relating to the PI but these are beyond the scope of the AusPAR.

V. 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

Information on the condition being treated

LAL-D is a very rare, serious and life threatening lysosomal storage disorder caused by mutations affecting a single gene. It is associated with significant morbidity and mortality affecting individuals from infancy through to adulthood. LAL-D presenting in infants is a medical emergency with rapid disease progression over a period of weeks that is typically fatal within the first 6 months of life.

LAL-D is an autosomal recessive lysosomal storage disorder characterised by a genetic defect resulting in a marked decrease or loss in activity of the lysosomal acid lipase (LAL) enzyme. Deficient LAL enzyme activity results in progressive complications due to the lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the liver, spleen, intestine and the walls of blood vessels. The resulting lipid accumulation in the liver leads to hepatomegaly, increased hepatic fat content, transaminase elevation signalling chronic liver injury, and progression to fibrosis, cirrhosis, and complications of end stage liver disease. In the spleen, LAL-D results in splenomegaly, anaemia and thrombocytopenia. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. In parallel, dyslipidaemia due to impaired degradation of lysosomal lipid is common with elevated low density lipoprotein cholesterol (LDL-c) and triglycerides, and reduced high density lipoprotein cholesterol (HDL-c). In addition to liver disease, patients with LAL-D experience increased risk for cardiovascular disease and accelerated atherosclerosis.

Current treatment options

Current treatment options for patients with LAL-D are limited to supportive therapies, including nutritional support, blood transfusions and albumin in an attempt to mitigate

some of the effects of this rapidly fatal disease (Study LAL-1-NH01). Although some temporary stabilisation of the clinical condition has been described, these interventions do not appear to substantially modify the outcome in affected patients.[21,22] With few exceptions, success has not been achieved using haematopoietic stem cell transplantation (HSCT) in infants due to its limited use and/or association with high mortality due to the condition of the infants at the time of diagnosis and the rapidly progressive nature of the disease. Additionally, HSCT carries its own inherent risks, including graft versus host disease and does not fully address all aspects of the disease as it only replaces haematopoietic cells and therefore cannot resolve hepatic or other complications of the enzyme deficiency.[23,24,25,26] In the natural history Study LAL-1-NH01, median survival was noted to be longer for patients who received HSCT (and/or liver transplant) compared to those who did not; however, survival is still quite poor with median age at death of 8.6 months.

Treatment for children or adults presenting with LAL-D is limited to liver transplant as liver function deteriorates, and attempts to manage dyslipidaemia through diet and the use of lipid lowering medications (LLMs). There is limited information in the medical literature on the long term outcomes of liver transplantation in patients with LAL-D.[27,28,29,30] In addition to the important risks associated with transplantation itself, and the required concomitant immunosuppression post-transplant, liver transplant does not fully address the root cause of disease since other cells and tissues, including cells of haematopoietic lineage which will repopulate the transplanted liver, will remain enzyme deficient in transplanted patients; hence, other disease complications may persist even if transplants are successful.

Clinical rationale

Sebelipase alfa is the first ERT to be developed for LAL-D and treatment with sebelipase alfa is intended to directly address the root cause of disease by replacement of the missing or deficient enzyme resulting in reduction of the accumulated substrates and restoration of normal lipid metabolism.

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalised into lysosomes. It catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to: free cholesterol, glycerol and free fatty acids. Replacement of LAL enzyme activity would potentially lead to reductions in liver fat content and transaminases, enable metabolism of cholesteryl esters and triglycerides in

[21] Hoeg, M et al. 1984 Cholesteryl Ester Storage Disease and Wolman Disease: Phenotypic Variants of Lysosomal Acid Cholesteryl Ester Hydrolase Deficiency. *Am J Hum Genet* 1984; 36:1190-1203
[22] Meyers WF et al. 1985. The use of parenteral hyperalimentation and elemental formula feeding in the treatment of Wolman disease. *Nutrition Research* 1985; 5: 423-429
[23] Krivit W et al, 2000 Wolman disease successfully treated by bone marrow transplantation. *Bone Marrow Transplantation* 2000; 26: 567–570
[24] Stein J et al. 2007. Successful treatment of Wolman disease by unrelated umbilical cord blood transplantation. *Eur J Pediatr* 2007; 166:663–666
[25] Tolar J, et al. 2009 Long-term metabolic, endocrine, and neuropsychological outcome of hematopoietic cell transplantation for Wolman disease. *Bone Marrow Transplantation* 2009; 43, 21–27.
[26] Yanir A, et al 2013 Unfavourable outcome of hematopoietic stem cell transplantation in two siblings with Wolman disease due to graft failure and hepatic complications. *Molecular Genetics and Metabolism* 2013; 109: 224–226
[27] Ferry D et al, 1991. Liver transplantation for cholesteryl ester storage disease. *Journal of Paediatric Gastroenterology and Nutrition* 1991: 12: 376-378
[28] Krivit, W et al, 1992. Wolman's Disease: A Review of Treatment with Bone Marrow Transplantation And Considerations for the Future *Bone marrow transplantation* 1992.
[29] Kale S, et al 1995. Case Report: End-Stage Renal Disease in a Patient with Cholesteryl Ester Storage Disease following Successful Liver Transplantation and Cyclosporine Immunosuppression. *Journal of Paediatric Gastroenterology and Nutrition* 1995: 20: 95-97
[30] Hansen K, et al. 2008 Metabolic liver disease in children. *Liver Transplantation* 2008; 14: 713-733

the lysosome, leading to reductions in LDL-c, non-HDL-c, and triglycerides, and increases in HDL-c. As a result of substrate reduction in the intestine, treatment with proposed sebelipase alfa could also lead to an improvement in growth. Enzyme replacement therapy in patients with LAL-D is a rational approach given the demonstrated medical value and long term safety of ERTs for other Lysosomal Storage Disorders (LSDs), including Gaucher disease, Pompe disease, Fabry disease, and the mucopolysaccharidoses.

The sebelipase alfa formulation used in clinical trials is the formulation proposed for marketing and no biopharmaceutic bridging studies were required. Some changes were made to the drug substance manufacturing process during development;[31] but no significant changes have been made to the overall process since initiation of pivotal clinical trials.

There is lack of any effective and safe treatment that directly addresses the root cause of LAL-D and current treatment options are limited to supportive therapies. The clinical rationale for use of sebelipase alfa for long term ERT of LAL-D is valid and acceptable.

Guidance

Contents of the clinical dossier

Clinical pharmacology studies:

- Study LAL-CL01: A Phase I/II open label multicentre study to evaluate the safety, tolerability and pharmacokinetics of SBC-102 in adult patients with liver dysfunction due to lysosomal acid lipase deficiency.
- Study SBC-103: A population pharmacokinetics and pharmacokinetic pharmacodynamic graphical evaluation of sebelipase alfa (SBC-102) for subjects with lysosomal acid lipase deficiency.

Pivotal controlled efficacy/ safety studies:

- Study LAL-CL02: A Phase III, multicentre, randomised, placebo controlled study of SBC-102 in patients with lysosomal acid lipase deficiency (also known as ARISE (Acid Lipase Replacement Investigating Safety and Efficacy)).

Uncontrolled efficacy/safety studies:

- Study LAL-CL03: A Phase III, open label, multicentre, dose escalation study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of SBC-102 in children with growth failure due to lysosomal acid lipase deficiency
- Study LAL-CL04: An open label multicentre extension study to evaluate the long term safety, tolerability, and efficacy of sebelipase alfa in adult subjects with liver dysfunction due to lysosomal acid lipase deficiency who previously received treatment in Study LAL-CL01.

In addition, the sponsor submitted an Integrated Analysis of Safety.

Other reports:

- Study LAL-1-NH01: An observational, multinational, multicentre natural history study of patients diagnosed with LAL-D presenting in infancy (historically called Wolman disease or LAL-D/Wolman phenotype).

[31] Some additional controls and process optimisation were implemented for the proposed commercial process. These process changes were developed and implemented to ensure batch-to-batch consistency of the quality, safety and potency of the Drug Substance, as well as to augment viral reduction capacity of the purification process.

- Study LAL-2-NH01: An observational, multinational, multicentre study of the clinical characteristics and disease progression of patients with lysosomal acid lipase deficiency/cholesterol ester storage disease phenotype using data from the clinical charts of a sufficient number of children and adults presenting with LAL-D.

Recently initiated studies (only study protocols were provided in the submitted dossier):

- Study LAL-CL06: An open label, multicentre study to evaluate the safety and efficacy of SBC-102 (United States adopted name: sebelipase alfa) in a broad population of subjects[32] with lysosomal acid lipase deficiency (LAL-D).
- Study LAL-CL08: A Phase II, open label, multicentre, repeat dose, study of sebelipase alfa in infants with rapidly progressive LAL-D.

The submission also contained literature references, clinical overview, summaries of clinical pharmacology, clinical efficacy and clinical safety.

Paediatric data

Fifty six of 84 patients (67%) who received sebelipase alfa during clinical studies (Studies LAL-CL01/LAL-CL04, LAL-CL02 and LAL-CL03) were in the paediatric and adolescent age range (1 month up to 18 years).

Good clinical practice

All studies have been conducted in accordance with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) consolidated guidelines and the ethical principles of the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Due to the rare nature of the disease being treated, there were no studies in healthy subjects. Hence, all discussion below relates to PK findings in patients with LAL-D. Studies providing PK data are shown in Table 4, below.

[32] Such subjects may have been excluded from enrolment in other studies of LAL-D because of age, disease progression, and previous treatment by hematopoietic stem cell or liver transplantation, less common disease manifestations, or disease characteristics that would preclude participation in a placebo controlled Study.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	None	
PK in special populations	Target population § Single dose	None
	Multi-dose	Study LAL-CL01
	Hepatic impairment	Study LAL-CL01
	Renal impairment	None
	Neonates/infants/children/adolescents (limited information in patients > 18 years of age)	Study LAL-CL03 (infants)
	Elderly	None
	Other special population	None
Genetic/ gender related PK	Males versus females	
	Other genetic variables	
PK interactions		None
Population PK analyses	Healthy subjects	None
	Target population	Study SYN201301

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

In the Phase I/II Study LAL-CL01, SBC-102 serum concentrations increased rapidly during the first 10 to 15 minutes of the 2 hour infusion, with a further slower increase thereafter. Median time to maximum observed serum concentration (T_{max}) ranged from 0.67 to 1.80 hours, and appeared to increase with increasing dose. At the end of infusion, serum concentrations fell rapidly for the 1 and 3 mg/kg dose (mean t½ = 0.111 to 0.166 hours). This fall was less rapid for the 0.35 mg/kg dose (mean t½ = 1.825 at Day 0 and 0.966 at Day 21). Decreases in the mean clearance were noted in the 3 $mg \cdot kg^{-1}$ dose cohort relative to the other dose cohorts at both Day 0 and Day 21.

SBC-102 serum concentrations were reasonably dose proportional over the 3 fold increase in dose from 0.35 mg/kg to 1 mg/kg based on median values for AUC and C_{max} in this limited study population. Concentrations increased in a greater than dose proportional manner (approximately 10 fold) over the 3 fold increase in dose from 1 mg/kg to 3 mg/kg, which suggests that either binding or serum clearance mechanisms for SBC-102 may become saturated between 1 mg/kg to 3 mg/kg.

Decreases in volume of distribution (V_z) of SBC-102 were noted with increasing dose and after multiple dosing within the 0.35 mg/kg and 1 mg/kg dose cohort. In both these cohorts, the reduction in V_z between Day 0 and Day 21 did not alter the subject's rank order with respect to the parameter value. This suggests that the variability in V_z may reflect inter-individual differences in a saturable distribution process (binding or uptake) of SBC-102. The appearance of saturation is more likely with increasing magnitude of dose and dosing duration. It would be expected that changes in V_z would lead to differences in half-life between Day 0 and Day 21, but half-life was time and dose independent with exception of the 0.35 mg/kg dose group. The longer half-life noted following the 0.35 mg/kg dose is consistent with the higher volume of distribution relative to clearance for this dose in comparison with other doses (1 mg/kg and 3 mg/kg).

The PK of sebelipase alfa was described by a 1 compartment disposition model with a dual input model to allow for variability in infusion rate due to the flush. Sebelipase alfa showed linearity in doses of 0.35 to 1 mg/kg, and nonlinearity observed at a dose of 3 mg/kg. Total body clearance (CL) in the linear dose range, and therefore, exposure, was affected by body surface area (BSA.) As BSA was highly correlated with age, exposure therefore varied across subject age. Summary statistics of exposure variables for all subjects in Studies LAL-CL02 and LAL-CL03 suggested that there was no evidence of sebelipase alfa accumulation over time, with similar values of CL, volume of distribution of the central compartment (V_c), t½, T_{max}, C_{max}, and AUC observed at Week 0 and Week 22 by dose.

During the covariate analysis of the population pharmacokinetics model for sebelipase alfa, age, body weight, and sex were not found to have a significant influence on CL and V_c of sebelipase alfa. Sebelipase alfa has not been investigated in patients 2 to 4 years of age. There is limited information on PKs in patients > 18 years of age.

There is limited information on the impact of anti-drug antibodies on sebelipase alfa pharmacokinetics.

Sebelipase alfa is expected to be metabolically degraded through peptide hydrolysis. Hence, impaired liver function is not expected to affect the pharmacokinetics of sebelipase alfa. There is a lack of data in patients with severe hepatic impairment. Renal elimination of sebelipase alfa is considered a minor pathway for clearance. There is a lack of data in patients with renal impairment. No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of sebelipase alfa.

Overall, sebelipase alfa demonstrates PK characteristics consistent with other ERTs whose uptake and biodistribution are mediated by mannose and mannose 6-phosphate receptor dependent mechanisms.[33] The PK properties are predictable, with no changes associated with long term dosing through to 104 weeks. In Study LAL-CL01, the absence of anti-sebelipase alfa antibodies in adults with extended dosing precludes evaluation of effect of antibody formation on the PK profile of sebelipase alfa.

The PK aspects of the proposed PI are satisfactory.

Pharmacodynamics

Studies providing pharmacodynamic data

Studies providing pharmacodynamic data are shown in Table 5, below.

[33] Stahl PD, et al 1978 Evidence for receptor-mediated binding of glycoproteins, glycoconjugates, and lysosomal glycosides by alveolar macrophages. *Proc Natl Acad Sci U S A*. 1978; 75: 1399-1403.

Table 5: Submitted pharmacodynamic studies

Pharmacodynamics (PD) topic	Subtopic	Study ID
Primary pharmacology	Effect on PD parameter; liver enzymes	LAL-CL01
	Effect on PD parameter; serum lipids	LAL-CL01
Secondary pharmacology	Development of anti-drug antibodies	
Gender other genetic and age related differences in PD response	No data	
PD interactions	No data	
Population PD and PK-PD analyses	Healthy subjects	None
	Target population	SYN201301

Evaluator's conclusions on pharmacodynamics

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalised into lysosomes. It catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. Replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in LDL-c, non-HDL-c, and triglycerides, and increases in HDL-c. Improvement in growth occurs as a result of substrate reduction in the intestine.

In clinical trials, after initiation of dosing with sebelipase alfa, breakdown of accumulated lysosomal lipid led to initial increases in LDL-c and triglycerides within the first 2 to 4 weeks of treatment. In general, following increases in LDL-c and triglycerides, these parameters decreased to below pre-treatment values within 8 weeks of treatment with sebelipase alfa.

In all patients with elevated alanine aminotransferase (ALT) values at Baseline (82 of 84 patients in clinical trials), reductions in ALT values were observed, generally within 2 weeks after initiation of treatment with sebelipase alfa. Treatment interruption resulted in increases in LDL-c and ALT values and decreases in HDL-c.

Though there is a risk of immunogenicity with any ERT, the overall rate of immunogenicity in studies with sebelipase alfa appears low. Subjects who tested positive for anti-drug antibodies (ADAs) were evaluated for sebelipase alfa neutralising antibodies by measuring LAL enzyme activity and the cellular uptake of LAL. The population PK analysis of sebelipase alfa revealed no relevant effect of ADA positivity on the exposure to sebelipase alfa. The incidence of ADA positivity was higher in infants compared with children and adults. No evidence of any impact of ADAs on efficacy parameters was observed in children or adults, and although some potential impact on efficacy was observed in one infant positive for ADAs, the contribution of the ADA to the relative slowing of weight gain

in this infant was not definitively established (as there were multiple concurrent confounding medical factors that also could impact weight gain and growth).

Dosage selection for the pivotal studies

Results of the Phase I/II Study LAL-CL01 in adults with LAL-D provided adequate evidence to support testing the following doses of sebelipase alfa in the two pivotal studies:

- Study LAL-CL02 in adults and children with LAL-D: 1 mg/kg every other week dose administered by IV infusion; over 2 hours with option to reduce infusion duration to 1 hour if tolerated).
- Study LAL-CL03 in infants with LAL-D: 1 mg/kg every week with option to increase dose to 3 mg/kg for infants who present with rapidly progressive disease administered by IV infusion (over 2 hours). It is important to note that the option to reduce infusion duration to 1 hour was not evaluated in infants.

For further details of dosage selection for the pivotal studies please see Attachment 2 (Extract from the Clinical Evaluation report).

Efficacy

Studies providing efficacy data

- Study LAL-CL02: A pivotal, Phase III, multicentre, randomised, placebo controlled study of SBC-102 in patients with lysosomal acid lipase deficiency (also known as ARISE (Acid Lipase Replacement investigating safety and efficacy)).
- Study LAL-CL03: A, Phase II/III, open label, multicentre, dose escalation study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of SBC-102 in children with growth failure due to lysosomal acid lipase deficiency
- Study LAL-CL04: A Phase II, open label multicentre extension study to evaluate the long term safety, tolerability, and efficacy of sebelipase alfa in adult subjects with liver dysfunction due to lysosomal acid lipase deficiency who previously received treatment in Study LAL-CL01.

Evaluator's conclusions on efficacy

LAL-D is a very rare, serious and life threatening lysosomal storage disorder caused by mutations affecting a single gene. It is associated with significant morbidity and mortality affecting individuals from infancy through to adulthood. LAL-D presenting in infants is a medical emergency with rapid disease progression over a period of weeks that is typically fatal within the first 6 months of life. Current treatment options only include supportive therapies and there are no approved treatments addressing the root cause of the disease.

The main evidence for efficacy of sebelipase alfa was provided by the well conducted, Phase III, double blind, placebo controlled Study LAL-CL02 involving 66 patients with LAL-D (children and adults, with 71% aged > 18 years). The study was conducted in a broad range of subjects at different stages of disease progression including subjects with histologically confirmed cirrhosis and different genotypes. Study LAL-CL03 was the only study which evaluated the effect of sebelipase alfa in 9 infants with growth failure. This group of patients with LAL-D represents subgroup with serious complications and high mortality and morbidity risks. Overall, subjects enrolled in these 2 main studies were representative of the target patient population for the proposed indication.

In pivotal Study LAL-CL02, ERT with sebelipase alfa 1 mg/kg every other week (administered by IV infusion over 2 hours with option to reduce infusion duration to 1 hour if tolerated) during the 20 week double blind treatment period resulted in clinically meaningful reductions in ongoing liver cell injury, as evidenced by statistically significant improvements in the primary endpoint of ALT normalisation over placebo, with marked decreases in ALT and AST levels. Reductions in liver cell injury were accompanied by clinically relevant reductions in other markers of liver dysfunction, including gamma glutamyl transferase (GGT) and bilirubin. Sebelipase alfa also improved LAL-D related dyslipidaemia, with clinically meaningful and statistically significant reductions in LDL-c accompanied by statistically significant decreases in triglycerides, increases in HDL-c, and favourable changes in other abnormalities associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). Sebelipase alfa produced statistically significant decreases in liver fat fractions assessed by magnetic resonance imaging (MRI) and reductions in liver and spleen volume reflecting reductions in lysosomal lipid accumulation, which is directly related to LAL enzyme deficiency which is the root cause of the disease. Clinical endpoints such as cardiovascular morbidity/mortality or effects on liver histopathology would have required larger sample size with longer double blind treatment periods which was not possible due to the low prevalence and variable disease progression associated with this multisystem disorder. During the open label treatment period, these improvements were maintained in the subjects treated with sebelipase alfa during the double blind period, and a similar pattern of response was observed in subjects switched from placebo to 1 mg/kg every other week (qow) sebelipase alfa.

In Study LAL-CL03, 9 infants with LAL-D and growth failure were treated with sebelipase alfa (1 mg/kg every week with option to increase dose to 3 mg/kg for infants who present with rapidly progressive disease administered by IV infusion over 2 hours). These infants presented with immediately life threatening multi systemic disease and their baseline characteristics were consistent with those reported among the patients in natural history Study LAL-1-NH01, supporting the comparison of survival data and outcomes between these 2 populations. Hence the study design and primary efficacy endpoint of survival was appropriate. Efficacy of sebelipase alfa was demonstrated in this subgroup of patients with poor prognosis with 67% (95% CI = 29.93%, 92.51%) of sebelipase alfa treated subjects surviving to 12 months of age compared with 0% (0, 16.11%) of untreated patients in a historical control group. Sebelipase alfa also produced clinically meaningful improvements in growth (WFA percentile), biochemical markers of liver injury, hepatosplenomegaly, and haematological abnormalities such as anaemia and thrombocytopenia, and lipid profile.

Results from Study LAL-CL04 showed that the previously observed early benefits of enzyme replacement with sebelipase alfa that were reported in Study LAL-CL01 can be achieved with qow dosing and continue through Week 104 with sustained normalisation of transaminases, sustained improvements on serum lipids, and reduction in fat fraction in the liver in adult subjects with LAL-D.

Overall, there was adequate evidence to support efficacy of sebelipase alfa for long term ERT in patients of all ages with lysosomal acid lipase deficiency (LAL-D).

The efficacy sections of the proposed PI are satisfactory.

Safety

Studies providing safety data

Six clinical studies have been initiated to evaluate sebelipase alfa treatment in infants, children, and adults with LAL-D. (Studies LAL-CL03 and LAL-CL08 in infants, Studies LAL-CL02 and LAL-CL06 included children and adults, and Studies LAL-CL01 and

LAL-CL04 included adults only) An initial comprehensive Integrated Safety Analysis;[34] and an updated Integrated Safety Analysis of relevant new safety information (the D120 Safety Update);[35] were conducted (see Table 21 in Attachment 2). The D120 Safety Update was based on a dynamic database rather than on a cleaned, locked database. The pooling of data for the integrated analyses supporting this application was restricted to subjects who were administered at least 1 dose (partial or complete) of sebelipase alfa in the 4 fully enrolled studies included in the Integrated Safety Analysis (pooled Safety Set) and the 4 fully enrolled studies and 2 additional ongoing studies included in the D120 Safety Update (updated pooled Safety Set), Adverse events for both the Pooled Safety Set and the updated pooled Safety Set were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0.

Pooled safety assessment was conducted to determine if any safety signals would be revealed that were not otherwise evident in the individual clinical studies but this exploratory analysis across the entire enrolled subject population was limited due to differences in the rate of disease progression, frequency of intercurrent illness and requirements for invasive procedures for disease management. Furthermore, management of patients during the treatment period with the study drug varied across subject populations from infants with rapidly progressive disease, who are frequently hospitalised due to more severe symptoms, to children and adults, whose progression to serious complications is more variable.

Safety information was also available for 3 patients who received sebelipase alfa treatment under a compassionate use protocol. Data from the 2 observational, non-interventional studies (Studies LAL-1-NH01 and LAL-2-NH01) were not included in the pooled safety set and only used as reference to historical controls in comparison to patients treated with sebelipase alfa.

Patient exposure

In the Integrated Safety Database across 4 studies, a total of 84 subjects with LAL-D have received treatment with sebelipase alfa, including 9 infants, 47 children, and 28 adults.

Across the 6 studies included in the D120 safety update, 106 subjects with LAL-D have received treatment with sebelipase alfa, including 14 infants, 57 children, and 35 adults.

Table 6 (shown below) gives the duration of study drug exposure in the pooled Safety Set overall and by study.

[34] Data cut-off dates between 30 May 2014 and 27 June 2014 (depending on the study).
[35] Analysis cut-off date of 26 January 2015 for all 6 studies.

Table 6: Duration of study drug exposure in the pooled Safety Set overall; and by study

Dose Regimen Statistic	Study			Pooled Safety Set (N=84)
	LAL-CL01/ LAL-CL04 (N=9)	LAL-CL02 (N=66)	LAL-CL03 (N=9)	
0.35 mg/kg qw, months				
n	3	0	8	11
Mean (SD)	1.91 (0.07)	--	0.34 (0.19)	0.77 (0.75)
Median	1.91	--	0.43	0.46
Min, Max	1.84, 1.97	--	0.03, 0.46	0.03, 29.14
1 mg/kg qow, months				
n	5	66	0	71
Mean (SD)	27.61 (0.94)	4.73 (3.46)	--	6.34 (6.78)
Median	27.57	5.09	--	5.13
Min, Max	26.74, 29.14	0.03, 15.67	--	0.03, 29.14
1 mg/kg qw, months				
n	3	0	7	10
Mean (SD)	1.48 (0.65)	--	4.72 (6.96)	3.75 (5.90)
Median	1.84	--	2.27	1.86
Min, Max	0.72, 1.87	--	0.23, 20.14	0.23, 20.14
3 mg/kg qow, months				
n	3	0	1	4
Mean (SD)	26.23 (1.98)	--	7.59 (NA)	21.57 (9.46)
Median	27.17	--	7.59	25.56
Min, Max	23.95, 27.56	--	7.59, 7.59	7.59, 27.56
3 mg/kg qw, months				
n	3	0	6	9
Mean (SD)	1.86 (0.02)	--	10.68 (3.78)	7.74 (5.33)
Median	1.87	--	11.71	9.23
Min, Max	1.84, 1.87	--	3.94, 14.98	1.84, 14.98
5 mg/kg qw, months				
n	0	0	1	1
Mean (SD)	--	--	1.61 (NA)	1.61 (NA)
Median	--	--	1.61	1.61
Min, Max	--	--	1.61, 1.61	1.61, 1.61
Number of Infusions Received at Each Dose Level, n (%)[a]				
0.35 mg/kg qw	24 (33.3)	0	14 (88.9)	38 (13.1)
1 mg/kg qow	274 (55.6)	735 (100)	0	1009 (84.5)
1 mg/kg qw	20 (33.3)	0	141 (77.8)	161 (11.9)
3 mg/kg qow	173 (33.3)	0	17 (11.1)	190 (4.8)
3 mg/kg qw	24 (33.3)	0	278 (66.7)	302 (10.7)
5 mg/kg qw	0	0	8 (11.1)	8 (1.2)
Other[b]	0	0	4 (11.1)	4 (1.2)

Source: ISS Table 1.9A.

Max=maximum; Min=minimum; NA=not applicable; qow=once every other week; qw=once weekly; SD=standard deviation.

Subjects may have received study drug at different dose levels; therefore, within each study, a subject may be included in more than 1 dose category.

[a] The n (% of N) represents the total number of infusion received at that dosing regimen where subjects may be counted multiple times (n) followed by the incidence of subjects who received at least 1 infusion at the dose and regimen specified.

[b] One infusion each at doses of 0.2, 0.3, 0.5, and 0.75 mg/kg were administered to Subject 02-001 in Study LAL-CL03.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Liver parameters, including ALT, AST, GGT, alkaline phosphatase (ALP), and total bilirubin (TBil), decreased from baseline to the last assessment. In an analysis by study, reductions in ALT, AST, GGT, ALP, and TBil were apparent across all studies (see Table 7, below). In a few subjects, individual TBil values remained very high at the last assessment and a further medical review indicated that these high TBil values occurred in the context of worsening disease, including a subject in Study LAL-CL03 who died early in the course of treatment (TBil = 443 and 419 µmol/L at Baseline and at last assessment, respectively) and a subject who had evidence of liver decompensation and required an urgent liver transplant in Study LAL-CL01/LAL-CL04 (TBil = 25.1 and 129.3 µmol/L, respectively). Direct bilirubin showed minimal changes from Baseline to the last assessment in

Study LAL-CL01/LAL-CL04 and Study LAL-CL02, and increased from Baseline (27 µmol/L) to the last assessment (71 µmol/L) in Study LAL-CL03. The analysis of DBil in Study LAL-CL03 was based on available data for only 3 subjects, 2 of whom died early in the course of treatment and had marked increases in DBil shortly prior to death; the other subject had a decrease in DBil from Baseline to the last assessment.

In the pooled Safety Set overall, 1 subject (1/84; 1%) each had at least 1 ALT;[36] AST;[37] or GGT;[38] value > 5 x upper limit of normal (ULN) that was at least twice the highest pre-treatment value.

[36] The increase in ALT was reported for Subject LAL-CL03/01-002 who had a peak AST of 7.2 x ULN at about Week 92 in the context of an inflammatory component related to a suspected viral infection.
[37] The increase in AST was reported for Subject LAL-CL01/LAL-CL04/02-001 (peak AST = 5.5 x ULN), and occurred at Week 25. The reason for this isolated elevation in AST is unclear; AST returned to normal at the next assessment 2 weeks later.
[38] The increase in GGT was reported for Subject LAL-CL03/02-003, who had a GGT of 6 x ULN at Baseline that increased to a peak level of 17.2 x ULN at Week 1 and decreased thereafter and was normal by Week 4.

Table 7: Changes from Baseline to last assessment for select chemistry parameters, pooled Safety Set

Parameter	Pooled Safety Set (N=84)		
Statistic	Baseline	Last Assessment	Change
Alanine Aminotransferase (U/L)			
N	80	80	80
Mean (SD)	100.26 (51.054)	56.13 (47.583)	-44.13 (51.619)
Median	85.67	42.50	-38.67
Min, Max	16.0, 297.0	12.0, 367.0	-228.0, 179.0
Aspartate Aminotransferase (U/L)			
N	80	80	80
Mean (SD)	98.72 (107.582)	55.26 (54.388)	-43.45 (67.843)
Median	69.00	41.00	-27.33
Min, Max	37.0, 716.0	20.0, 439.0	-453.0, 42.3
Gamma-Glutamyl Transferase (U/L)			
N	79	79	79
Mean (SD)	65.95 (118.574)	34.23 (41.589)	-31.72 (83.064)
Median	37.00	23.00	-11.67
Min, Max	12.0, 1000.0	6.0, 312.0	-688.0, 5.3
Alkaline Phosphatase (U/L)			
N	81	81	81
Mean (SD)	243.80 (159.350)	222.27 (141.142)	-21.53 (101.924)
Median	256.33	227.00	-15.33
Min, Max	61.0, 977.0	42.0, 571.0	-823.0, 173.7
Total Bilirubin (µmol/L)			
N	80	80	80
Mean (SD)	24.22 (50.057)	23.60 (51.111)	-0.62 (16.665)
Median	13.67	11.00	-2.33
Min, Max	3.0, 443.0	2.0, 419.0	-44.5, 104.2
Direct Bilirubin (µmol/L)			
N	75	75	75
Mean (SD)	4.20 (4.861)	10.03 (44.299)	5.83 (44.424)
Median	2.67	3.00	0.00
Min, Max	0.0, 32.5	1.7, 376.3	-30.8, 376.3
Total Cholesterol (mmol/L)			
N	77	77	77
Mean (SD)	6.49 (1.867)	5.44 (1.979)	-1.05 (1.206)
Median	6.43	5.22	-1.30
Min, Max	2.2, 11.1	1.8, 11.2	-4.4, 1.8
High-Density Lipoprotein Cholesterol (mmol/L)			
N	77	77	77
Mean (SD)	0.81 (0.249)	0.98 (0.312)	0.17 (0.196)
Median	0.82	0.96	0.14
Min, Max	0.0, 1.3	0.3, 2.0	-0.3, 0.8
Low-Density Lipoprotein Cholesterol (mmol/L)			
N	77	77	77
Mean (SD)	4.89 (1.691)	3.87 (1.906)	-1.02 (1.232)
Median	4.83	3.70	-1.28
Min, Max	1.0, 9.6	0.7, 9.5	-3.2, 2.0
Non-High-Density Lipoprotein Cholesterol (mmol/L)			
N	64	64	64
Mean (SD)	5.96 (1.642)	4.80 (1.987)	-1.16 (1.279)
Median	5.82	4.59	-1.53
Min, Max	2.4, 10.2	1.3, 10.4	-3.5, 1.8
Triglycerides (mmol/L)			
N	77	77	77
Mean (SD)	1.75 (0.636)	1.34 (0.556)	-0.41 (0.568)
Median	1.57	1.27	-0.37
Min, Max	0.7, 3.5	0.4, 2.9	-1.8, 1.3

Source: ISS Table 1.5.2A.
Max=maximum; Min=minimum; SD=standard deviation.
Note: Only subjects with values at both Baseline and the last assessment were included in the analyses.

Other clinical chemistry

A transient increase in serum lipids (LDL-c, triglycerides, total cholesterol, and/or non-HDL cholesterol) was noted following initiation of sebelipase alfa therapy. From baseline to the last assessment, total cholesterol, LDL-c and triglyceride values decreased and HDL-c values increased for subjects in the pooled Safety Set (see Table 7, above; and

Table 30 of Attachment 2). All of these changes were consistent with an improvement in underlying disease and did not represent a safety concern for sebelipase alfa. Median total cholesterol, LDL-c, and triglyceride levels decreased from Baseline to the last assessment across all studies. Increases in median HDL-c were noted from Baseline to last assessment in all studies, and were most pronounced in Study LAL-CL03 (median increase of 0.30 mmol/L) and Study LAL-CL01/LAL-CL04 (median increase of 0.25 mmol/L). These results are consistent with the known mechanism of sebelipase alfa and are also influenced by the varying clinical presentation in subjects with LAL-D enrolled across the studies. No definitive associations were noted in the analysis of changes from Baseline in chemistry parameters by various subgroups (according to age, gender, race or baseline LLM use). No subject met the criteria for total cholesterol > 10.36 mmol/L (> 400 mg/dL) with at least a 50% increase from the baseline value for 2 consecutive assessments, or triglycerides > 9.04 mmol/L (> 800 mg/dL) at any assessment.

Haematology and haematological toxicity

Overall, mean values for RBC count, haemoglobin, haematocrit, and platelet count increased from baseline to the last assessment for subjects in the pooled Safety Set (see Table 31 of Attachment 2). An analysis by study indicated that these increases in RBC count, haemoglobin, haematocrit, and platelet count were influenced by the more pronounced haematological changes observed for infants in Study LAL-CL03. Several haematology parameters, including haemoglobin, haematocrit, RBCs and platelet count, showed more pronounced changes from Baseline to the last assessment for subjects in the < 2.00 years group compared with other age groups. All subjects in the < 2.00 year age group were enrolled in Study LAL-CL03 and many of the subjects in this study were receiving packed RBC and/or platelet concentrates as part of their supportive care. Most of the shifts in haematology parameters noted for the Pooled Safety Set were consistent with improvements in underlying disease, and did not represent a safety concern. Overall, most of the subjects who had clinically meaningful shifts in haematology parameters from Baseline to the last assessment were from Study LAL-CL02, which was not unexpected given the substantially greater number of subjects in this study (N = 66) compared with the other 2 studies (N = 9 for both studies).

For subjects in the Pooled Safety Set, median prothrombin times at the last assessment (12.70 sec) were similar to the median value observed at baseline (12.80 sec). Median international normalised ratio (INR) values and activated partial thromboplastin time (aPTT) also remained virtually unchanged from Baseline to the last assessment. Median changes in prothrombin time and INR were not remarkably different across studies. The median change in aPTT was greater in Study LAL-CL03 (increase of 5.80 sec) compared with Study LAL-CL01/ LAL-CL04 (increase of 0.80 sec) and Study LAL-CL02 (decrease of 0.10 sec). The increase in aPTT in Study LAL-CL03 was primarily driven by 1 subject who had an aPTT that was very low at Baseline (10.2 sec; lower limit of normal = 23 sec).[39] Interpretation of results was confounded by small number of patients and data and the fact that infants were known to have coagulopathies that required treatment with fresh frozen plasma.

Immunogenicity and immunological events

Immunogenicity

Serum antibodies that bind to recombinant human LAL were detected using an enzyme-linked immunosorbent assay (ELISA) screening assay and confirmed for specificity using a confirmatory ELISA. A subject was considered to be positive for ADAs at a given time point if he/she had a positive result on both the screening and confirmatory ELISAs. Antibody

[39] The cause of this is unclear and may represent a lab error but other medical reasons cannot be excluded.

titre was determined for all ADA positive subjects by serial dilution, beginning at a minimum required dilution (MRD) of 1:20.

Overall, 10 subjects in the pooled Safety Set (N = 84) tested positive for ADAs during at least 1 assessment. Of the 84 subjects in the Pooled Safety Set, 81 subjects had ADA testing at baseline and 65 subjects had ADA testing for at least one time point after initiation of treatment with sebelipase alfa (7 subjects in Study LAL-CL03, 49 subjects in Study LAL-CL02, and 9 subjects in Study LAL-CL01/LAL-CL04). For the 10 ADA positive subjects in the pooled Safety Set, the median time to first ADA positive result was 57 days (range 29 to 418 days). Maximum titres ranged from < 1/20 to 1/1142.

There was a marked difference in the proportion of infants in the ADA positive group (40.0%) compared with the ADA negative group (6.8%) and this, together with the limited number of ADA positive subjects overall (N = 10) and fluctuations in ADA positivity in these subjects over time, precluded any meaningful conclusions regarding effects on laboratory parameters by ADA status.

Table 8: Overview of treatment emergent adverse events in the pooled Safety Set and updated pooled Safety Set by antibody status and overall

	Pooled Safety Set, n (% of N)			Updated Pooled Safety Set, n (% of N)			
	Antibody Status[a, b]			Antibody Status[a, b]			
Category Subcategory	Positive (N=10)	Negative (N=74)	Overall (N=84)	Positive (N=12)	Negative (N=83)	Missing (N=11)	Overall (N=106)
Any TEAE	**10 (100.0)**	57 (77.0)	67 (79.8)	12 (100)	74 (89.2)	3 (27.3)	89 (84.0)
Onset during infusion and ≤4 hours after end of infusion	8 (80.0)	30 (40.5)	**38 (45.2)**	10 (83.3)	38 (45.8)	2 (18.2)	50 (47.2)
Onset during infusion and ≤24 hours after end of infusion	8 (80.0)	36 (48.6)	**44 (52.4)**	11 (91.7)	46 (55.4)	3 (27.3)	60 (56.6)
Any Related TEAE[c]	4 (40.0)	15 (20.3)	**19 (22.6)**	**5 (41.7)**	**26 (31.3)**	0	**31 (29.2)**
Onset during infusion and ≤4 hours after end of infusion	4 (40.0)	8 (10.8)	**12 (14.3)**	5 (41.7)	13 (15.7)	0	**18 (17.0)**
Onset during infusion and ≤24 hours after end of infusion	4 (40.0)	10 (13.5)	**14 (16.7)**	5 (41.7)	16 (19.3)	0	**21 (19.8)**
Any Treatment-Emergent SAE	4 (40.0)	8 (10.8)	**12 (14.3)**	**5 (41.7)**	**12 (14.5)**	**2 (18.2)**	**19 (7.9)**
Any Treatment Related SAE[c]	1 (10.0)	1 (1.4)	**2 (2.4)**	**1 (8.3)**	**3 (3.6)**	0	**4 (3.8)**
Any IAR[d]	4 (40.0)	6 (8.1)	**10 (11.9)**	**6 (50.0)**	**10 (12.0)**	0	**16 (15.1)**
Any TEAE Leading to Death	0	3 (4.1)	**3 (3.6)**	0	**4 (4.8)**	**1 (9.1)**	**5 (4.7)**
Any TEAE Leading to Study Discontinuation	0	0	0	0	0	0	0
Any TEAE Leading to Study Drug Discontinuation	0	1 (1.4)	**1 (1.2)**	0	**1 (1.2)**	0	**1 (0.9)**

Source: ISS Table 1.2.1J and Day 120 Safety Update Table 1.2.1J

ADA=anti-drug antibody; IAR=infusion-associated reaction; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Events that started on placebo, including those that continued during transition to sebelipase alfa, are not included.

[a] All TEAEs are included, regardless of antibody positive status and the timing of the event relative to first antibody positive result, where applicable.

[b] Subjects who had at least one positive ADA result during treatment are referred to as ADA positive, and subjects who never tested positive for ADA (including subjects who did not have available post-Baseline ADA testing) are referred to as ADA negative.

[c] Based on Investigator's assessment of whether event is at least possibly related to study drug.

[d] Based on Investigator's assessment of whether event is an infusion-associated reaction.

Hypersensitivity reactions

In the pooled Safety Set, a total of 16/84 (19.0%) subjects, including 5/9 (56.0%) infants and 11/75 (15.0%) children and adults, were reported to have experienced signs and symptoms either consistent with or potentially related to a hypersensitivity reaction. All these potential hypersensitivity reactions were mild or moderate in severity with the exception of severe treatment emergent adverse events (TEAE) in 3 subjects.

In the updated pooled Safety Set, a total of 21/106 (19.8%) subjects, including 9/14 infants (64.3%) and 12/92 children and adults (13.0%), experienced signs and symptoms either consistent with or potentially related to a hypersensitivity reaction**.** The updated pooled Safety Set included 5 new subjects with potential hypersensitivity reactions. All new potential hypersensitivity reactions were mild or moderate in severity, with the exception of severe hypersensitivity reactions occurring in 2 subjects.

No clear relationship between the presence of ADAs and hypersensitivity reactions was apparent. Furthermore, the TEAE profile seen among ADA positive subjects was consistent with that in the study population as a whole (that is, Pooled Safety Set), and no ADA positive subject experienced a severe TEAE, serious adverse event (SAE), or TEAE that led to study drug discontinuation.

Three subjects experienced signs and symptoms consistent with an anaphylactic reaction:

- In Study LAL-CL02, a subject experienced an anaphylactic reaction during open label treatment with sebelipase alfa 1 mg/kg qow. Treatment has been paused pending further evaluation.
- In Study LAL-CL08, an infant experienced signs and symptoms of anaphylaxis, 15 mins from start of the sixth infusion at 1 mg/kg once weekly. All symptoms resolved on discontinuation of treatment and this subject continues on treatment in the study with no further reports of IARs.
- In Study LAL-CL06, a subject experienced an SAE of anaphylactic reaction on study Day 86 (seventh infusion) after 90 minutes of infusion of 1 mg/kg qow sebelipase alfa. The subject continues in the study, receiving sebelipase alfa infusions under a desensitisation protocol.

Due to the low level of immunogenicity found in the clinical studies of sebelipase alfa, immunogenicity was not considered in the exposure response analyses of efficacy endpoints or safety endpoints (occurrence of IARs). The population PK analysis of sebelipase alfa revealed no relevant effect of ADA positivity on the exposure to sebelipase alfa. In Study LAL-CL02 (in children and adults) and Study LAL-CL04 (in adults), there were no relevant effects of ADAs on the clinical efficacy and safety findings. In Study LAL-CL03 (in infants), however, some potential impact on efficacy was observed in one infant positive for ADAs.

Post marketing data

Sebelipase alfa received marketing approval in the European Union and the United States on 28 August 2015 and 8 December 2015, respectively. The sponsor has stated that no new safety concerns associated with sebelipase alfa administration have been identified to date based on cumulative safety data received in the post marketing setting. However, no periodic safety update reports (PSURs) were provided for evaluation in the submitted dossier.

Evaluator's conclusions on safety

An integrated analysis of the safety data was conducted to assess any safety signals not otherwise previously reported from analyses performed in the individual studies. The integrated analysis was performed using safety data from open label studies (Studies LAL-CL01/ LAL-CL04 and LAL-CL03) and a single randomised placebo controlled clinical trial (Study LAL-CL02). Interpretation of results from this integrated safety analysis was limited by the marked differences in the rate of LAL-D disease progression, comorbidities and frequency of inter current illness in infants relative to the children and adults. Infants (10.7% of the Pooled Safety Set (9/84)) were already substantially clinically compromised at the start of sebelipase alfa treatment with important co-morbidities in addition to risks of serious complications related to the to rapidly progressive liver, haematological, and malabsorption. Children and adults (89.2% of the Pooled Safety Set [75/84]) had more variable progression to serious complications and presented with less comorbidities at the start of sebelipase alfa treatment. In addition, infants were treated for longer treatment periods at the 3 mg/kg once weekly (qw) dosing regimens as compared to other sebelipase alfa dosing regimens including the 3 mg/kg qow dosing regimen which primarily included adults.

When administered at doses up to 3 mg/kg qow in children and adults and up to 3 mg/kg qw in infants, the safety profile of sebelipase alfa was considered to be favourable. Dose increases up to 5 mg/kg qw in 2 infants, based on clinical response, did not substantially alter the safety profile. The majority of TEAEs were non-serious, mild or

moderate in severity, and reported as unrelated to treatment with sebelipase alfa. The use of LLMs by subjects who received sebelipase alfa did not appear to impact the safety profile of sebelipase alfa. The most common adverse events (AEs) in patients with rapidly progressive disease presenting within the first 6 months of life (≥ 30%) were diarrhoea, vomiting, fever, rhinitis, anaemia, cough, nasopharyngitis, and urticaria. Common AEs in the paediatric and adult patients (≥ 8%) included headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation, and nausea.

In clinical trials, 3 of 106 (3%) patients treated with Kanuma experienced signs and symptoms consistent with anaphylaxis. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival injection, dyspnoea, generalised and itchy rash, hyperaemia, swelling of eyelids, rhinorrhoea, severe respiratory distress, tachycardia, tachypnoea, and urticaria. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation. Signs and symptoms suggestive of a hypersensitivity reaction were identified in 21/106 (20%) subjects who received sebelipase alfa, including 9/14 (64%) infants and 12/92 (13%) children and adults (based on the updated pooled Safety Set). These events occurred most often during or within 4 hours of the infusion. Although a small number of subjects experienced severe reactions, no subject permanently discontinued treatment with sebelipase alfa due to a possible hypersensitivity reaction. Hypersensitivity reactions were successfully managed by temporarily interrupting the infusion, reducing the infusion rate, and administration of antipyretics, antihistamines and corticosteroids.

Twelve subjects in the updated pooled Safety Set tested positive for ADAs during the course of treatment with sebelipase alfa. A higher proportion of infants tested positive for ADAs at more than one time point compared to children and adults most likely due to fact that infants received higher doses of sebelipase alfa and more frequent dosing as compared to dosing regimens for the children and adults. A possible relationship of mutation status on the formation of ADAs could not be excluded as the majority of ADA positive subjects were categorised as 'Other' mutation. No apparent impact of ADA development on hypersensitivity reactions, including anaphylaxis, was identified.

The safety aspects of the proposed PI are satisfactory.

First round benefit-risk assessment

First round assessment of benefits

Table 9, shown below, gives a summary of the first round assessment of benefits.

Table 9: First round assessment of benefits

Benefits	Strengths and Uncertainties
In children and adults with LAL-D, sebelipase alfa was significantly more effective than placebo in normalisation of serum transaminases, correction of multiple dyslipidaemia parameters and reduction in hepatic fat content.	Survival or effect on clinical endpoints was not evaluated. However, efficacy was shown across multiple endpoints representing important clinical abnormalities in children and adults with LAL-D.

Benefits	Strengths and Uncertainties
Evidence of efficacy in terms of improved survival and positive clinically meaningful effects on the multi systemic manifestations of LAL-D shown in open label, uncontrolled study involving 9 infants with growth failure due to LAL-D.	Due to the more progressive and serious nature of the disease in infants and due to low prevalence, a placebo controlled study was not justified or possible in infants.
ERT with sebelipase alfa addresses the root cause of the disease. Currently available treatment options only include supportive therapies.	Sebelipase alfa replaces the missing or deficient enzyme leading to statistically significant and clinically meaningful reductions of the accumulated substrates and restoration of lipid metabolism
Favourable safety profile.	Majority of TEAEs were non-serious, mild or moderate in severity, and reported as unrelated to treatment with sebelipase alfa.

First round assessment of risks

Table 10, shown below, gives the first round assessment of risk.

Table 10: First round assessment of risks

Risks	Strengths and Uncertainties
Risk of hypersensitivity including anaphylaxis.	Signs and symptoms suggestive of a hypersensitivity reaction were identified in 21/106 (20%) subjects who received sebelipase alfa, including 9/14 (64%) infants and 12/92 (13%) children and adults. These events occurred most often during or within 4 hours of the infusion. No subject permanently discontinued treatment with sebelipase alfa due to a possible hypersensitivity reaction. Hypersensitivity reactions were successfully managed by temporarily interrupting the infusion, reducing the infusion rate, and administration of antipyretics and antihistamines with occasional use of corticosteroids
Development of anti-drug antibodies (ADA)	A higher proportion of infants tested positive for ADAs at more than one time point compared to children and adults most likely due to fact that infants received higher doses of sebelipase alfa and more frequent dosing as compared to dosing regimens for the children and adults. No apparent impact of ADA development on hypersensitivity reactions, including anaphylaxis, was identified.

First round assessment of benefit-risk balance

The clinical development programme for sebelipase alfa was designed to provide evidence of safety and efficacy across the full spectrum of patients with LAL-D. Six clinical studies have been initiated to evaluate sebelipase alfa treatment in infants, children, and adults with LAL-D. Across the 4 studies submitted in the current dossier (Studies LAL-CL02, LAL-CL03, LAL-CL01, LAL-CL04), a total of 84 subjects with LAL-D, including 9 infants, 47 children and 28 adults, have received treatment with sebelipase alfa as of the data cut-offs for reporting the primary analyses of PK, PD, efficacy, and safety, and a total of 106 subjects (14 infants and 92 children and adults) have received sebelipase alfa as of the data cut-off for an updated safety analysis (which also included some data from the ongoing studies (Studies LAL-CL06 and LAL-CL08). In addition, the sponsor has completed a natural history study (Study LAL-01-NH01) in infants which provides a historical control for interpretation of the results of the interventional study in infants and an observational study (Study LAL-02-NH01) in children and adults which provides additional insights into the abnormalities associated with this disease across a broader population.

The pivotal development strategy included 2 studies focused on developing evidence of safety and efficacy in the target patient population. The first was a randomised, double blind, placebo controlled Study LAL-CL02, evaluating improvements in multiple clinically important disease related abnormalities in children and adults where the rate of disease progression is more variable. In this study, treatment with sebelipase alfa at proposed dose of 1 mg/kg qow was significantly more effective than placebo across multiple endpoints representing important clinical abnormalities in children and adults with LAL-D, including improvements over placebo in normalisation of serum transaminases, correction of multiple dyslipidaemia parameters, and reduction in hepatic fat content. Furthermore, the efficacy of sebelipase alfa was observed across subgroups based on demographic and baseline characteristics. During the open label treatment period, these improvements were maintained in the subjects treated with sebelipase alfa during the double blind period, and a similar pattern of response was observed in subjects switched from placebo to 1 mg/kg qow sebelipase alfa with sustained normalisation of transaminases, further reduction in fat fraction in the liver and further reductions in total cholesterol, LDL-c, and triglycerides, with increases in HDL-c.

The second study (that is, Study LAL-CL03) was based on demonstrating a survival benefit in infants with the most rapidly progressive presentation of this disease where a placebo controlled study would not be clinically or ethically acceptable. Use of the historical control was justified in the study in infants presenting with rapidly progressive disease given the reliably poor outcome in these patients. Infants with rapidly progressive LAL-D who received treatment with sebelipase alfa demonstrated prolonged survival compared with an untreated historical control group. Survival was accompanied by substantial and rapid improvements in liver disease parameters, growth, and haematological abnormalities.

While it is recognised that majority of endpoints used in these 2 main studies were surrogate endpoints, some of these assessments are used in clinical practice to monitor liver injury and the effectiveness of therapies in reducing cardiovascular risk. The consistent and substantial effects of sebelipase alfa treatment on these assessments, including reduction and normalisation of transaminase levels, improvements in multiple lipid parameters suggest that patients would likely be at reduced risk of important clinical events associated with disease progression that would occur in the absence of effective intervention. Clinical endpoints such as cardiovascular morbidity/mortality or effects on liver histopathology would have required larger sample size with longer double blind treatment periods which was not possible due to the low prevalence and variable disease progression associated with this multisystem disorder.

The 2 study populations that contributed main evidence for safety of sebelipase alfa were from Study LAL-CL03, with a small number of critically ill infants with the most rapidly progressive disease, and controlled Study LAL-CL02, which allowed for a more thorough evaluation due to a larger sample size and the use of a placebo group. The safety and tolerability profile of sebelipase alfa was considered to be favourable when administered at the recommended doses of 1 mg/kg qow in children and adults and 1 to 3 mg/kg qw in infants. The most commonly reported types of AEs were gastrointestinal disturbances, headache, pyrexia/body temperature increases, and upper respiratory signs and symptoms. The majority of TEAEs were non-serious, mild or moderate in severity, and reported as unrelated to treatment with sebelipase alfa. To date, there does not appear to be any apparent cumulative toxicity based on review of TEAE incidence over time on treatment. Review of the safety data across subgroups based on demographic and baseline characteristics did not reveal any group for which the risk of treatment would outweigh the benefits. The use of LLMs by subjects receiving sebelipase alfa does not appear to impact the safety profile of sebelipase alfa.

The safety profile in infants with the most rapidly progressive form of LAL-D was consistent with their more severe underlying condition and comorbidities. Not unexpectedly, SAEs were more frequent among infants in Study LAL-CL03 (8 of 9 subjects, 89%) compared to children and adults in Study LAL-CL02 (4 of 75 subjects, 5%). The most common types of SAEs were infections, primarily catheter site or device related infections in infants; these types of infections occurred early in treatment likely due to the compromised study of these subjects at study entry. There were no safety signals for sebelipase alfa treatment based on review of haematology, clinical chemistry, vital signs, or ECG parameters.

Infusion associated reactions are relatively common for protein containing medicinal products which are administered parentally. Overall, 19.8% of subjects treated with sebelipase alfa were determined to have experienced signs and symptoms that could be consistent with or related to hypersensitivity reactions. These events were observed more frequently in infants (64.3%) than in children and adults (13.0%). The majority of the events occurred during or within 4 hours of the completion of the infusion and were mild in severity. Although a small number of subjects experienced severe reactions, no subject has permanently discontinued treatment with sebelipase alfa due to a possible hypersensitivity reaction. Hypersensitivity reactions, including anaphylaxis, have been observed with other ERTs, including those used to treat Gaucher disease and mucopolysaccharidoses. The proposed prescribing information for sebelipase alfa includes appropriate warnings and precautions for hypersensitivity reactions, including anaphylaxis, specifically to stop the infusion and initiate appropriate medical treatment if a severe reaction is observed.

Overall, a higher proportion of infants (4/7, 57%) were positive for sebelipase alfa antibodies during at least one assessment compared to children and adults (6/58, 10%). Median time to first ADA positive result was approximately 2 months. All of these subjects were able to continue treatment without interruption, although the long term implications regarding the effect of ADAs on the efficacy of sebelipase alfa is not known at this stage. No clear relationship between the presence of ADAs and IARs or the overall TEAE profile was apparent.

Clinical studies did not include elderly subjects and excluded subjects with known egg allergies, and the risks of treatment with sebelipase alfa versus the potential benefits should be carefully considered in these patients.

Treatment with sebelipase alfa in infants has been shown to prolong survival in this very ill and vulnerable patient population; the improvement in survival was accompanied by substantial and rapid improvements in hepatic disease, growth, and haematological abnormalities. In children and adults, treatment with sebelipase alfa led to statistically

significant and clinically meaningful improvements in serum transaminase levels, correction of dyslipidaemia, and reduction in hepatic fat content. These results demonstrate that sebelipase alfa is effectively addressing the root cause of disease across the full spectrum of patients affected with LAL-D. Importantly, the safety and tolerability profile of sebelipase alfa is consistent with expectations and was favourable when administered at proposed doses up to 3 mg/kg qow in children and adults and doses up to 5 mg/kg qw in infants.

Currently, there are no safe or effective therapies for this serious and life threatening disease. Statins and other lipid modifying agents have been used in attempts to affect abnormal blood lipid levels, but dyslipidaemia is persistent in many patients despite use of these drugs, and liver disease progresses despite their use. In the context of approvals of drugs developed for other rare genetic lipid disorders, regulatory authorities have stated that in the absence of cardiovascular outcomes data, decisions to approve novel LDL lowering therapies are not only influenced by the direction and magnitude of drug-induced changes in LDL-c, but also by the effects of the drug on other lipid parameters and markers of cardio-metabolic risk, as well as evidence for off-target toxicity. Sebelipase alfa meets these criteria and the potential for off-target toxicity is limited. HSCT and liver transplant have also been utilised in attempts to mitigate the effects of LAL-D, but these both have significant limitations and are associated with independent toxicities. No therapy has been shown to be safe or effective for the treatment of infants with rapidly progressive LAL-D. HSCT has been used experimentally in infants but has a high morbidity and mortality.

Sebelipase alfa provides a major advance in the treatment of this serious and life threatening disease through direct replacement of the missing or deficient enzyme. Overall, the benefit-risk assessment for sebelipase alfa is favourable for its proposed use as lifelong ERT in infants, children and adults with LAL-D.

First round recommendation regarding authorisation

It is recommended that Kanuma (sebelipase alfa) be approved for the following proposed indication:

> *Kanuma (sebelipase alfa) is indicated for long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).*

The second round recommendation by the clinical evaluator was the same as the first round with no changes made as there were no significant questions raised in the evaluation.

VI. Pharmacovigilance findings

Risk management plan

- The sponsor has applied to register a new biological entity, sebelipase alfa (Kanuma). Kanuma has been designated orphan drug status by the TGA and is proposed to be used as long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).
- Kanuma is available as a 2 mg/mL solution which is diluted with sodium chloride 0.9% for IV infusion over 1 to 2 hours. The proposed dosing regimen is 1 to 3 mg/kg once weekly for infants less than 6 months and 1 mg/kg fortnightly for children and adults.

- The sponsor has submitted EU-RMP version 1.0 (20 August 2015; data lock point (DLP) 8 September 2014) and ASA version1.0 (April 2016) in support of this application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 11.

Table 11: Summary of Safety Concerns

Summary of safety concerns		Pharmaco-vigilance[40]		Risk Minimisation[41]	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity reactions including anaphylaxis	ü	ü	ü	ü*
Important potential risks	ADA development impacting response to drug	ü	ü	ü	ü*
	Use in patients with egg allergy	ü	–	ü	–
Missing information	Safety and efficacy in patients older than 65 years of age	ü	ü	ü	–
	Safety and efficacy in paediatric population between 2 to 4 years of age	ü	ü	ü	–
	Use in pregnant and lactating women	ü	ü	ü	–
	Long term safety and efficacy data	ü	ü	ü	–

*Additional risk minimisation activities proposed in the EU RMP only.

- Additional pharmacovigilance activities include two clinical trials and one international observational disease and clinical outcomes registry. The PI includes a statement encouraging Australian prescribers to enrol their patients in the global registry.
- Additional risk minimisation activities are not proposed for Australia. In the EU, health care professional educational materials are proposed as additional risk minimisation activities for the two related safety concerns identified in Table 11. This lack of educational materials in Australia was considered acceptable for the following reasons:

[40] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[41] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

- hypersensitivity reactions are not an unexpected safety concern for a biological medicine.
- Australian patients will have access to ADA testing (following hypersensitivity reactions or loss of efficacy) through the patient registry.
- The PI provides adequate advice for both these safety concerns.

Outstanding recommendations

The recommendations made in the first round evaluation, along with consideration of the sponsor's response were provided. The sponsor has adequately addressed all recommendations. There are no new or outstanding recommendations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> Implement EU-RMP (version 1.0, dated 20 August 2015, data lock point 8 September 2014) with Australian Specific Annex (version 1.0, dated April 2016) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Introduction

Sebelipase alfa is a first in class recombinant human lysosomal acid lipase. Liposomal acid lipase deficiency (LAL-D) is a very rare, life threatening autosomal recessive lysosomal storage disorder caused by mutations affecting a single gene. It is associated with significant morbidity and mortality affecting individuals from infancy through to adulthood. LAL-D presenting in infants is a medical emergency with rapid disease progression over a period of weeks that is typically fatal within the first 6 months of life.

Deficient LAL enzyme activity results in progressive complications due to the lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the liver, spleen, intestine and the walls of blood vessels. The resulting lipid accumulation in the liver leads to hepatomegaly, transaminase elevation, and progression to fibrosis and cirrhosis. LAL-D results in splenomegaly, anaemia and thrombocytopenia. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. In parallel, dyslipidaemia due to impaired degradation of lysosomal lipid is common with elevated low density lipoprotein cholesterol and triglycerides, and reduced high density lipoprotein cholesterol. In addition to liver disease, patients with LAL-D experience increased risk for cardiovascular disease and accelerated atherosclerosis.

Current treatment options for infants with LAL-D are limited to supportive therapies, including nutritional support, blood transfusions and albumin in an attempt to mitigate some of the effects of this rapidly fatal disease. Survival is poor with median age at death of 8.6 months. Treatment for children or adults presenting with LAL-D is limited to liver

transplant as liver function deteriorates, and attempts to manage dyslipidaemia through diet and the use of lipid lowering medications.

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalised into lysosomes. Sebelipase alfa catalyses the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

Quality

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) produced by recombinant DNA technology and purified from the egg white of genetically engineered chickens (transgenic *Gallus gallus*). Purified sebelipase alfa is a monomeric glycoprotein containing 6 N-linked glycosylation sites with a molecular weight of approximately 55 kD.

The quality evaluator has no objection to the registration of sebelipase alfa, contingent on finalisation of GMP certification. Batch release will be a condition of registration.

Nonclinical

The nonclinical evaluator has no objections to the registration of Kanuma. In vitro, sebelipase alfa was shown to be taken up by cells, localise to lysosomes, and restore LAL enzyme activity in LAL-D patient cells. In vivo in a rat model of LAL-D, doses of sebelipase alfa equivalent to that proposed clinically (based on mg/kg) were shown to increase hepatic LAL activity and reverse the hallmark pathology of LAL-D including organomegaly and tissue LAL substrate accumulation, dyslipidaemia, and a failure to thrive. In vitro and in vivo results were consistent with broad tissue uptake. These data support the proposed clinical indication. Safety pharmacology studies of the effects of sebelipase alfa on the monkey cardiovascular system and rat respiratory and central nervous systems did not raise any safety concerns.

In laboratory animal species (rats, rabbits and cynomolgus monkeys), as in humans, sebelipase alfa exposure was supra-proportional to dose above approximately 1 mg/kg (the proposed dose in adults and children) and was generally not increased by repeat dosing (dosing for 6 months in monkeys being the exception). Sebelipase alfa exhibited a short serum half-life and was rapidly cleared from the circulation after the completion of IV infusion. The volume of distribution in all species was limited, as anticipated for a drug of this nature. The repeat dose toxicity of sebelipase alfa administered by IV infusion was assessed in studies of up to 4 weeks duration in rats and 6 months in monkeys and maximum exposures (AUC) were high. There were no findings considered to be of toxicological concern. Transient dose dependent hypersensitivity reactions were frequently observed in both vehicle and drug treated rats during or immediately following dosing; a common finding in rats administered foreign recombinant proteins; but infrequently in monkeys. Infusion associated hypersensitivity reactions were observed in some patients in the clinical studies and corresponding statements are included in the PI and RMP. No concerns were raised for local toxic effects of sebelipase alfa at the site of IV infusion.

Anti-drug antibodies were present in the sera of most rats and monkeys after repeat dosing with sebelipase alfa, yet were not correlated with exposure, toxicity, or the pharmacodynamics of sebelipase alfa in a rat model of LAL-D. Monkeys dosed repeatedly for 6 months tested positive for anti-ovalbumin antibodies, consistent with sebelipase alfa being produced from chicken egg whites, which may have implications for patients with egg allergies.

Consistent with the ICH guideline;[13] no genotoxicity or carcinogenicity studies were conducted. In comprehensive reproductive toxicity studies in rats and rabbits, sebelipase alfa exposure was high and no concerns were raised for reproductive safety from a nonclinical perspective. Pregnancy Category B1 is warranted, rather than the sponsor's proposal for Category B2.

Clinical

In the clinical development programme, 84 subjects with LAL-D, including 9 infants, 47 children and 28 adults received treatment with sebelipase alfa.

The clinical evaluator recommended authorisation for the sponsor's proposed indication. This recommendation is provided subject to the PI being updated as requested.

The clinical dossier included the following data:

- 1 clinical pharmacology study (Study LAL-CL01)
- 1 population pharmacokinetic evaluation
- 1 pivotal efficacy/safety study (Study LAL-CL02)
- 1 open label Phase III efficacy/safety study (Study LAL-CL03)
- 1 open label extension study (Study LAL-CL04)
- 2 observational natural history studies (Study LAL-1-NH01 in infants; and Study LAL-2-NH01 in children and adults).

Pharmacology

The main sebelipase alfa PK data are based on only three subjects. AUC and C_{max} were dose-proportional from 0.35 to 1 mg/kg, but significantly greater than dose-proportional on moving to the 3 mg/kg dose. Median half-life was 0.78 hours for the 0.35 mg/kg dose and 0.11 to 0.13 hours for the 1 and 3 mg/kg doses, respectively.

Sebelipase alfa reduces transaminase levels within 1 to 2 weeks of treatment initiation. There was little effect of dose on time-course or magnitude of effect. Effects on lipids were seen within 2 to 4 weeks and were more pronounced at the highest dose (3 mg/kg).

Efficacy

In Study LAL-CL01, adults were treated with 0.35, 1, or 3 mg/kg sebelipase alfa weekly for 4 weeks. Subjects who participated in extension Study LAL-CL04 transitioned to an every other week dosing regimen (1 or 3 mg/kg). All doses were associated with reductions in liver enzymes and improvements in serum lipids, which were maintained on switching to an every other week regimen.

Study LAL-CL02 was a pivotal, phase 3, multicentre, randomised, placebo controlled study of sebelipase alfa in 66 children and adults with LAL-D. The primary objective was to demonstrate efficacy of sebelipase alfa relative to placebo, based on normalisation of ALT. Secondary efficacy measures included decrease in LDL-c; decrease in non- HDL-c; normalisation of AST; decrease in triglycerides; increase in HDL-c; decrease in liver fat content and liver volume; and improvement in hepatic histology. Subjects were aged over 4 years, had a diagnosis of LAL-D and ALT ≥ 1.5 x ULN. The main exclusion criterion was severe hepatic dysfunction (Child-Pugh Class C). Subjects were randomised to sebelipase alfa 1 mg/kg every other week, or matching placebo, for 20 weeks, followed by a 130 week open label period. During the open label period, a dose increase to 3 mg/kg was permitted

in the event of an inadequate clinical response, and a dose reduction to 0.35 mg/kg was permitted in the event of poor tolerability.

The median age was 13.0 years, with 36% aged less than 12 years and 29% over 18 years. 50% were male. Median age at the first LAL related abnormality was 4 years, with the most common abnormality being elevated transaminases (47% in both groups).

All but 2 subjects received all 11 study drug infusions during the double blind period. A statistically significant greater proportion of subjects in the sebelipase alfa group than in the placebo group achieved normalisation in ALT by the last time point in the double blind period (31% versus 7%, $p = 0.0271$). Sebelipase alfa was also associated with significant improvements in LDL-c (-28.42% versus -6.25%, $p < 0.0001$), a greater rate of AST normalisation (42% versus 3%, $p = 0.0003$), and greater improvements in triglycerides, HDL-c, and liver histology, compared to placebo. Efficacy of sebelipase alfa appeared to improve with increasing age; however, this analysis is limited by the small number of subjects in each age category.

Study LAL-CL03 was a Phase II/III open label dose escalation study in nine children aged 1 to 6 months with growth retardation due to LAL-D. Starting dose was 0.35 mg/kg weekly, which could be escalated to 1 mg/kg and then to 3 mg/kg. Primary efficacy endpoint was survival; secondary endpoints included growth parameters and hepatic enzyme changes. Study duration was up to 4 years. Six subjects survived to 12 months of age (all six were escalated to a dose of 3 mg/kg weekly), compared to none of 21 comparable infants in the natural history Study LAL-1-NH01. Three subjects survived to 18 months, and two to 24 months. The six subjects surviving to 12 months all had increased weight-for-age percentiles on treatment. Seven of nine infants had ALT above ULN at baseline; ALT decreased rapidly on treatment, with median ALT decrease at week 4 being 66%.

Study LAL-CL04 was an open label extension study of eight adults previously treated in Study LAL-CL01. Subjects were transitioned to a 1 or 3 mg/kg every other week dosing regimen. All subjects had normalisation of both AST and ALT from 25 to 104 weeks of treatment, accompanied by reductions in low density lipoprotein (LDL) and triglycerides, along with reductions in liver volume and liver fat content.

Safety

The pooled safety dataset comprised 84 patients. 84% of subjects reported an adverse event, with 29% considered treatment related. The most frequent adverse events were diarrhoea (28.3%), fever (24.5%), headache (23.6%), nasopharyngitis (22.6%), cough (21.7%), vomiting (17.9%), rhinitis (17.0%), upper respiratory tract infection (16.0%), abdominal pain (15.1%), nausea (12.3%), oropharyngeal pain (12.3%), rhinorrhoea (11.3%), and gastroenteritis (10.4%). There was a higher frequency of adverse events in the 3 mg/kg group, although there were only 9 subjects in this group.

There were six deaths reported amongst patients receiving sebelipase alfa, all in infants with rapidly progressive disease. Other serious adverse events reported by more than one subject were fever, catheter site infection, and device related infection (N = 2 for each). Three subjects treated with sebelipase alfa experienced signs and symptoms consistent with anaphylaxis, occurring up to a year after treatment initiation. 20% of subjects experienced signs and symptoms consistent with a hypersensitivity reaction, commonly during or up to 4 hours after infusion. Such reactions were more common in infants (64% versus 13% for children and adults). No subject discontinued treatment due to a hypersensitivity reaction. 12 subjects tested positive for anti-drug antibodies, again more commonly in infants.

The sponsor stated that no new safety concerns have arisen post-market; however, no data was provided to support this.

Risk management plan

The Pharmacovigilance and Special Access Branch (PSAB) has accepted the EU-RMP for Kanuma (sebelipase alfa) (version 1.0, dated 20 August 2015, data lock point 8 September 2014) with Australian Specific Annex (version 1.0, dated April 2016).

Additional pharmacovigilance activities in the EU-RMP include two clinical trials and one international observational disease and clinical outcomes registry. The PI includes a statement encouraging Australian prescribers to enrol their patients in the global registry.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 11, above.

Additional risk minimisation activities are not proposed for Australia. In the EU, health care professional educational materials are proposed as additional risk minimisation activities for the two related safety concerns identified in Table 11. This lack of educational materials in Australia was considered acceptable.

Risk-benefit analysis

Quality

The quality evaluator has no objection to the registration of Kanuma, subject to finalisation of GMP certification. Batch release will be a condition of registration.

Nonclinical

The nonclinical evaluator has no objections to the registration of Kanuma.

Clinical

Efficacy

The main evidence for efficacy was from Study LAL-CL02, which demonstrated clinically meaningful improvements in markers of liver cell injury compared to placebo. Study LAL-CL03 showed efficacy in infants with life threatening disease compared to historical data. Study LAL-CL04 showed sustained efficacy benefit after switching to an every other week dosing schedule for up to 104 weeks.

Safety

Adequate safety was demonstrated in a pooled safety data set comprising 84 patients. There were six deaths, all in infants with rapidly progressive disease. Hypersensitivity occurred in 20% of patients, more commonly in infants, including three subjects with anaphylaxis.

Conclusion

Quality, efficacy, and safety of Kanuma (sebelipase alfa) solution for infusion 2 mg/mL have been established for the proposed indication. The Delegate decided to approve the registration of the product without seeking the advice to the ACM for the following reasons: The quality, nonclinical and clinical evaluators had no objections to the registration; sebelipase alfa is a designated orphan drug in Australia; the product is currently registered in the USA, Europe, and Japan; and this is consistent with current TGA practice.

Delegate's considerations

The following conditions of registration are proposed:

1. Implementation in Australia of the EU Risk Management Plan for Kanuma (sebelipase alfa) (version 1.0, dated 20 August 2015, data lock point 8 September 2014) with Australian Specific Annex (version 1.0, dated April 2016).
2. Batch release testing as outlined in the quality summary.
3. Submission of the ongoing studies LAL-CL06 and LAL-CL08, when completed.

Proposed action

The application (Submission PM-2016-01313-1-3) for registration of Kanuma (sebelipase alfa) should be approved, with the indication:

> *Kanuma (sebelipase alfa) is indicated for long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D)*.

Request for ACM advice

This submission was not presented to the Advisory Committee for Medicines (ACM).

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Kanuma sebelipase alfa (rce) 2 mg/mL injection intravenous infusion vial for, indicated for:

> *Kanuma (sebelipase alfa rce) is indicated for long term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).*

Specific conditions of registration applying to these goods

1. The sebelipase EU-Risk Management Plan (EU-RMP), version 1.0, dated 20 August 2015, data lock point 8 September 2014) with Australian Specific Annex; (version 1.0, dated April 2016), included with submission PM-2016-01313-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. All batches of Kanuma (sebelipase alfa) 2 mg/mL solution for IV infusion imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
3. Each batch of Kanuma (sebelipase alfa) 2 mg/mL solution for IV infusion 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.
4. The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
5. The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission:
   - Study LAL-CL06

– Study LAL-CL08

Attachment 1. Product Information

The PI for Kanuma 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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