25 June 2015
EMA/514387/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kanuma

International non-proprietary name: sebelipase alfa

Procedure No. EMEA/H/C/004004/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AUC_{cum}	Cumulative area under the plasma concentration-time curve
AUC_{ss}	Area under the concentration-time curve at steady-state
AS	Active substance
AST	Aspartate aminotransferase
ATU	Authorisation Temporaire d'Utilisation
BMIFA	Body mass index-for-age
BSA	Body surface area
CDC	Centres for Disease Control and Prevention
CLDQ	Chronic Liver Disease Questionnaire
CI	Confidence interval
CL	Apparent clearance
CRF	Case report form
DBS	Dried blood spot
EAS	Extension Analysis Set
EC	Ethics committee
ERT	Enzyme replacement therapy
ELISA	Enzyme-linked immunosorbent assay
EW	egg white
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FP	Finished product
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GlcNAc	N-acetylglucosamine
HCFA	Head circumference-for-age
HDL-c	High-density lipoprotein cholesterol
H&E	Haematoxylin and eosin
HeFH	Heterozygous familial hypercholesterolaemia
HFA	Height-for-age
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A

HRQoL	Health-Related Quality of Life
hs-CRP	High sensitivity C-reactive protein
HSCT	Haematopoietic stem cell transplant
HSA	Human serum albumin
IAR	Infusion-associated reaction
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
LAL	Lysosomal Acid Lipase
LDL-c	Low-density lipoprotein cholesterol
LFA	Length-for-age
LLM	Lipid-lowering medication
LLN	Lower limit of normal
LSD	Lysosomal Storage Disorder
M6P	mannose-6-phosphate
MCT	Medium chain triglyceride
MDV	Marek's Disease Virus
MEGE	Multi-echo gradient echo
MMR	Macrophage mannose receptor
MN	Multiples of normal
MRI	Magnetic resonance imaging
MTB	Master transgenic bank
1H-MRS	Magnetic resonance spectroscopy
MUACRA	Mid-upper arm circumference-for-age
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
Non-HDL-C	Non-high-density lipoprotein cholesterol
NOR	Normal Operating Range
OOS	Out Of Specification
OV	ovalbumin
PBMC	Peripheral blood mononuclear cells
PCR	Quantitative Polymerase Chain Reaction
PD	Pharmacodynamic

PES	Primary Efficacy Analysis Set
PK	Pharmacokinetics
PP	Process parameter
PPN	Peripheral parenteral nutrition
PPQ	Process performance qualification
PT	Prothrombin Time
PV	Process Validation
qow	Every-other-week
qw	Once weekly
rhLAL	Recombinant human lysosomal acid lipase
SD	Standard deviation
SE	Standard error
SF-36	36 item Short Form Health Survey
SMA	Smooth muscle actin
SmPC	Summary of product characteristics
SPF	specific pathogen free
TFHN	Transfusion-free haemoglobin normalisation
TPN	Total parenteral nutrition
UAS	Unformulated active substance
UFDF	Ultrafiltration Diafiltration
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WFA	Weight-for-age
WFH	Weight-for-height
WFI	Water for Injections
WFL	Weight-for-length
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Synageva BioPharma Ltd submitted on 24 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Kanuma, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2014.

Kanuma was designated as an orphan medicinal product EU/3/10/827 on 17/12/2010. Kanuma was designated as an orphan medicinal product in the following indication: Treatment of lysosomal acid lipase deficiency.

The applicant applied for the following indication: long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that sebelipase alfa was considered to be a new active substance.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0179/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0179/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

New active Substance status

The applicant requested the active substance sebelipase alfa contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 19 July 2012. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturer of the active substance

Fujifilm Diosynth Biotechnologies USA Inc
6051 George Watts Hill Drive
Research Triangle Park
North Carolina
NC 27709 United States

Manufacturer responsible for batch release

Almac Pharma Services Ltd.
Seagoe Industrial Estate
Craigavon
Co Armagh
BT63 5UA
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Bart Van der Schueren

Co-Rapporteur: Dinah Duarte

CHMP Peer reviewer: Pieter de Graeff

PRAC Rapporteur: Qun-Ying Yue

- The application was received by the EMA on 24 November 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 20 November 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2015.
- The PRAC RMP Advice and assessment overview was endorsed by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 April 2015.

• The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2015.

• The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2015.

• The PRAC RMP Advice and assessment overview was endorsed by PRAC on 11 June 2015.

• The Rapporteurs circulated the Joint updated Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 June 2015.

• During the meeting on 25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Kanuma.

2. Scientific discussion

2.1. Introduction

The target disease of the ERT product sebelipase alfa is known as LAL deficiency, and 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.

LAL deficiency is a lysosomal storage disorder (LSD) caused by mutations affecting the *LIPA* gene encoding LAL located on chromosome 10q23.2-q23.3. Lal enzyme plays a key role in the metabolism and degradation of cholesteryl esters and triglycerides, and its marked reduction or absence leads to accumulation of these lipid substrates in the lysosomes of various tissues and cell types throughout the body, particularly affecting the liver, leading to fibrosis, organ dysfunction and failure, as well as the intestine, leading to malabsorption and adverse effects on growth, and other issues that may result from these.

LAL deficiency has two distinct forms of presenting itself, with the most severe one being the rapidly progressive presentation in young infants associated with a variety of mutations in the gene, and was historically seen as a separate syndrome known as Wolman disease. It has an incidence of approximately 1.89 individuals per million and afflicted infants rarely live past the age of 6 months. Clinical manifestation is usually observed as growth failure, as well as severe hepatic disease, as evidenced by massive hepatomegaly, elevation of transaminases, hyperbilirubinaemia, coagulopathy, and hypoalbuminaemia. Liver fibrosis and cirrhosis develop rapidly and have also been described.

In contrast, LAL deficiency presenting in children and adults, the most frequently described form and historically known as cholesteryl ester storage disease (CESD), is frequently associated with an exon 8 splice-junction mutation c.849G>A (also commonly referred to as E8SJM-1), which has the potential to allow generation of full length transcripts allowing for the production of low levels of residual enzyme activity, and the incidence of this form is estimated between 7.7 and 25 per million, and higher mutation frequencies may exist among people of Iranian Jewish descent or Middle Eastern descent. The disease presentation can be variable, hepatic manifestations typically dominate the clinical picture with marked hepatomegaly, elevation of transaminases signalling chronic liver injury, increased hepatic tissue levels of cholesteryl esters, and liver fibrosis and

cirrhosis manifesting early in life, but dyslipidaemia is also common, with a lipid profile that is indistinguishable from other more common hypercholesterolaemias such as heterozygous familial hypercholesterolaemia (HeFH) and includes elevations in cholesterol, low-density lipoprotein cholesterol (LDL-c) and triglycerides, and decreased levels of high-density lipoprotein cholesterol (HDL-c). These lipid abnormalities coupled with the impairment of degradation of cholesteryl esters by macrophages are known to be associated with increased cardiovascular risk.

There is currently limited information regarding specific molecular mechanisms beyond clinical presentation that predict the rate of disease progression leading to clinical events such as decompensated liver disease, bleeding varices, or the requirement for liver transplantation. Beyond the rapidly progressive clinical presentation in infancy, prognostic factors predictive of rate of disease progression and risk of clinical events in children and adults have not been identified.

Likewise there is limited information regarding the utility of mutation status, residual enzyme activity, or other laboratory parameters in predicting the rate of disease progression in patients with LAL deficiency.

The current best way of diagnosing LAL deficiency is by DBS Enzyme activity measurement, though this method cannot predict rates of disease progression. LAL deficiency presents and progresses along a clinical continuum with predominant liver pathology and dyslipidaemia, as well as other clinical manifestations associated with lysosomal accumulation of cholesteryl esters and triglycerides.

To date there are no safe and effective therapies available to treat patients with LAL deficiency, and treatment options for infants are limited to a variety of supportive therapies, including nutritional support, blood transfusions, and albumin, in order mitigate some effects of the affliction. Nevertheless, these infants are marked for death. Haematopoietic stem cell transplantation (HSCT) in infants has been tried as a curative treatment, but results have been less than satisfactory. In addition HSCT is a risky procedure that carries its own share of inherent issues.

Treatment for children or adults presenting with LAL deficiency is limited to liver transplant as liver function deteriorates, and attempts to manage dyslipidaemia through diet and the use of lipid-lowering medications (LLMs). At present, there is limited information in the medical literature on the long-term outcomes of liver transplantation in patients with LAL deficiency. Liver transplantation itself also carries inherent significant risks, and requires concomitant immunosuppression. Furthermore, 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.

Thus in conclusion, LAL deficiency is a serious, life-threatening disease for which a significant unmet medical need exists requiring new safe and effective therapies.

Sebelipase alfa is an ERT that addresses the root cause of enzyme deficiency in patients with LAL deficiency thereby reducing the pathological effects of accumulated lysosomal lipid substrates.

It is an rhLAL enzyme, purified from egg white of transgenic hens (*Gallus gallus*) with the same amino acid sequence as the native human enzyme. As with the native enzyme, sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids in the lysosomes of target cells.

In the proposed mechanism of action, infused sebelipase alfa binds via glycans expressed on the protein to macrophage mannose receptors or mannose-6-phosphate receptors on relevant cell types and is subsequently internalised and localised to the lysosomal compartment. Once localised to the lysosome, sebelipase alfa hydrolyzes accumulated substrate in LAL-deficient cells, thus reducing the pathological effects in affected tissues.

2.2. Quality aspects

2.2.1. Introduction

The active substance, sebelipase alfa, is a recombinant form of human lysosomal acid lipase (hLAL). This enzyme catalyzes the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids and is as such involved in the maintenance of a normal lipid metabolism. It is the first recombinant product expressed in transgenic chicken (*Gallus gallus)* and purified from egg white of transgenic hens.

The finished product is presented as a sterile liquid concentrate for injection intended for single use intravenous infusion containing 20 mg (2 mg/mL) of the active substance sebelipase alfa. Prior to intravenous administration, the finished product is diluted with 0.9% sodium chloride injection USP/Ph. Eur.

2.2.2. Active Substance

General information

Recombinant human lysosomal acid lipase (rhLAL) or sebelipase alfa is a glycoprotein containing 378 amino acids in the range of 53-55 kDa. Sebelipase alfa is expressed in transgenic chicken (*Gallus gallus)* and purified from egg white of transgenic hens. Purified sebelipase alfa contains 6 N-linked glycosylation sites. The glycans target uptake via the macrophage mannose or mannose-6-phosphate receptors expressed on a number of cell types including Kupffer cells and hepatocytes in which substrate accumulation leads to disease pathogenesis.

Manufacture, characterisation and process controls

Manufacture

Sebelipase alfa is produced by recombinant DNA technology in egg white (EW) of transgenic chicken *Gallus gallus.* The eggs are defined as the starting material. The manufacturing process of the active substance comprises 10 steps.

Eggs are collected and EW is harvested, pooled and frozen for storage. pH-adjustment and clarification of thawed EW enable its processability on the first chromatography column with the aim to capture sebelipase alfa. Host cell proteins (EW proteins) are precipitated in the eluate by pH drop followed by viral inactivation with further pH drop. Purification steps remove EW proteins, adventitious agents and residual DNA. The last chromatography step serves to complete the purification of sebelipase alfa by further decreasing remaining levels of EW protein. The eluate is the unformulated active substance (UAS). The UAS is concentrated, diafiltered and formulated with the addition of human serum albumin (HSA) to yield the AS (active substance). HSA is used to stabilise the desired protein. Human serum albumin used as an excipient in Kanuma meets multi-compendial requirements including USP, Ph. Eur., and JP. Sufficient information regarding the quality of HSA has been provided and the quality of HSA is considered adequate.

The manufacturing process of sebelipase alfa active substance is well defined and overall considered adequately controlled. Process characterization and validation have been investigated for each manufacturing step and process performance qualification of full scale batches was satisfactorily completed. Critical manufacturing process steps have been defined and in-process controls are in place throughout the process. Hold time periods for the intermediates during purification and lifetime of chromatography columns have been satisfactorily addressed.

Critical manufacturing process steps have been defined and in-process controls are in place throughout the process.

Origin, source, and history of transgenic line development

A line of transgenic hens and males has been established containing the gene encoding hLAL. For the creation of transgenic animals a retroviral vector was developed encoding the hLAL sequence within non-coding, regulatory elements of the gene for tissue specificity. Replication deficient viral particles carrying the hLAL-encoding retroviral vector were generated via transfection of an immortalised chicken cell line. For integration of the hLAL sequence into the chicken genome the viral particles were injected in chicken embryos. One male with sufficient level of transgene cassette content in its semen as determined by PCR was chosen as the founder animal, generation zero (G0), to generate G1 hemizygotic transgenic animals, that all carried one copy of the transgene. G1 hen was selected due to highest levels of hLAL in EW. Subsequent genetic characterisation of this hen confirmed the correct size of the transgene, integration of a single copy of the transgene into *Gallus gallus* and the correct hLAL sequence. Of the transgene G1 generation, 3 males with the same genetic characteristics of the transgene were selected for generation of the G2 transgene progeny. Transgene G2 hens were the first animals to constitute the Production Line, after a match of the genetic characteristics with that of G1 hen had been reconfirmed for a proportional number of animals. The production line includes all hens of G2 and following generations either hemizygous or homozygous for the transgene. Since generation G5, propagation of further generations has occurred only via breeding campaigns between hLAL positive hens and males. Breeding campaigns are conducted only via artificial insemination of hens.

Genetic stability of the transgene is regularly evaluated with animals of a defined ratio relative to the overall animal number of each generation by verification of transgene sequence, consistency of its genomic integration site, verification of hLAL sequence and evaluation of rhLAL enzyme activity. To preserve the genetic lineage multiple self-sustaining production facilities are maintained and fertile eggs are exchanged between facilities for stocking and/or restocking other facilities. Semen from sires of each generation used effectively in breeding campaigns is cryopreserved in liquid nitrogen tanks at different facilities.

The new expression platform in transgenic hens is well described, including the generation of the transgenic hens. An action plan is available on how to deal with the unlikely event of changes observed in the transgene. If a change in the transgene sequence would be observed in any hatch group from a new generation, then investigations would primarily expand on the new generation and if necessary go back to the parental generation affected. Any confirmed change of transgene would lead to exclusion of these animals from production (cull) and continuation with confirmed unaffected animals. Furthermore, in comparison to cell culture expression platforms where a Master Cell Bank and/or a Working Cell Bank are defined and characterized, a Master Transgenic Bank (MTB) is as such not established for the transgenic animal production line. Instead, the execution of the Production Line Release Specification testing, essentially establishes the MTB for every new generation. In addition, acceptable measures were introduced to address genetic line preservation.

Control of critical steps and intermediates

The control strategy follows a risk based approach. Critical controls were defined based on process characterisation results, parameters used during viral clearance validation or specifications. As a process performance quality attribute, yield is monitored throughout the process. Correlation of process parameters with process performance and its impact on quality attributes was re-investigated before scale-up to the commercial process by selected process characterisation studies. The ranges re-evaluated were those established for the pivotal clinical process. Several

hold points are defined throughout the manufacturing process and have been adequately supported by hold time studies.

Process validation

Five consecutive process performance qualification lots were manufactured at the intended commercial scale and evaluated against operational, analytical and microbiological criteria. Hold times have been validated extensively during process validation by separate evaluation of intermediates at the several hold points. Overall validation can be considered successful.

Manufacturing process development

While establishment of the transgene production line with *Gallus gallus* as egg-laying "producer organism" is a new production platform, a very traditional approach was chosen to purification of EW process development. Critical process parameters and critical quality attributes were defined based on safety considerations (prevention of contamination with adventitious agents) and on their impact of process performance and product yield.

The control strategy was built upon the correlation of process parameters with process performance and/or quality characteristics. The control strategy follows a risk based approach. Process characterisation studies were performed to highlight the criticality of various input parameters on process performance with a focus on clearance of EW proteins.

Comparability investigations confirmed that there was no impact of the changes introduced during process development on the quality attributes of sebelipase alfa. Additional process modifications were implemented as a result of process characterisation studies and to prepare for process validation. These modifications were aimed to increase robustness of the manufacturing procedure and optimise the scale to ensure consistency in purification. None of these measures has had an impact on quality attributes as demonstrated by further product comparability studies.

Manufacturing process development has been described with satisfactory detail, adequately supported by process data and consequently no concerns were raised on process development.

Characterisation

The primary structure of sebelipase has been confirmed. N-terminal variants were identified. The potential impact on safety and efficacy and in particular the potential immunological effects when N-terminal heterogeneity as found in sebelipase is used in humans has been discussed. Based on the Signal P 4.1 algorithm analysis, it is argued that the primary N-termini of sebelipase alfa are likely similar to the naturally secreted forms of the protein. Furthermore, N-terminal heterogeneity is not predicted to have any safety implications as the forms of sebelipase alfa differ by only several residues. Glycosylation of sebelipase has been adequately investigated. Avian glycostructures differ to human ones as they exhibit rather pre-mature structures when compared with mature human N-glycan structures. Moreover, the avian glycostructures contain neither sialyl groups nor fucose representative for mature human glycostructures. The potential impact on safety and efficacy when avian glycostructures as found in sebelipase are used in humans is discussed as follows. Given that most if not all known human LAL mutations in patients with LAL deficiency will produce forms of LAL that will at some stage in protein maturation contain normal N-terminal amino acid signal peptide sequences, any differences in sebelipase alfa N-terminal composition are unlikely to be immunologically relevant.

Sebelipase alfa binding to the mannose 6-phosphate receptor (M6PR) and the macrophage mannose receptor (MMR) was adequately characterized and the proposed assays are considered adequate to mirror the complex functionality of sebelipase alfa for the purpose of active substance release.

Forced degradation studies to investigate the potential degradation pathways of sebelipase alfa have been conducted by applying photo stress, oxidation and thermal stress conditions.

Specification

Since the data base is currently limited, the Applicant was recommended to revise the proposed active substance specifications once 30 additional commercial scale batches of sebelipase alfa have been manufactured.

The description of analytical methods provides sufficient information on respective sample and standard preparation and calculations. In addition, full validation reports have been submitted and allow a reasonable evaluation of the validation issues. All methods are considered suitably validated for their intended use.

Batch data are available for the commercial manufacturing process as well as the pivotal clinical process and the initial process. All batches used for clinical phases are included as well as all active substance PV, comparability and stability batches.

Qualification data for the reference material used to date including release as well as characterisation data have been submitted. Establishment and qualification of future reference materials is sufficiently described.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a sterile liquid concentrate for solution intended for single use intravenous infusion. The product is presented in one strength (2 mg/ml) in a 10 ml glass vial (containing 20 mg of active substance, sebelipase alfa) and contains sodium citrate dihydrate, citric acid monohydrate and human serum albumin. Preservatives are not present in the product. Prior to intravenous administration, the finished product is diluted with 0.9% sodium chloride injection USP/Ph. Eur.

The finished product is supplied in a clear, Type I borosilicate glass 10 R vial with a butyl, fluoropolymer coated stopper and an aluminium crimp seal with a polypropylene flip-off cap.

Each vial is filled to a target volume of 10.5 mL to ensure the withdrawal of 10.0 mL of the product for further dilution prior to administration.

Manufacture of the product and process controls

The manufacturing process of the Sebelipase alfa finished product has been adequately described. It starts with pooling of the active substance, followed by a bioburden reduction filtration and subsequent sterile filtration and aseptic filling into the vials, stoppering and crimping. No reprocessing is foreseen. Process validation summaries were provided in the dossier regarding the various aspects of the manufacturing process.

The batch analysis data of the process performance qualification (PPQ) runs showed that the PPQ batches met the finished product release specification.

Pharmaceutical Development

Overall, the manufacturing process development of the sebelipase alfa finished product is well described. Initial studies showed that aggregates occurred after one week storage under real-time (2-8 °C) and accelerated (25 °C) conditions when sebelipase alfa was formulated without HSA. Consequently, a formulation containing HSA was optimised which appears justified. Nevertheless, particles can be observed in some vials after storage at both 2-8 °C and 25 °C. It is noted that the

occasional appearance of proteinaceous particles was investigated during process development and it seems that these have been present throughout the product's development history. Sufficient information has been presented to conclude that these inherent particles are not expected to impact the quality of the product.

Sebelipase needs to be diluted with 0.9% saline before administration. Multiple compatibility studies employing various infusion bags and in-line filters were performed. Filter stacking occurred with 4.5 cm^2 filters and higher concentrated solutions however this did not necessarily correlate with decreased sebelipase recovery. It is recommended in the SmPC to use a low-protein binding 0.2 µm filter with a surface area of greater than 4.5 cm^2 as available in order to avoid filter occlusion. The storage conditions of the readily diluted infusion in the SmPC correspond well to the results of the compatibility/in-use stability studies.

Product specification

The specifications established for the finished product cover the main quality attributes with regard to appearance, identity, purity, pH, potency, quantity, extractable volume, sub-visible particles, sterility and endotoxin.

Most of the analytical procedures performed with the finished product are similar to that performed with the active substance. The proposed finished product specification will also be revised once 30 additional commercial scale batches have been manufactured.

Batch analyses were provided of all the batches used in pre-clinical and clinical studies. No OOS results occurred. The criticality of quality attributes was evaluated. Detailed reports regarding the evaluation process and outcome for justification of the proposed specifications have been provided.

Stability of the product

Long-term and accelerated stability data have been provided for 12 batches of sebelipase alfa finished product, including clinical and process validation batches. The production batch size of the finished product has been provided and therefore, it seems that all stability batches can be considered representative of the intended commercial finished product. Overall, the stability data presented support the claimed shelf life and storage conditions as defined in the SmPC.

Adventitious agents

Viral Safety

Egg white (EW) from transgenic *Gallus gallus* is used for production of Sebelipase alfa. Human serum albumin (HSA) is used as an excipient for the active substance and is a licensed medical product. Comprehensive information regarding the quality of HSA has been provided. A plasma master file is linked to the plasma used for manufacture of HSA and the quality is therefore considered adequate.

Sebelipase alfa is purified from the EW of eggs from transgenic *Gallus gallus* hens carrying the rhLAL gene. The animal production line as well as the EW is controlled for contamination with adventitious / endogenous viruses. The control strategy regarding the animals follows at large the Ph. Eur. monograph 5.2.2 "Chicken flocks free from specified pathogens for the production and quality control of vaccines" and comprises monthly serological testing of the chicken for several relevant viruses. EW is tested via PCR for vertically transmissible viruses and for human pathogenic West Nile virus (WNV) and Influenza A (IFA). The Applicant's approach of routine testing the bulk egg white by PCR (although considered difficult due to its viscous nature) instead of testing the animals has been comprehensively justified by an overall risk mitigation strategy. This strategy foresees performing the PCRs for vertically transmitted agents and WNV/NDV once on blood from all production animals 16-20 weeks of age. Furthermore, the routine viral PCR testing for the

respective agents will be performed on the clarified egg white, in addition to testing of bottled egg white. Studies on the sample uniformity and LOD of PCRs on the bottled egg white complement the risk mitigation strategy. This overall approach is considered acceptable. In case of positive virus findings in animals, an action plan has been established for handling of infected animals, their eggs and housing. Information has been also provided on the eggs derived from infected animals, which in general will not be used for production unless it has been assured by further testing, that no risk to product quality or patient safety is conferred by them.

The housing strategy of the animals has been described in detail and is in general endorsed. Satisfactory clarifications have been provided regarding the exact nature of the foodstuff used and possible transportations of animals between facilities.

The capacity of the manufacturing process to clear viruses has been analysed in 3 studies. The overall reduction values determined are in principal considered adequate to ensure virus safety and the representativeness of down-scale models has been confirmed. Also, nanofilter type and manufacturer have been stated and process parameters provided.

Overall, the control strategy for virus safety of the sebelipase alfa manufacturing process contains several complementary steps to mitigate the risk for virus contamination. This approach is considered to be satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance, sebelipase alfa, was of acceptable quality. Adequate evidence regarding the manufacturing process has been provided. Specification limits and analytical methods presented are in general suitable to control the quality of the active substance and finished product. However, the CHMP recommended some points for further investigation.

Sufficient and adequately detailed evidence regarding the manufacturing process has been provided. The method of manufacture has been satisfactorily described and the validation data shows consistent manufacture.

The stability program is in general considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (sebelipase alfa) and the finished product have been appropriately characterised and in general satisfactory documentation has been provided. The results indicate that sebelipase alfa as well as the finished product can be reproducibly manufactured.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

Non clinical aspects

2.2.7. Introduction

The nonclinical development programme which includes pharmacology, PK/TK and toxicology studies provided in the application is consistent with the ICH M3 [R2], ICH S6 [R1], and ICH S7A guidelines.

Pharmacology

Primary pharmacodynamic studies

In vitro experiments showed the uptake of sebelipase alfa into MMR-expressing rat macrophages and transport to the lysosomes. The specificity of the MMR in the cellular uptake of sebelipase alfa was further confirmed by mannose dose-dependent competitive inhibition assays. Additionally, in LAL-deficient human fibroblasts isolated from an infant, sebelipase alfa was found to be endocytosed by the M6P-expressing cells and to dose-dependently restore the LAL activity.

In vivo, the pharmacologic properties of sebelipase alfa were investigated in the "Yoshida" rat model. This homozygous LAL-deficient rat exhibits multiple abnormalities analogous to the human disease including accumulation of cholesteryl ester and triglycerides in the lysosomes of many tissues (in particular, liver, spleen, and small intestine) and marked organomegaly, elevated serum transaminases, growth failure, and early death.

In the LAL-deficient rat, qw or qow administration of sebelipase alfa restored LAL enzymatic activity and led to improvements in the abnormalities caused by LAL deficiency in a dose-dependent manner. LAL-deficient rats treated with sebelipase alfa weekly starting at 4 weeks of age at dose levels of 0.35 mg/kg or greater gained more weight than vehicle-treated animals. The percentage increase in body weight during treatment with higher dosages was similar to weight gain observed in the WT rats.

A treatment-related, dose-dependent reduction in the size of key organs adversely affected by LAL deficiency was demonstrated for the liver, small intestine, and spleen. Reduction in organomegaly was seen at lower doses. Generally, the higher dose (3mg/kg) in a weekly regimen demonstrated a greater response in overall growth and improved hepatic and gastrointestinal tract histopathology.

The positive effects of sebelipase alfa were demonstrated after both short (4 weeks) and long-term (19 weeks) treatment and they were maintained even in the presence of ADAs. The positive effects of sebelipase alfa in more advanced disease (8 weeks of age) were comparable to the effects observed with earlier treatment initiation (4 weeks of age). There was evidence of additional benefit with weekly dosing regimens relative to every other week dosing. Whereas, a monthly treatment regimen with sebelipase alfa at 3 mg/kg showed reduction in organomegaly, normalisation of serum transaminases, and improvement of growth, these effects were not consistently sustained with the monthly regimen. In addition, some hepatic histopathological abnormalities persisted at the end of treatment. Although the monthly treatment regimen resulted in favourable effects including longer survival and improvements in the phenotypic abnormalities compared to vehicle treatment, the once- monthly regimen was a less than fully efficacious treatment regimen compared to the effects seen with a once weekly and every other week regimen.

For both qw and qow schedules, similar pharmacological effects and normalisation of the disease were noted in LAL-deficient rats given weekly sebelipase alfa at the highest doses (3 mg/kg and 5 mg/kg), establishing 3 mg/kg as the maximally effective dose for both treatment regimens. The results in LAL-deficient rats indicated that a more frequent dose regimen than once weekly dosing was not required to achieve disease control and normalization in a preclinical setting.

An evaluation of the time course of pharmacologic abnormalities following cessation of treatment demonstrated that the beneficial effects of sebelipase alfa required continued administration in the LAL-deficient rat, as expected based on other ERTs for lysosomal disorders.

Sebelipase alfa is being proposed for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) Deficiency. The efficacy of sebelipase alfa in LAL-deficient rats was evaluated as early as 4 weeks since this age in the rat corresponds to approximately a 2-5

year old child thus providing preclinical support for the evaluation of children in the clinic. Dosing < 4-weeks of age was not evaluated in LAL deficient rats since disease manifestations begin around 3-4 weeks of age in this model. Delayed sebelipase alfa administration in 8-week old rats through either 12 weeks of age or chronic dosing up to 26 weeks of age provided preclinical proof of concept for the use of sebelipase alfa in adolescent and adult patients respectively.

Secondary pharmacology programme

No secondary PD studies were performed by the Applicant, which is considered acceptable given the nature of the product (recombinant form of the endogenous human lysosomal acid lipase (hLAL)).

Safety pharmacology programme

Safety pharmacology studies did not reveal adverse effects with regards to the CNS, respiratory or cardiovascular systems. In the rat, weekly infusion of sebelipase alfa at dose up to 50 mg/kg for 4 weeks produced no neurotoxic effects. No statistically significant or biologically relevant changes in the respiratory parameters were observed in rats given a single infusion of sebelipase alfa at dose levels up to 50 mg/kg. There were no sebelipase alfa-related adverse cardiovascular effects observed in the Cynomolgus monkey following single infusion at dose levels up to 50 mg/kg.

Pharmacodynamic interactions programme

No pharmacodynamic drug interactions studies were performed by the Applicant, which is considered acceptable given the nature of the product (recombinant form of the endogenous human lysosomal acid lipase (hLAL)).

2.2.8. Pharmacokinetics

Following a single bolus IV administration in the rat, sebelipase alfa was rapidly cleared from the circulation and the uptake appeared to be saturable.

The TK profile of repeated-doses of sebelipase alfa was evaluated in SD rat, Cynomolgus monkey and pregnant New Zealand White rabbit. The IV infusion (over a 3-6h period), which is the intended clinical route of administration, was selected in those studies. In all the species investigated, maximum sebelipase alfa concentration was reached during or shortly after the infusion.

Plasma half-life for sebelipase alfa was on the order of minutes to hours in all of the nonclinical studies, which is very short relative to dosing interval of even once weekly; the consistent finding in the nonclinical studies that each pre-dose value has returned to zero or negligibly above “baseline” additionally supports that accumulation is not significant after a period of up to a week following administration.

In the rat and monkey, as well as in the definitive reproductive toxicology study in rabbits, systemic exposure increased in a greater than dose-proportional manner at dose levels between 3 and 60 mg/kg.

There was no notable correlation between the presence of ADAs and sebelipase alfa systemic exposure in all the animal species tested.

In the 6-month repeated dose study in the monkey, post exposure (AUClast) increased greater than 2-fold, suggesting a change in the PK behaviour of sebelipase alfa during 6 months of weekly dosing. The exact mechanism of this increase is not known but it is not considered to be due to accumulation. Variation in serum concentration (Cmax or AUClast) did not correlate with the presence of ADAs.

In the rat, there was an apparent gender difference in sebelipase alfa exposure, where male Cmax and AUClast values generally exceeded those for females, by a factor of 1.42-3.20. No gender difference with regards to sebelipase alfa exposure was noted in the monkey. No metabolism studies were performed for sebelipase alfa. Sebelipase alfa is a protein with identical amino acid sequence as the endogenous human enzyme and is expected to be metabolically degraded through peptide hydrolysis.

No excretion studies were performed for sebelipase alfa. The properties of this enzyme are the same as for endogenous proteins.

Studies on pharmacokinetic drug interactions have not been conducted. Sebelipase alfa is an enzyme replacement approach for a missing endogenous enzyme. No scientific rationale was identified that warranted specific nonclinical PK drug interaction studies.

2.2.9. Toxicology

The nonclinical program supporting sebelipase alfa safety assessment included a single dose toxicity study conducted in the Cynomolgus monkey, and repeated dose toxicity studies conducted in the SD and in the Cynomolgus monkey. Reproductive toxicity studies were conducted in the rat and in the rabbit.

For the toxicological studies, both the formulation and the route of administration (infusion) were selected to mimic the intended use of sebelipase alfa in the clinic.

Single dose toxicity

No evidence of toxicity was observed when sebelipase alfa was administered as a single dose up to 40 mg/kg in the Cynomolgus monkey.

Repeat dose toxicity –

The repeat-dose toxicity of sebelipase alfa was assessed following administration via intravenous infusion once weekly for 4 weeks. At the initiation of dosing animals were 9 to 10 weeks old (rats) and 2-3 years old (juvenile cynomolgus monkey). The toxicological effects of sebelipase alfa was assessed in juvenile (2.3 to 2.9 years of age) cynomolgus monkeys following weekly intravenous infusion of sebelipase alfa for 6 months.

In the rat, sebelipase alfa was well tolerated following once weekly dosing for 4 weeks at doses up to 50 mg/kg. Clinical observations included swelling of the nose and/or paws and red discolouration of the skin of the paws. These transient findings that occurred on the day of dosing and appeared to be dose related were anticipated based on the specific response of the rat to polysaccharides and glycoproteins. These symptoms were alleviated by diphenhydramine.

Toxicity in Juvenile animals

Juvenile Cynomolgus monkeys administered sebelipase alfa at dosages similar to those in rats did not demonstrate any comparable overt clinical signs indicative of a hypersensitivity-like reaction.

In the 4-week repeated-dose study conducted in the juvenile monkey, sebelipase alfa was well tolerated at doses up to 50 mg/kg. There were no treatment-related deaths, and no sebelipase alfa-related adverse effects were noted for clinical observations, body weight, ophthalmic examinations, clinical pathology parameters, organ weight, or macroscopic and microscopic findings.

In the 6-month study conducted in the juvenile monkey, multifocal myocardial degeneration and fibrosis were observed in the heart of 1 female receiving the highest dose of sebelipase alfa (30 mg/kg). The incidence of this findings falls within the historical control ranges at the test facility

and is consistent with published literature. As there was no evidence for dose response trends with regards to changes in heart histopathology and no treatment related clinical signs or abnormal ECG conductance in the treated monkeys a relationship between sebelipase alfa administration and cardiac toxicity is considered unlikely. The no observed adverse effect level (NOAEL) of sebelipase alfa when administered by intravenous infusion for 6 months (one dose/week) to juvenile Cynomolgus monkeys is 30 mg/kg.

Genotoxicity and Carcinogenicity

No genotoxicity or carcinogenicity studies were conducted and that is considered satisfactory according to the available guidelines.

Reproduction Toxicity

In reproductive toxicity studies in the rat, sebelipase alfa was administered approximately every 3 days at dose levels up to 60 mg/kg in embryo-foetal development studies (to pregnant female rats during gestation); fertility studies (to male and female rats prior to, during, and after mating); and pre- and postnatal development studies (to pregnant female rats postcoitum and postpartum).

In the reproductive toxicity studies in the rat, sebelipase alfa was well tolerated. There were no adverse maternal effects; no evidence of embryolethality, or teratogenicity; and no sebelipase alfa-related deaths. There were no adverse effects on reproductive function, fertility, or early embryonic development in either male or female rats.

In the offspring, there were no adverse effects on survival, physical or sensory/behavioural development, or reproductive competence.

In the reproduction toxicity, fertility and pre-post natal development studies, transient, non-life threatening clinical observations consistent with the well-characterised response of the rat to polysaccharides and glycoproteins such as swelling and scratching were observed on dosing days. The onset and severity of these signs were dose dependent, and the symptoms were generally alleviated by diphenhydramine.

In addition, clinical signs indicative of a more severe hypersensitivity reaction were observed starting with the 50mg/kg in the embryo-foetal development studies and the fertility studies.

Embryo-foetal development toxicity studies were conducted in the rabbit with sebelipase alfa at doses up to 50 mg/kg every third day during gestation.

In a pilot dose-finding study no adverse maternal effects were noted but increased incidence of embryolethality was observed at the highest dose (50 mg/kg) only.

In the definitive study, sebelipase alfa up to 50 mg/kg/dose had no effect on the number resorptions in pregnant rabbits and no sebelipase alfa-related embryolethality was observed. In both of these studies in rabbits, no sebelipase alfa-related adverse clinical signs were observed, and there was no evidence of fetotoxicity or teratogenicity.

Toxicokinetic data

The presence of anti-sebelipase alfa ADAs was detected in some animals in rat, monkey, and rabbit toxicology studies. There did not appear to be a notable correlation between ADA status and sebelipase alfa systemic exposure in any study.

Local Tolerance

Local tolerance was studied in conjunction with the 4-week and 6-month repeated-dose toxicity studies. Overall, histopathological findings were comparable between control and sebelipase-treated animals so that adverse effects on local tolerance are not anticipated with sebelipase alfa.

2.2.10. Ecotoxicity / environmental risk assessment

According to the Guideline on the environmental risk assessment (ERA) of medicinal products for human use [EMEA/CHMP/SWP/4447/00], peptides and proteins are excluded from the need for an environmental risk assessment. An ERA is therefore not available.

2.2.11. Discussion on non-clinical aspects

Sebelipase alfa did not induce toxicological effects when administered via intravenous infusion to cynomolgus monkeys as a single dose (up to 40 mg/kg). However, this study is considered of limited value in terms of safety assessment to support the repeat dose regimen planned for clinical use.

Assessment of paediatric data on non-clinical aspects

The repeat-dose toxicity of sebelipase alfa was assessed following administration via intravenous infusion once weekly for 4 weeks (rat and juvenile monkey) and for 6 months (juvenile monkey). The reversibility, persistence, or delayed occurrence of any sebelipase alfa-induced effect was evaluated after a 2-week recovery phase. At the initiation of dosing animals were 9-10 weeks old (rats) and 2-3 years old (Juvenile Cynomolgus monkey).

The immunogenicity and toxicokinetics parameters have been addressed in the context of the repeat dose toxicity program. According to results, the antibody titre did not appear to correlate with the systemic exposure or plasma sebelipase alfa concentration.

In general, sebelipase alfa administered by intravenous infusion was well tolerated for four weeks, at doses up to 50 mg/kg (in male and female S-D rats and cynomolgus monkeys pre-treated with diphenhydramine). Moreover, no clinical relevant safety concerns have been identified in the repeat dose study conducted in juvenile monkeys weekly dosed by intravenous infusion at doses up to 30 mg/kg during 6 months.

The NOAEL (expressed as the HED) in the rat (50 mg/kg for 4 weeks; HED = 8.1 mg/kg) and monkey (50 mg/kg for 4 weeks; HED = 16.1 mg/kg and 30 mg/kg for 6 months; HED = 9.7 mg/kg) provide for a safety margin of 2.7 to 5.4 times a clinical dose of 3 mg/kg.

In the reproductive toxicity studies in the rat, sebelipase alfa administered approximately every 3 days at dose levels up to 60 mg/kg was well tolerated. There were no adverse maternal effects; no evidence of embryolethality, foetotoxicity, or teratogenicity; and no sebelipase alfa-related deaths. There were no adverse effects on reproductive function, fertility, or early embryonic development in either male or female rats. In the offspring, there were no adverse effects on survival, physical or sensory/behavioural development, or reproductive competence.

In reproductive toxicity studies in the rabbit, sebelipase alfa was well tolerated. In a pilot dose-finding study, administration of sebelipase alfa every 3 days at doses up to 50 mg/kg/dose during gestation resulted in no adverse maternal effects. An increase in late resorptions evidenced embryo-lethality at 50 mg/kg only. In the definitive study, sebelipase alfa up to 50 mg/kg/dose had no effect on the number resorptions in pregnant rabbits and no sebelipase alfa-related embryo-lethality was observed. In both of these studies in rabbits, no sebelipase alfa-related adverse clinical signs were observed, and there was no evidence of foetotoxicity or teratogenicity.

In reproductive toxicity studies after administration every 3 days or twice weekly, the NOAEL was 60 mg/kg (the highest dose tested) for male and female fertility, embryonic development, maternal toxicity, reproductive toxicity, and development of the F1 generation in the rat; and 50 mg/kg (the highest dose tested) for fertility and embryonic development in the rabbit; providing a safety margin of 1.1 to 5.4 times a clinical dose of 3 mg/kg.

2.2.12. Conclusion on the non-clinical aspects

The non-clinical aspects have been adequately investigated and support the use in patients.

2.3. Clinical aspects

2.3.1. Introduction

The clinical development programme for sebelipase alfa has been focused on providing evidence of safety and efficacy across the full spectrum of patients with LAL deficiency. This development strategy included generation of evidence of safety and effectiveness based on improvements in multiple disease-related abnormalities in children and adults where a placebo-controlled study was feasible, and demonstrating an impact on survival in infants where a placebo-controlled study would not be clinically or ethically acceptable because of the rapid progression and early mortality associated with this presentation of the disease.

An overview of the studies in support of the efficacy and safety of sebelipase alfa in the long-term treatment of subjects with LAL deficiency is provided in Table 1.

Across these studies, a total of 84 subjects with LAL deficiency have received treatment with sebelipase alfa, including 9 infants, 47 children and 28 adults. In addition, Synageva has completed a natural history study in infants which provides a historical control for interpretation of the results of the interventional study in infants and an observational study in children and adults which provides additional insights into the abnormalities associated with this disease across a broader population.

GCP

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

- Tabular overview of clinical studies

Study Identifier (Status)	Study Design	Study Objective(s)	LAL Deficiency Population	Dosage Regimen	Treatment Duration	No. of Subjects	Primary Efficacy Endpoint
LAL-1-NH01 (Complete)	Observational, noninterventional	Chart review of children with LAL Deficiency	Pediatric (≤2 years)	N/A	N/A	35	N/A
LAL-2-NH01 (Complete)	Observational, noninterventional	Chart review of children and adults with LAL Deficiency	Pediatric / adult (≥5 years)	N/A	N/A	49	N/A
LAL-2-NH01 Substudy (Complete)	Abdominal imaging and laboratory sample collection for patients in LAL-2-NH01	Abdominal imaging, substrate analysis, laboratory sample collection	Pediatric / adult (≥8 years)	N/A	N/A	23	N/A
LAL-CL01 (Complete)	Phase 1/2, single-arm, open-label, dose escalation	Safety, PK, and PD	Adult (≥18 years)	3 cohorts: 0.35, 1, and 3 mg/kg qw IV	4 weeks	9 (3/cohort)	N/A
LAL-CL02 (Double-blind period complete; Open-label period ongoing)	Phase 3, randomised, double-blind, placebo-controlled; followed by open-label extension	Efficacy, Safety, and PK	Pediatric / adult (≥4 years)	1 mg/kg qow IV	20 weeks double-blind followed by open-label up to 130 weeks	66 (36 sebelipase alfa / 30 placebo)	Normalisation of ALT
LAL-CL03 (Primary analysis complete; Follow-up ongoing)	Phase 2/3, single-arm, open-label	Efficacy, Safety, and PK	Pediatric (≤2 years)	Dose escalation from 0.35 to 1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 208 weeks	9	Survival at 12 months
LAL-CL04 (Enrolment; complete; Follow-up ongoing)	Phase 2, single-arm, open-label extension for subjects who completed LAL-CL01	Efficacy and Safety	Adult (≥18 years)	0.35, 1, or 3 mg/kg, qw IV for 4 weeks; 1 or 3 mg/kg qow IV	Up to 156 weeks	8	N/A
LAL-CL06 (Initiated)	Single-arm, open-label	Efficacy, Safety, and PK	Pediatric / adult (> 8 months)	1 mg/kg qow IV	Up to 96 weeks	Up to 20 planned	N/A
LAL-CL08 (Initiated)	Single-arm, open-label	Efficacy, Safety, and PK	Pediatric (< 8 months)	1 mg/kg qw IV; Up to 3 or 5 mg/kg qw IV	Up to 156 weeks	Up to 10 planned	N/A

ALT = alanine aminotransferase; IV = intravenous; LAL = lysosomal acid lipase; N/A = not applicable; PK = pharmacokinetic; qow = once every other week; qw = once weekly

At the time of the submission, all sebelipase alfa clinical studies, with the exception of Study LAL-CL01, were ongoing to obtain long-term safety and efficacy data and to allow subjects access to sebelipase alfa for uninterrupted ERT. Cut-offs were chosen to reflect a clinically meaningful milestone for each study: the completion of the primary efficacy assessments for Studies LAL-CL02 and LAL-CL03, and the completion of 2 years of study treatment and follow-up (Week 104) for subjects enrolled in Study LAL-CL04.

The PK, PD and/or efficacy and safety properties of sebelipase alfa were investigated in 84 subjects with LAL deficiency in

- two Phase 1/2 studies in adults (Study LAL-CL01, and its ongoing extension study, Study LAL-CL04)
- two ongoing pivotal studies, one Phase 3 study in children and adults (Study LAL-CL02) and one Phase 2/3 study in infants (Study LAL-CL03).

All the studies involved multiple dosing, with the maximum treatment duration ranging between 3 and 4 years. The doses of sebelipase alfa evaluated ranged from 0.35 mg qw to 3 mg/kg qw and qow.

The initial clinical study LAL-CL01 included 9 subjects were treated with sebelipase alfa in rising dose cohorts of 0.35, 1.0 or 3.0 mg/kg (3 subjects each) administered IV qw for 4 weeks. Subjects who completed treatment were permitted to enrol in Study LAL-CL04, designed to provide long-term efficacy and safety data. The extension study is currently ongoing, as of the data cut-off for reporting of 05 Feb 2014, all 8 subjects who entered the study remain on long-term treatment with sebelipase alfa.

The pivotal Phase 3 study in children and adults with LAL deficiency, LAL-CL02, was designed to investigate the effects of sebelipase alfa relative to placebo on a broad range of important disease-related abnormalities. The double-blind, placebo-controlled study was followed by an open-label extension period where subjects randomised to placebo are permitted to cross over to sebelipase alfa. The study has completed enrolment with 66 subjects randomised. Final results from the double-blind treatment period are included in this submission. A total of 65 subjects remain on treatment in the open-label extension period as of the data cut-off for reporting of 30 May 2014.

The pivotal Phase 2/3 study in infants, LAL-CL03, is designed to evaluate the safety, tolerability, efficacy, PK and PD of sebelipase alfa in subjects with LAL deficiency who developed growth failure before 6 months of age. The study has completed enrolment with 9 infants treated. Final results for the primary analysis of survival to 12 months are included in this submission. Six subjects remain on treatment as of the data cut-off for reporting of 10 June 2014.

The clinical development programme also includes 2 studies initiated in 2014. Study LAL-CL06 is an open-label Phase 2 study in paediatric and adult subjects with LAL deficiency who are not eligible for other current sebelipase alfa clinical studies due to age, disease progression, previous treatment by HSCT or liver transplantation, or less common disease manifestations. Subjects 2 to 4 years of age are specifically targeted in this study as part of Synageva's European Union (EU) Paediatric Investigation Plan.

The second study, LAL-CL08, is an open-label Phase 2 study in infants with LAL deficiency who have clinical evidence of rapidly progressive disease before 8 months of age.

2.3.2. Pharmacokinetics

Bioanalytical methods

Validation of the bioanalytical methods used to quantify sebelipase alfa and detect and characterized ADA were presented.

We can conclude that the bioanalytical method proposed by the Applicant to determine sebelipase alfa concentration is not optimal due to:

- The lack of use of a lysosomal acid lipase specific inhibitor and the lack of specificity of the assay leading to possible interference by other forms of lipase and esterases possibly present in study samples;

- The higher variability of the method than usually accepted due to the measure of analyte activity using small volumes and

- The failure to demonstrate adequate selectivity with lipaemic serum samples and therefore the potential interference of endogenous lipids present in the study samples

In the context of LAL deficiency, an orphan disease, pharmacodynamics of sebelipase alfa (sebelipase alfa is targeted to key cell types by glycan structures which allow uptake and trafficking to the lysosome by the mannose receptor and the mannose-6-phosphate receptor.

In the lysosome sebelipase alfa is able to catalyse the hydrolysis of accumulated cholesteryl esters and triglycerides generating free cholesterol and free fatty acids which can then leave the lysosome and enter the normal cellular pathways for lipid metabolism and given the unmet medical need of the disease, the issues raised for the determination of sebelipase alfa in serum for PK analysis are considered to be further investigated post approval.

Concerning the antibody assays, the Applicant is requested to determine the screening cut-point of the target population with the data of the samples from the studies LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08, once they become available for the update of the POPPK analysis

upon completion of the ongoing studies. The 95% confidence interval related to the newly computed cut-point should be provided to allow adequate comparison with the validated cut-point determined with samples from healthy drug-naïve subjects (see POPPK analysis below).

The above request together with the two additional listed below will need to be investigated and addressed post approval in order to fully characterized the bioanalytical methods.

1. The final sample analysis reports should be provided upon completion of the following studies: LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08 studies;

2. The final report of the parallelism study is targeted for Q3 2015 and should be submitted to complete the current validation report of the method for the determination of sebelipase in human serum using enzymatic activity assay.

Absorption

Sebelipase alfa is an IV formulation, and no significant changes were made to the manufacturing process since initiation of pivotal clinical development; therefore, no bioavailability, bioequivalence or food effect studies were performed as part of the clinical development programme.

Distribution

According to the applicant, the PK of sebelipase alfa was described by a 1-compartment model with Vc and CL.

After multiple-dose qw administration in subjects with LAL deficiency, the median Vz on Day 21 decreased with increasing dose. In Study LAL-CL01, the median Vz was markedly higher with the 0.35 mg/kg dose (788.2 mL/kg; N=3) than with the 1 and 3 mg/kg doses (70.01 and 22.05 mL/kg, respectively; each N=3). The lower Vz at higher doses indicates that more sebelipase alfa was in the systemic circulation at the higher doses, due to saturation of the uptake mechanism.

After multiple-dose administration of the 1 and 3 mg/kg doses in Study LAL-CL01 (qw administration) and its extension study, Study LAL-CL04 (qow administration), the median Vz ranged between 70.0 and 229 mL/kg with the 1 mg/kg dose (N=3 to 5) and between 21.1 and 50.4 mL/kg with the 3 mg/kg dose (N=1 to 3), with no consistent trends over time relative to the initial administration on Day 0 of Study LAL-CL01.

Protein binding data have not been provided by the applicant.

Metabolism Elimination

No specific excretion or metabolism studies in human have been performed with sebelipase alfa. As a fully human recombinant human LAL enzyme, sebelipase alfa is expected to be metabolised in the same manner as other endogenous proteins (degraded into small peptides and amino acids via catabolic pathways), and subject to similar elimination.

The plasma elimination of sebelipase alfa was rapid at all doses. After multiple-dose qw administration in Study LAL-CL01, the median $t_{1/2}$ of sebelipase alfa on Day 21 was 0.78 h with the 0.35 mg/kg dose and shorter, at 0.11 and 0.13 h, with the 1 and 3 mg/kg doses, respectively.
After multiple-dose administration of the 1 and 3 mg/kg doses in Study LAL-CL01 (qw administration) and its extension study, Study LAL-CL04 (qow administration), the median $t_{1/2}$ ranged between 0.11 and 0.26 h with the 1 mg/kg dose and between 0.11 and 0.21 h with the 3 mg/kg dose, with no consistent trends over time relative to the initial administration on Day 0 of Study LAL-CL01.

After multiple-dose qw administration in Study LAL-CL01, the median CL of sebelipase alfa on Day 21 was similar with the 0.35 and 1 mg/kg doses, and approximately 4- to 5-fold lower with the 3

mg/kg dose. After multiple-dose administration of the 1 and 3 mg/kg doses in Study LAL-CL01 (qw administration) and its extension study, Study LAL-CL04 (qow administration), the median CL ranged between 541 and 900 mL/h/kg with the 1 mg/kg dose and between 108 and 165 mL/h/kg with the 3 mg/kg dose, with no consistent trends over time relative to the initial administration on Day 0 of Study LAL-CL01.

Based on the population pharmacokinetics model, clearance appears to slightly increase with age and body weight for the dose 0.35 mg/kg and 1 mg/kg. For infants, the interpretation of the results obtained with the dose 0.35 mg/kg and 3 mg/kg dose, is limited by the small number of subjects.

Because sebelipase alfa is a recombinant human LAL enzyme, renal excretion and hepatic enzyme-mediated metabolism are not expected to represent major elimination routes. Thus, variations in renal and hepatic function are not expected to affect the elimination of sebelipase alfa, as also indicated by covariate analysis during development of the population PK model for sebelipase alfa.

No pharmacokinetics of metabolites have been studied which is acceptable.

Specific enzymes involved in the metabolism are unknown but the risk of clinically relevant genetic polymorphism is low.

Serum exposure to sebelipase alfa increased in a reasonably dose-proportional manner between the 0.35 and 1 mg/kg doses (Study LAL-CL01) and in a more than dose proportional manner between the 1 and 3 mg/kg doses (Studies LAL-CL01 and LAL-CL04). Based on median values for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, the difference in exposure to sebelipase alfa between the 1 and 3 mg/kg doses was consistently more than dose proportional on Day 21 and at Weeks 24, 52, and 104. At each of these visits, the 3-fold increase in dose resulted in approximately 10- to 15-fold increases in exposure, which suggests that, consistent with the reduced clearance at the higher dose level, either receptor binding or serum clearance mechanisms for sebelipase alfa may become saturated between these 2 dose levels.
Concerning the amount of data available at the time of the analysis, the applicant commits to update the POP PK model as suggested and to expand the model to a population PK/PD model at the time data from phase III study will be available.

Dose proportionality and time dependencies

Although in this study there were some changes in post-infusion PK parameters with increasing dose, there was no evidence for drug accumulation with either the 1 or 3 mg/kg doses, based on the absence of any increase in pre-infusion concentrations of sebelipase alfa in Study LAL-CL04 (0 ng/mL in all subjects apart from the 1 instance, described in LAL-CL04 CSR Section 12.1.1) and the overall lack of increasing median values for AUC0-last, AUC0-inf, and C_{max} that were measured over time. The 30% to 45% decreases in these parameters observed between Weeks 52 and 104 in the 1 mg/kg dose were within the range of variability observed for these parameters across the continuum of Studies LAL-CL01 and LAL-CL04. Similarly, for a given dose, the CL of sebelipase alfa was relatively consistent across the continuum of Studies LAL-CL01 and LAL-CL04. Thus, there was no overall trend for change over time in the exposure to sebelipase alfa, which was also confirmed by the population analysis of PK parameters in Study LAL-CL02. However, these results should be taken with caution due to the very limited number of patients. Since Study LAL-CL04 is currently ongoing in subjects who completed study LAL-CL01, the MAH should provide updated data after completion of the LAL-CL04 study (30 October 2017).

The values of % CV for intra-individual variability have been reported by the applicant. Sebelipase alfa demonstrates a moderate intra-individual variability for C_{max} both in Study LAL-CL01 and LAL-

CL04. For AUC_{last}, Sebelipase alfa shows also a moderate intra-individual variability in Study LAL-CL01 but a low intra-patient variability in Study LAL-CL04.

Population PK

Based upon serum concentration data obtained from children and infants in Studies LAL-CL02, and from LAL-CL03, using sparse sampling, a population PK model was developed to describe the concentration-time data for sebelipase alfa from these two clinical studies. Observations for adults were obtained from LAL-CL01, LAL-CL04 and LAL-CL02 studies.

According to this POP PK analysis, exposure to sebelipase alfa varies across subject age, which results in proportionately higher exposures in older subjects compared to younger subjects.

However, the amount of data available at the time of the analysis limited the reliability of the evaluated PK profile and did not allow exploring adequately the time-dependent and exposure (dose and concentration)-dependent non-linearity, and the effects of body size and maturation on the PK.

The model should be refined to include updated data from ongoing studies in children/infants, to differentiate children/ infants and adults, to discuss the effect of body size and maturation of the PK and to ensure that time, exposure and non-linearity parameters are adequately addressed. Once a refined population PK model has been obtained, expansion to a population PK/PD model should be considered, which would allow further assessment of whether and how plasma concentrations of sebelipase alfa are linked to PD outcomes, or whether an indirect effect is present, e.g. due to a delayed distribution to an effect site such as the lysosomal compartment.

BQL data were excluded from the analysis. At the time of the update of the POP PK model with the results of the phase III ongoing studies, the applicant is strongly advised to correctly handle BQL data if their rate remains relatively high.

The very sparse data collected during the infusion did not allow the adequate estimation of the parameters. At the time of refinement of the model after completion of phase III studies, the applicant is strongly advised to carefully consider the (clinical) impact of unreliable data on the model parameter estimates. A sensitivity analysis showing the results of modelling with and without these data should be performed.
The Applicant committed to provide updated POP PK information in the post marketing setting by 31 March 2019.

Finally, a discussion on the impact of possible underexposing infants and lower aged children when using a body-weight based dosing whereas the actual effect of body size on clearance is better described by an allometric function should be provided. This should also be done at the time of refinement of the model after completion of phase III studies. The model will also be updated when ongoing studies (LAL-CL06 and LAL-CL08) are completed and therefore more data available on long term follow up of patients, including children aged from 2 to 4 years old.

Overall, in section 5.2 of the SmPC, the results of pharmacokinetic studies in the different paediatric age groups have been summarised adequately with a comparison to adults.

Special populations

The 4 clinical studies included in the current submission were all conducted in subjects with LAL deficiency in populations that were intended to be representative of patients with LAL deficiency in clinical practice, including children (≥ 4 years) and adults as well as infants (≤ 2 years).
The ongoing study LAL-CL06 would be informative for the population of children aged from 2 to 4 years. Among the 2 ongoing pivotal studies one Phase 3 study was conducted in children and adults (Study LAL-CL02) and 1 Phase 2/3 study in infants (Study LAL-CL03).

Drug-drug PK interactions

No pharmacokinetic drug-drug interactions have been conducted with sebelipase alfa. This has been adequately reflected in section 4.5 of the SmPC. This is considered acceptable for an enzyme intended to be used in enzyme replacement therapy. However it is expected that any evidence of product interactions should be reported post-authorisation.

Immunogenicity

The data presented below describe the information available at submission. Further data was provided in the context of a safety update at the answer to the D120 LoQ and are discussed later in the safety part of this report.

Positive ADA titres were observed in adults and children participating in Study LAL-CL02 and infants participating in Study LAL-CL03.

Only a single isolated ADA-positive result was reported in one subject in Study LAL-CL04, which was considered a spurious finding. The Applicant reported that this subject was tested positive on one occasion, namely Week 4, with a titre of 1:160 and judged that this result fell probably into the 5% false positive range since none of the subsequent samples were determined to be ADA positive. In addition, this is supported by the very low titer observed. Given the results seen in the efficacy and safety evaluation, and that the subject's titres remained low, and that this was an isolated observation, it is considered that this aberrant data point is of minor interest and no cause for concern from a clinical point of view.

In Study LAL-CL02, 5 of the 35 subjects with data in the sebelipase alfa group had at least one positive ADA titre during the double-blind period. Concurrent testing of sebelipase alfa concentrations and ADA titres was available at Week 0 (when all subjects were ADA negative) and Week 22. In general, ADA titres were low and unsustained. During the double-blind period, 3 subjects had positive ADA titres at only a single time point, and 2 subjects had positive titres at more than 1 time point. Two of the 5 subjects with a positive ADA titre were positive by Week 4, the first post-Baseline time point assessed, and by the end of the double-blind period at Week 20, only 1 subject had a positive titre. Two of the subjects with positive ADA titres during the double-blind period were also positive during the open-label period, but with low titres and had become non-positive by the last time points assessed prior to data cut-off. None of the subjects in the placebo group had a positive ADA titre during the double-blind period, and none of these subjects had a positive titre after initiating sebelipase alfa in the open-label period through Week 20, the last time point assessed.

The Applicant reported that none of the subjects developed neutralizing antibodies at any time but this observation is discrepant depending on the summary report consulted. At Week 22, 4 of the 5 subjects who had positive ADA titres at any time during the study were ADA negative. No patients continued to present positive ADA titres at the data cut-off. The estimated PK parameters were

generally consistent between Weeks 0 and 22, irrespective of whether the subjects had been ADA-positive at any time during the study.

In Study LAL-CL03, 4 of the 7 subjects with data had positive ADA titres during at least one assessment. In these 4 subjects, positive titres first occurred at Week 5, Week 8 (2 subjects), or Week 59. Three of the subjects were receiving sebelipase alfa at a dose of 1 mg/kg qw, and one at a dose of 3 mg/kg qw.

Persistence of positive ADA titres was observed in 3 subjects and 2 of them had a negative titre at their last assessment prior data cut-off. Two of the 4 subjects tested positive were also tested positive for neutralizing antibodies (inhibition of the LAL enzyme activity and the LAL cellular uptake).

Two of the above subjects tested positive for neutralising antibodies concurrent with the first report of positive ADA titre. One subject had a comparatively low level of inhibition (18.9%) when first tested at Week 5, and thereafter had a high level of inhibition (70.9% to 90.3%). The other subject had a high level of inhibition when first tested at Week 8 (83.2%) and continued to have a high level of inhibition through Week 48 (82.1% to 89.8%); this subject was ADA negative at the last assessment, and thus neutralising antibody activity was not evaluated for this time point.

The former of the two above subjects showed possible signs of ADA effect on clinical response with suboptimal rates of growth, even when the dose was increased to 3mg/kg qw. Thus the dosing was upped to 5 mg/kg qw. Other factors other than ADA development could have contributed to the slow growth response though as other markers of efficacy showed the expected improvements.

Therefore, in general ADA positivity did not show any untoward effects on markers of efficacy nor safety in neither infants nor children and adults. However very limited data are available to assess any apparent impact of immunogenicity, in terms of ADA or neutralising antibody formation, on the exposure to sebelipase alfa.

Finally when seen according to mutation status, no ADAs were detected in any of the 11 subjects who were homozygous for the c.894G>A mutation, whereas they were detected in 2 of the 17 subjects who were compound or presumed compound heterozygous for the c.894G>A mutation, and in 3 of the 8 subjects classified in the “other” mutation category in LAL-CL02. No differences in titres were observed between these 2 ADA-positive genotype groups.

In Study LAL-CL03, none of the subjects had the c.894G>A mutation and all 4 of the ADA-positive subjects were classified in the “other” mutation category.

From the covariate analyses of the POP PK, it can be inferred that having more than one consecutive positive ADA result or an isolated positive ADA result would have no relevant effect on the exposure to sebelipase alfa. In addition, based on the final dataset used for POP PK, it was unlikely that either a categorical ADA-positive status (> 1 consecutive positive ADA titre) or a positive ADA titre would be able to explain a possible decrease in sebelipase alfa exposure. However, due to the limited number of patients developing ADA in the whole studies considered, no definitive conclusion could be drawn up to now on PK parameters.

In addition, the applicant is requested to provide for adequate surveillance of antibody formation and commit to study the PK profile in antibody positive patients. Information in relation to ADA antibodies is mentioned in section 4.4 of the SmPC. Additionally collecting of information in the registry in the post authorization setting is requested. Treating physicians should be made aware of the registry, the procedures to be followed and the data that would need to be submitted.

2.3.3. Pharmacodynamics

Mechanism of action

Biopharmaceutics

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic Gallus, with the same amino acid sequence as the native human enzyme. It 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- acetylglucosamine (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

Primary and Secondary pharmacology

Evidence of biological activity

Evidence of biological activity is based upon the results seen in studies LAL-CL02 and LAL-CL01/CL04.

In the latter, a rapid response in serum lipids (initial increases in LDL-c, triglycerides, and total cholesterol) on initiation of sebelipase alfa treatment (accompanied by decreases in liver transaminases and increase in HDL-c) was seen. Biologically this is not unexpected as these are probably the lipids that were heaped in the liver and saw rapid release after the initial treatment. These responses reversed when sebelipase alfa treatment ceased after 4 doses in Study LAL-CL01, followed by sustained decreases in serum lipids along with the sustained decreases in liver transaminases when longer-term treatment in Study LAL-CL04 started. The initial peaks seen in the LAL-CL01 part of this dual study were not seen in the long-term extension study, lending credence to the idea that the peaks were due to hepatically stored lipids being released.

These findings were also echoed in LAL-CL02, which saw initial peak increases in serum lipids after sebelipase alfa treatment around 2 to 4 weeks after initial administration, after which serum levels decreased below baseline from Week 6 of treatment onward. Liver transaminases also showed significant improvements after treatment. The group of patients that were on placebo during the double-blind phase of the trials again echoed these findings as soon as they were switched to sebelipase alfa ERT when entering the open-label period.

Thus in conclusion, the results obtained after initiating sebelipase alfa treatment in Study LAL-CL01 and its extension study, Study LAL-CL04, as well as in the double-blind and open-label periods of Study LAL-CL02, provide evidence that enzyme replacement therapy with sebelipase alfa in subjects with LAL deficiency mobilises accumulated lysosomal lipid, normalizes liver transaminases, and improves the serum lipid profile.

The transient increases in these serum lipids following initiation of treatment are consistent with increased availability of free cholesterol and fatty acids in the cell leading to increased secretion of very-low-density lipoprotein and/or down-regulation of the LDL-c receptor.

Additionally, decreased HDL-c levels have also been described in patients with LAL deficiency and a link has been established between LAL activity, cholesteryl ester, and triglyceride breakdown products, and expression of the ABCA1 transporter, which is important for reverse cholesterol transport. With sustained sebelipase alfa treatment in Studies LAL-CL04 and LAL-CL02, HDL-c

levels increased significantly by as early as 6 weeks after initiating treatment, leading to further credence of biological activity.

Efficacy endpoints

The efficacy endpoints considered in the graphical analysis of exposure-response relationships included ALT, LDL-c, triglycerides, HDL-c, total cholesterol, and liver fat content.

In the graphical analysis of all data from Studies LAL-CL01, LAL-CL04, and LAL-CL02, subjects with higher ALT Baseline values (defined as ≥ 3x ULN) showed a similar relative change from Baseline and ALT Baseline values did not affect the response to sebelipase alfa treatment over time for any other efficacy endpoints.

ALT, LDL-c, triglycerides, and total cholesterol decreased over time, whereas HDL-c was found to increase over time. The limited data available for percentage liver fat also suggested a decrease in fat content over time. Taken together, these results were consistent with a positive response to treatment with sebelipase alfa for these efficacy endpoints.

Infants (< 1 year at Baseline) in Study LAL-CL03 were found to have generally lower absolute HDL-c values and initially (up to Week 50) lower absolute ALT, LDL-c, triglyceride, and total cholesterol values than children, adolescents, and adults in the other studies. However, the changes from Baseline in these endpoints were comparable across all age groups over time with comparable trends in all efficacy endpoints.

Subjects receiving concomitant lipid lowering medication (LLM) had generally lower absolute LDL-c and total cholesterol values; however, response to sebelipase alfa treatment did not appear to be affected by concomitant LLM as the change from Baseline in all efficacy endpoints appeared comparable over time between subjects receiving concomitant LLM and subjects not receiving concomitant LLM. This suggests that the combined effect of sebelipase alfa and LLM is additive, not synergistic.

A strong positive correlation was observed between LDL-c and total cholesterol, while more moderate correlation was observed between triglycerides and HDL-c (negative), LDL-c (positive), and total cholesterol (positive), and mild correlations between liver fat content and LDL-c, triglycerides, and total cholesterol (all positive). No correlations were apparent between ALT and the other continuous efficacy endpoints variables.

Dosing

The doses of sebelipase alfa investigated in the clinical studies were expected to provide therapeutic effects on the basis of nonclinical findings:

- In a 4-week study, the minimum effective dose of sebelipase alfa in the nonclinical rat model of LAL deficiency was 0.35 mg/kg qw, and was generally comparable to the PD effects of sebelipase alfa administered at a dose of 1 mg/kg qow. These data suggested that a qow dose of less than 1 mg/kg would have a decreased probability of demonstrating efficacy.

- In the nonclinical rat model of LAL deficiency, the PD effects of sebelipase alfa were broadly comparable at the 2 highest qw dosing regimens (3 mg/kg qw and 5 mg/kg qw) and the 2 highest qow dosing regimens (3 mg/kg qow and 5 mg/kg qow) studied. These data indicated that 3 mg/kg would be a maximally effective dose with both qw and qow administration.

- In adults and children with LAL deficiency, substrate accumulation and pathology are most prominent in the liver and spleen. Dose-response analysis in the nonclinical rat model demonstrated that substrate was substantially reduced in these organs with a 1 and 3 mg/kg qow regimen. Favourable effects on body weight gain and intestinal organ weight showed more notable

dose dependence and more marked improvement with the 3 mg/kg qow regimen, and improved effects with more frequent qw dosing regimens.

The doses of sebelipase alfa that were then evaluated in the clinical studies ranged from 0.35 mg qw to 3 mg/kg qw and qow, with adults in LAL-CL01 being treated with 0.35, 1, or 3 mg/kg qw doses of sebelipase alfa and those that went on to LAL-CL04 then being initially treated with qw doses and then transitioned to a qow dosing regimen (1 or 3 mg/kg). In LAL-CL02 active treatment at all timepoints consisted of 1 mg/kg qow. Infants in LAL-CL03 nfants were initially treated with sebelipase alfa at a dose of 0.35 mg/kg qw, then escalated to 1 mg/kg qw, then to 3 mg/kg qw if a suboptimal clinical response was seen (weight-for-age), and they could escalate to 5 mg/kg qw at maximum.

The decision to use different dose schedules (qw versus qow) in the studies conducted in infants (Study LAL-CL03) and in adults and children (Study LAL-CL02) was initially based on the fact that although preclinical studies demonstrated that substantial reductions in organ size and lipid content of the liver and spleen were achieved with lower doses, other tissues more frequently abnormal in infants, including the gastrointestinal tract, benefited from both higher doses and a qw dosing schedule. Further support for the benefits of qw dosing were provided by differences in the beneficial effect on weight gain. Secondly, investigation of the off rate for the effects of sebelipase alfa treatment on liver transaminases provided support for the utility of qow dosing in patients with prominent liver manifestations.

The basis for the observed differences in dose and dose frequency requirements in infants compared to children and adults has not been definitively established. The c.894G>A mutation, which is thought to allow production of small amounts of normal enzyme, is substantially more common in affected children and adults and the small amounts of residual enzyme in these patients may be an important modifier of the rate of reaccumulation of lysosomal lipid during the interval between infusions.

2.3.4. Discussion on clinical pharmacology

Pharmacodynamics

In general, the pharmacodynamics for sebelipase alfa show that treatment in LAL-deficient subjects, both those suffering from the early-onset rapidly progressing form and those with the more conventional mutations that give rise to the late-onset form, is able to improve the biomarkers that are used to identify LAL deficiency (transaminases and serum lipid content), with a clear relation between exposure and response.

Pharmacokinetics

The POP PK modelling approach includes all available data from studies LAL-CL01, LAL-CL02, LAL-CL03 and LAL-CL04 and is considered well described and documented. The approach used might be endorsed in overall.

Based on the results from the POP PK analysis, a non-linear relationship between body weight and CL was found, which results in proportionately higher exposures in larger subjects compared to smaller subjects. Additionally, no effect of gender on the clearance or volume of distribution has been reported.

It is noted that an uniform bodyweight normalization of the dose proposed for all the age ranges (1 mg/kg) in the posology section while an allometric function was used to include BSA levels as a covariate on CL, in the PK analysis.

According to the POP PK analysis, exposure to sebelipase alfa varies across subject age, which results in proportionately higher exposures in older subjects compared to younger subjects. The amount of data available at the time of the analysis limited the reliability of the evaluated PK profile and did not allow exploring adequately the time-dependent and exposure (dose and concentration)-dependent non-linearity, and the effects of body size and maturation on the PK.

In the post authorization setting, the model should be refined to include updated data from ongoing studies in children/infants, to differentiate children/infants and adults, to discuss the effect of body size and maturation of the PK and to ensure that time, exposure and non-linearity parameters are adequately addressed. Further, expansion to a population PK/PD model should be considered, which would allow further assessment of whether and how plasma concentrations of sebelipase alfa are linked to PD outcomes, or whether an indirect effect is present, e.g. due to a delayed distribution to an effect site such as the lysosomal compartment.

BQL data were excluded from the analysis. At the time of the update of the POP PK model with the results of the phase III ongoing studies, the applicant is strongly advised to correctly handle BQL data if their rate remains relatively high.

At the time of refinement of the model after completion of phase III studies, in the post authorisation setting, the applicant is strongly advised to carefully consider the clinical impact of unreliable data on the model parameter estimates. A sensitivity analysis showing the results of modelling with and without these data should be performed.

Overall, it is recommended that the model is updated when ongoing studies (LAL-CL06 and LAL-CL08) are completed and therefore more data available on long term follow up of patients, including children aged from 2 to 4 years old (timelines by 31 March 2019).

A quantitative population PK/PD model which is currently lacking should be developed to explore the impact of the bodyweight-based dosing on the PD biomarkers. This should also be done at the time of refinement of the model after completion of phase III studies. A discussion on the impact of possible underexposing infants and lower aged children and overdosing in the overweight patients when using a body-weight based dosing whereas the actual effect of body size on clearance is better described by an allometric function and should be provided post approval.

The aspects of absorption, distribution and biotransformation are correctly discussed by the applicant but no specific studies have been performed to evaluate the pharmacokinetics of sebelipase in patients with decreased renal function. This is acceptable because sebelipase alfa is a recombinant human LAL enzyme of relatively high-MW (55 kDa), renal excretion is not expected to represent a major elimination route. Additionally, variations in renal function are not expected to affect the elimination of sebelipase alfa, as also indicated by covariate analysis during development of the population PK model for sebelipase alfa.

No pharmacokinetic drug-drug interactions have been conducted with sebelipase alfa which is acceptable for an enzyme intended to be used in enzyme replacement therapy.

Children and adults included in the studies have evidence of significant hepatic involvement (Child Plugh A and B). Few data are available in infants with severe hepatic impairment (only two subjects clearly classified as Child-Pugh C in Study LAL-CL03).

The influence of race on sebelipase alfa PK has not been analysed by non-compartmental methods as all subjects included in Studies LAL-CL01 and LAL-CL04 are reported as Caucasian. Since 82% of the subjects included in the POP PK analysis are reported as Caucasian, no effect of race on the clearance or volume of distribution of sebelipase alfa could be established as the predominance of Caucasians precludes the identification of an effect even if one existed. This lack of PK data in the other ethnic groups has been adequately reflected in the SmPC in special populations.

Data for elderly patients are unavailable. No PK data in patients older than 65 has been provided. The lack of data for this specific population of patients has been clearly stated in the section 5.2 of the SmPC.

Finally, the wording introduced in section 4.2 of the SmPC is considered acceptable and describes adequately the current data in relation to special populations.
No dosing adjustment can be recommended in patients with renal impairment or hepatic impairment and a contra-indication in severe renal impairment due to lack of data is not appropriate in the case of sebelipase alfa.

The effect of hepatic impairment on sebelipase alfa pharmacokinetics appears negligible as indicated by covariate analysis during development of the population PK model for sebelipase alfa. In studies LAL-CL01, LAL-CL02 and LAL-CL04, subjects had no severe hepatic dysfunction (Child-Pugh C) and in study LAL-CL03 there are two subjects who are clearly classified as Child-Pugh C.
The lack of data was adequately reflected in the section 5.2 of the SmPC.

Special populations:

Renal or hepatic impairment

"No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of sebelipase alfa. See section 5.2.)"

The following wording in the Section 5.2 of the SmPC is also endorsed.

SmPC:

"Sebelipase alfa is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, 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."

Immunogenicity
The issue of immunogenicity and the immune system's response to the exogenous recombinant LAL enzyme raises some concern, thus a warning is provided in the SmPC in relation of ADA antibodies and ADA testing.

In the initial data set in infants with rapid-onset disease, of the 7 patients whom survived until their 12th month of life there were 5 whom tested ADA positive, for which 2 developed neutralising antibodies. One of these latter two showed consistently high neutralizing AB titres and exhibited symptoms of growth failure. On the other hand, other markers of efficacy were affected positively.

Five of 7 subjects presenting with ADA positivity represents a high percentage. Likewise 2 out of 7 subjects developing neutralising antibodies represents close to 30% of the study population.

The limited amount of patients available for this trial makes it impossible to draw definite conclusions on these observations, and thus monitoring of all patients during usage is recommended. Additionally the ongoing study in infants (LAL-08) is considered essential to continue gathering long term efficacy and safety data especially in relation to immunogenicity.

In adults, there seem to be less a cause for concern, as only a small fraction of patients became ADA positive, and in all cases the ADA induction was transient and did not coincide with signs of impact on the efficacy of the treatment.

Nevertheless, the occurrence observed indicates that immunogenic responses to treatment are possible in all aetiologies of the disease and can occur at any time, thus meaning that vigilance on the long term usage is necessary.

The bio-molecular typing of the immune response, in particular the development of neutralizing ADAs and the type of antibodies involved is currently not entirely clear and answering the above concerns would be considered an advantage.

Collection of further information on immunogenicity will be done through the post authorization setting (registry) and in the ongoing clinical studies. Treating physicians should be made aware of the registry, the procedures to be followed and the data that would need to be submitted, through educational materials provided.

These pharmacovigilance activities will also be able to detect early warning if antibodies arise in response to the exogenous recombinant LAL. Additionally the there is a need to study immunity against the ERT in the long-term, as ERTs are more likely to be used on a lifelong basis.

2.3.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of sebelipase alfa has been investigated to an acceptable extent. However, given the nature of the orphan disease and the high unmet medical need, PK parameters were determined in a limited number of patients and some issues should be investigated in the post marketing setting.

A quantitative population PK/PD model should be developed to explore the impact of the bodyweight-based dosing on the PD biomarkers at the time of refinement of the model after completion of phase III studies.

Additionally the impact of possible underexposing infants and lower aged children and overexposing the overweight patients when using a body-weight based dosing whereas the actual effect of body size on clearance is better described by an allometric function should be provided.

The full details in relation to the post authorization measure to be provided are all detailed below to ensure that all aspects will be taken into account. Objective: To provide further refinement of PK parameters and expand to a population PK/PD model at the time data from phase III study will be available should be provided. According to the current POP PK analysis, exposure to sebelipase alfa varies across subject age, which results in proportionately higher exposures in older subjects compared to younger subjects. In addition, a non-linear relationship between body weight and CL was found, which results in proportionately higher exposures in larger subjects compared to smaller subjects. The amount of data available at the time of the analysis limited the reliability of the evaluated PK profile and did not allow exploring adequately the time-dependent and exposure (dose and concentration)-dependent non-linearity, and the effects of body size and maturation on the PK. The model should be refined to include updated data from ongoing studies in children/infants, to differentiate children/infants and adults, to discuss the effect of body size and maturation of the PK and to ensure that time, exposure and non-linearity parameters are adequately addressed. Once a refined population PK model has been obtained, expansion to a population PK/PD model should be considered, which would allow further assessment of whether and how plasma concentrations of sebelipase alfa are linked to PD outcomes, or whether an indirect effect is present, e.g. due to a delayed distribution to an effect site such as the lysosomal compartment.

BQL data were excluded from the analysis. At the time of the update of the POP PK model with the results of the phase III ongoing studies, the applicant is strongly advised to correctly handle BQL data if their rate remains relatively high.

The very sparse data collected during the infusion did not allow the adequate estimation of the parameters. At the time of refinement of the model after completion of phase III studies, the applicant is strongly advised to carefully consider the (clinical) impact of unreliable data on the model parameter estimates. A sensitivity analysis showing the results of modelling with and without these data should be performed.

A discussion on the impact of possible underexposing infants and lower aged children and overexposing the overweight patients when using a body-weight based dosing whereas the actual effect of body size on clearance is better described by an allometric function should be provided. This should also be done at the time of refinement of the model after completion of phase III studies.

Finally, the screening cut-point of the target population for ADA detection should be determined with the data of the whole sample from phase III study. The 95% confidence interval related to the newly computed cut-point should also be provided to allow adequate comparison with the validated cut-point determined with samples from healthy drug-naïve subjects.

Overall, the development is acceptable and the data support approval. However the main concern is the question of immunogenic responses to the administration of endogenous LAL-enzyme. Nevertheless, a pattern could not be discovered, and the majority of events were entirely transient without any apparent negative influence on the subject or treatment results. A possible decrease in efficacy was sometimes suspected although one should be aware that it is not proven beyond a reason of doubt that this was due to the ADA development, could be adequately managed by dose adaptation (see later).

This will be further characterised through long-term post-approval safety and efficacy monitoring, including collection of immunogenic AEs (registry, ongoing studies and risk minimisation activities). This is adequately reflected in the RMP.

2.4. Clinical efficacy

The Applicant submitted data of 4 studies in support of the efficacy part of the dossier; two pivotal trials of which one in infants with Wolman disease (LAL-CL03) and one in children and adults with LAL deficiency (LAL-CL02), which also support the dose response.

2.4.1. Dose-response studies- Main studies

2.4.1.1. Study LAL-CL03

Title: An Open Label, Multicenter, 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

Methods

The study consisted of a screening period of up to 3 weeks, a treatment period of up to 4 years, and a follow-up visit at least 30 days after the last dose of investigational medicinal product (IMP).

Duration of main phase: Up to 4 years for each subject.

Study Participants

The participants were infants with Wolman disease.

Treatments

All subjects received sebelipase alfa, administered by IV infusion at a starting dose of 0.35 mg/kg or 0.2 mg/kg, and escalating to 1 mg/kg qw and 3 mg/kg qw, as applicable.

Dosing frequency could be reduced to qow for subjects who had been on treatment for at least 96 weeks and had been receiving a stable dose for at least 24 weeks. Dose reductions were permitted in the event of poor tolerability. Fourteen Synageva drug lots of sebelipase alfa were administered in this study.

Outcomes/endpoints

Primary endpoint: Proportion of subjects in the Primary Efficacy Set (PES) surviving to 12 months of age
Secondary endpoints:

- Proportion of subjects surviving at 18 and 24 months of age
- Median age at death
- Changes from baseline in percentiles and/or z-scores for weight-for-age (WFA), weight-for-length or height (WFL/WFH), length or height-for-age (LFA/HFA), head circumference-for-age (HCFA), and mid-upper arm circumference-for-age (MUACFA)
- Dichotomous growth status indicators of underweight, wasting, and stunting
- Changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum ferritin
- Normalisation of hemoglobin levels without requirement for blood transfusion.

Limited PK sampling was performed, as blood volume permitted, to measure sebelipase alfa concentrations within critical time windows.

Safety endpoints:
Safety was evaluated based on the incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and infusion-associated reactions (IARs), as well as results of clinical laboratory results (chemistry, haematology, urinalysis, and anti-drug antibodies [ADAs]), vital sign measurements, physical examinations, electrocardiograms (ECGs), and information on use of concomitant medications/therapies.

Sample size

9 eligible subjects enrolled

Participants flow

After confirmation of study eligibility based on screening assessments, subjects initiated weekly IV infusions with sebelipase alfa. All subjects who initiated treatment under the LAL-CL03 protocol received a starting dose of 0.35 mg/kg weekly (qw), and were escalated to a dose of 1 mg/kg qw

once acceptable safety and tolerability had been demonstrated during at least 2 infusions at the dose of 0.35 mg/kg.

Results

The data cut-off for the application was 3 years, one month and six days since initiation.
All subjects received sebelipase alfa, administered by IV infusion at a starting dose of 0.35 mg/kg (8 subjects) or 0.2 mg/kg (1 subject), and escalating to 1 mg/kg qw and 3 mg/kg qw, as applicable.

Dosing frequency could be reduced to qow for subjects who had been on treatment for at least 96 weeks and had been receiving a stable dose for at least 24 weeks. Dose reductions were permitted in the event of poor tolerability. One subject who had a continued suboptimal response in association with the presence of neutralising antibodies received a dose increase to 5 mg/kg qw.

One subject initiated treatment with sebelipase alfa under a Temporary Use Authorisation (Autorisation Temporaire d'Utilisation; ATU) prior to enrolling in LAL-CL03; this subject received a gradual dose escalation from 0.2 mg/kg to 1 mg/kg over a period of 4 weeks under the ATU and thereafter continued on a dose of 1 mg/kg qw and was transitioned into extension study LAL-CL05 (Week 40) and then into study LAL-CL03 (Week 85) at this dose.

Subjects who had a suboptimal clinical response after receiving at least 4 infusions at a dose of 1 mg/kg could be considered for a further dose escalation to 3 mg/kg qw, contingent upon acceptable safety and tolerability of preceding infusions. Subjects on long-term treatment (at least 96 weeks) who had been on a stable dose of sebelipase alfa for at least 24 weeks could be considered for a reduction in infusion frequency to every-other-week (qow) infusions of sebelipase alfa.

Such subjects received sebelipase alfa at the same dose (per infusion) that they had been receiving on their stable qw dosing schedule. Any subject receiving qow dosing who subsequently met criteria for a suboptimal clinical response was to either revert to his/her stable qw dosing schedule or, if applicable, escalate in dose from 1 mg/kg qow to 3 mg/kg qow. Dose reductions were permitted in the event of poor tolerability.

Survival

Sebelipase alfa demonstrated a clinically meaningful improvement in survival in subjects with LAL deficiency presenting in infancy who had documented growth failure or other evidence of rapidly progressive disease within the first 6 months of life.

For the primary efficacy set (PES), the proportion of subjects surviving to 12 months of age was 67% (exact 95% CI = 29.93%, 92.51%).

The ages of the surviving subjects at their last available assessment were 12.0, 15.7, 15.8, 20.4, 25.1, and 42.2 months, and thus the proportion of subjects in the PES surviving to 18 and 24 months of age were 33% (3 of 9 subjects) and 22% (2 of 9 subjects).

Growth

Growth improvements were observed for all 6 surviving subjects. For WFA percentile, one subject improved across 2 major centiles, 2 subjects improved across 3 major centiles, 1 subject improved across 4 major centiles, and 1 subject improved across 5 major centiles from baseline through the last assessment prior to data cut-off. Two of these subjects had substantive increases in WFA within the first 6 weeks and continuing throughout treatment, 1 subject having a more gradual increase in WFA throughout treatment, and 3 subjects showing an initial growth deceleration with increases in WFA beginning between Month 3 and 6. Data for other growth parameters (LFA, mid-

upper arm circumference-for-age [MUACFA], head circumference-for-age [HCFA], body mass index-for-age [BMIFA], and WFL) supported the trends observed for WFA: 2 subjects had an increasing trend in all growth parameters from the onset of treatment, 3 subjects had an initial decreasing trend in all or most growth parameters, after which improvements were noted in all parameters, and 1 subject had a more gradual and fluctuating growth response but demonstrated an overall improvement in all parameters by the last assessment.

Developmental milestones

Development milestones, as assessed by the Denver II, were primarily normal for those subjects who were on treatment with sebelipase alfa for 24 weeks or longer. No subject tested as abnormal in any skill area at any time point, and "suspect" test results were reported in only a few instances in gross motor and language skills.

Effects on Serum Transaminases

Liver parameters improved in all 6 surviving subjects. Reductions in serum transaminases were evident by Week 1, when all subjects were receiving sebelipase alfa at a dose of ≤ 0.35 mg/kg, and decreased further by Week 4, 2 weeks after most subjects escalated to 1 mg/kg qw (median reduction from Baseline = -55.5 U/L for AST, n = 4 and -33.0 U/L for ALT, n = 5), and remained fairly stable thereafter. Normalisation of transaminase levels was achieved for 4 of the 6 subjects with elevated Baseline AST and all 4 subjects with elevated Baseline ALT, with normal levels achieved in these subjects between Week 1 and Week 5. Three subjects had transient elevations in serum transaminases shortly prior to the data cut-off, which were temporally associated with a switch from a qw to qow dosing regimen (1 subject) or were noted in association with a severe viral infection (1 subject) or a study ultrasound that was positive for gallstones (1 subject). Levels were generally stable (and remained normal to near-normal in subjects who had normalised) through the data cut-off.

During the conduct of this study, emerging clinical data indicated that some subjects in the study were developing antibodies to sebelipase alfa, and thus could be developing neutralising antibodies with the potential to impact efficacy. In response to observations in one subject, the protocol was amended to allow a further dose escalation to 5 mg/kg qw in the specific situation where a subject receiving a dose of 3 mg/kg qw met the protocol definition for suboptimal response. This suboptimal response was observed in association with the presence of neutralising antibodies. Dose escalation to 5 mg/kg and dose continuation (after the first 2 infusions of 5 mg/kg) were undertaken in consultation with the SC. (see further discussion in the report).

2.4.1.2. Study LAL-CL02

***Title*:** A Multicenter, Randomized, Placebo-controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency (ARISE [Acid Lipase Replacement Investigating Safety and Efficacy]) (LAL-CL02)

Methods/Study participants

This multicentre, randomised, placebo-controlled study was designed to evaluate the safety and efficacy of sebelipase alfa in patients with LAL deficiency.

The study consisted of a screening period of up to 6 weeks, a 20-week double-blind treatment period, an open-label period of up to 130 weeks, and a follow- up phone call at least 4 weeks after the last dose of study drug. Subjects in the placebo group could crossover to receive sebelipase alfa upon entry into the open-label period.

Randomisation

Subjects were randomised to treatment following completion of all screening assessments and confirmation of study eligibility. Randomisation was stratified by the following parameters: age at randomization (< 12 years, ≥ 12 years); average screening ALT level (< 3 × ULN, ≥ 3 × ULN); and use of lipid-lowering medications (LLM).

The patients were followed up in an open label extension.

Sample size

36 subjects were planned.

Treatments

Every-other-week (qow) IV infusions of sebelipase alfa at a dose of 1 mg/kg, for a total of 11 infusions over this 20-week period. No dose modifications were permitted during the double-blind treatment period. Subjects who demonstrated evidence of significant clinical progression on blinded study drug were permitted to discontinue from the double-blind treatment period and transition to open-label treatment with sebelipase alfa at a dose of 1 mg/kg qow. Subjects may also have been considered for a further dose escalation to 3 mg/kg qow in the event of inadequate clinical response during open-label treatment, as described below.

Placebo infusions were identical in volume (based on a subject's weight) and administered over the same duration as infusions of sebelipase alfa in the SA group.

Outcomes/endpoints

Efficacy and safety assessments were performed at regular intervals throughout the study. In addition, the PK of sebelipase alfa and effects on health-related quality of life (HRQOL) were characterised at selected time points. Blood and urine samples also were collected for an additional analysis of potential disease- related biomarkers in this population. An independent safety committee (SC) appointed by the Sponsor provided additional oversight of subject safety in this study through periodic and ad-hoc reviews of safety data.

Primary endpoint: Proportion of subjects who achieved ALT normalisation (i.e., ALT below the age- and gender-specific ULN provided by the central laboratory performing the assay) at the last visit in the double-blind treatment period.

Secondary endpoints: Changes (improvement or normalisation rates, as applicable) from baseline to the end of the double-blind treatment period (Week 20):

- relative reduction in LDL-c
- relative reduction in non-HDL-c
- the proportion of subjects with an abnormal baseline AST (i.e., > ULN) who achieved AST normalisation, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay
- relative reduction in triglycerides
- relative increase in HDL-c; and, in the subset of subjects for whom the assessments were performed
- relative reduction in liver fat content
- the proportion of subjects who showed improvement in liver histopathology
- relative reduction in liver volume

Results

Baseline Disease Characteristics

All 66 subjects had a confirmed diagnosis of LAL deficiency, based on DBS LAL enzyme testing, at baseline. Genetic testing showed that overall, 85% of subjects had at least one copy of the previously described c.849G>A common exon 8 splice junction mutation (32% homozygotes, 53% compound heterozygotes); the remaining 10 subjects had other distinct mutations.

The median age at onset of the first LAL deficiency related abnormalities was reported to be 4 years overall, with a similar median age at onset of 5 and 4 years in the SA and placebo groups, respectively. Overall, 44% of subjects had a history or evidence of medically important chronic liver disease at baseline, including cirrhosis, portal hypertension, and/or coagulopathy.

As required by the entrance criteria, all subjects had an ALT > 1.5 × ULN at baseline. In the SA and placebo groups, mean baseline ALT values were 105.1 U/L and 99.0 U/L, respectively. All but 1 subject in the placebo group had elevated AST values at baseline; mean AST values were 86.6 U/L and 78.2 U/L in the SA and placebo groups, respectively. The mean GGT was similar in the SA group and placebo group at baseline (52.4 and 52.0 U/L, respectively); 36% of subjects in the SA group and 40% of subjects in the placebo group had elevated baseline GGT levels.

Baseline assessments of lipids demonstrated marked dyslipidaemia. Mean LDL-c values were 189.9 mg/dL (4.9 mmol/L) and 229.5 mg/dL (5.9 mmol/L) in the SA and placebo groups, respectively. Overall, more than half (58%) of subjects had LDL-c values in the very high range (> 190 mg/dL).

Hypertriglyceridaemia, defined as TG levels ≥ 200 mg/dL, was seen in 21% of subjects. Mean HDL-c values were 32.4 mg/dL (0.8 mmol/L) and 33.4 mg/dL (0.9 mmol/L) in the SA and placebo groups, respectively. Statistically significant differences between groups were seen with regard to cholesterol and non-HDL-c at baseline, with higher mean values seen in the placebo group than in the SA group. In the SA and placebo groups, mean baseline cholesterol values were 252.5 mg/dL (6.53 mmol/L) and 296.7 mg/dL (7.67 mmol/L), respectively (p=0.0341), and mean baseline non-HDL-c values were 220.5 mg/dL (5.7 mmol/L) and 263.8 mg/dL (6.8 mmol/L), respectively (p=0.0341).

Baseline liver pathology was available in 32 subjects in the FAS, including 19 subjects in the SA group and 13 subjects in the placebo group. As assessed by the blinded central reviewer, all (100%) subjects with baseline biopsies had evidence of fibrosis. A total of 5 (26%) of 19 subjects in the SA group and 5 (38%) of 13 subjects in the placebo group with biopsy data available for analysis had Ishak fibrosis scores of 5 or 6, indicating either early or incomplete cirrhosis or probable or definite cirrhosis, respectively.

Multi-echo gradient-echo (MEGE) assessment of fat content was available in 35 subjects in the SA group and 26 subjects in the placebo group. At baseline, the mean liver fat content, as assessed by MEGE, was 8.5%, with similar mean liver fat content of 8.75% and 8.16% in the SA and placebo groups, respectively. Liver volume assessments by MRI were available in 36 subjects in the SA group and 28 subjects in the placebo group. The mean baseline liver volume, as assessed by MRI, was 1.46 multiples of normal (MN) overall, with similar mean liver volumes of 1.44 and 1.50 MN in the SA and placebo groups, respectively.

Extent of Exposure:

Thirty-five of 36 subjects in the SA group and 29 of 30 subjects in the placebo group received all eleven study drug infusions during the double-blind treatment period, as planned. One subject in the SA group received only 2 of 11 study drug infusions; this subject withdrew from the double-blind treatment period of the study after experiencing a severe atypical infusion-related reaction.

In the placebo group, one subject received 10 of 11 study drug infusions; this subject missed the planned study drug infusion at Week 8 because she had chickenpox and it was decided to hold study drug until the event resolved.

When data from the open-label period were considered, the maximum number of sebelipase alfa infusions received as of the cut-off for this report was 35.

Overall, 35 subjects in the SA group received at least 12 study drug infusions, with 8 subjects receiving at least 20 study drug infusions through the cut-off for this report. In the placebo/SA group, exposure to sebelipase alfa had not reached the level seen in the SA group during the double-blind treatment period as of the cut-off for this report. Half (15) of subjects in the placebo/SA group had received at least 5 infusions during the open-label period as of the cut-off for this report.

Per protocol, infusions were completed over approximately 2 hours from Week 0 to Week 22, and were to be administered over approximately 1 hour starting at Week 24. As of the cut-off for this report, 40 subjects, 21 in the SA group and 19 in the placebo/SA group, received at least 1 sebelipase infusion at over approximately 1 hour during the open-label period; the maximum number of infusions administered over approximately 1 hour for an individual subject was 21.

Efficacy:

Primary Endpoint:

1. ALT normalisation: A greater proportion of subjects in the SA group (31%) than in the placebo group (7%) achieved normalisation in ALT by the last time point in the double-blind period, a 24% difference between groups in favour of SA; the difference between groups was statistically significant (p=0.0271). All subjects in the SA group demonstrated a decrease in ALT; the mean decrease in ALT in the SA group was -57.9 U/L representing a mean percent decrease from baseline of -53%. In contrast, the decrease from baseline to the last time point in the double-blind period in the placebo group was -6.7 U/L, representing a -6% mean percent decrease from baseline.

Secondary Endpoints:

2. LDL-c Reduction: a greater mean percent change from baseline in LDL-c was seen in the SA group than in the placebo group (-28.42% versus -6.25%, respectively), a -22.17% difference between groups in favour of SA; the difference between groups was statistically significant (p<0.0001).

3. Non-HDL-c Reduction: a greater mean percent reduction in non-HDL-c was seen in the SA group than in the placebo group (-27.97% versus -6.94%, respectively), a -21.04% difference between groups in favour of SA; the difference between groups was statistically significant (p<0.0001).

4. AST Normalisation: a greater proportion of subjects in the SA group (42%) than in the placebo group (3%) experienced normalisation in AST by the last time point in the double-blind period, a 39% difference between groups in favour of SA; the difference between groups was statistically significant (p=0.0003). The mean decrease in AST in the SA group was -41.9 U/L, representing a mean percent decrease from baseline of -44%. In contrast, the decrease from baseline to the last time point in the double-blind period in the placebo group was -6.3 U/L, representing a -7% mean percent decrease from baseline.

5. TG Reduction: a greater mean percent decrease from baseline to the last time point in the double- blind period in TG was seen in the SA group than in the placebo group (-25.45% versus -11.14%, respectively), a -14.30% difference between groups in favour of SA; the difference between groups was statistically significant (p=0.0375).

6. HDL-c Increase: a greater mean percent increase from baseline to the last time point in the double- blind period in HDL-c was seen in the SA group than in the placebo group (19.57% versus -0.29%, respectively), a 19.86% difference between groups in favour of SA; this difference between groups was statistically significant ($p<0.0001$).

7. Liver Fat Content Reduction: a greater mean percent decrease from baseline to the last time point in the double-blind period in liver fat content was seen in the SA group than in the placebo group (-31.98% versus -4.21%, respectively), a -27.77% difference between groups in favour of SA; this difference between groups was statistically significant ($p<0.0001$).

8. Liver Histology Improvement: a greater proportion of subjects in the SA group (63%) than in the placebo group (40%) experienced improvement in liver histology (steatosis by morphometry) from baseline to the last time point in the double-blind period, as determined by central blinded read. This 23% difference between groups in favour of SA was not statistically significant ($p=0.4216$). As this result was not statistically significant, formal hypothesis testing stopped at this point in the sequence.

9. Liver Volume Reduction: a greater mean percent decrease from baseline in liver volume was seen in the SA group than in the placebo group at the last time point in the double-blind treatment period (-10.28% versus -2.66%, respectively), a -7.62% difference between groups in favour of SA. However, the SAP did not allow formal statistical testing of this endpoint.

Findings in the PP Set were similar to those in the FAS.

In summary, sebelipase alfa was statistically significantly more effective than placebo in improving a broad range of disease-related abnormalities, including normalisation of serum transaminases (ALT and AST), improvement in dyslipidemia (reductions in LDL-c, non-HDL-c, and TG, and increases in HDL-c), and reduction in liver fat content as assessed by MRI. Furthermore, sebelipase alfa treatment produced clear reductions in MRI-estimated liver volume during the 20-week double-blind treatment period. The positive effects of sebelipase alfa seen in sebelipase alfa-treated subjects were very consistent, with a highly similar pattern of response in the subjects treated initially with sebelipase alfa and in those who switched to sebelipase alfa in the open-label treatment period. Furthermore, evidence of the consistency of efficacy of sebelipase alfa was seen across the analysed study subgroups.

2.4.1.3. Summary of main study(ies)

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

Table 1: Summary of efficacy for trial LAL-CL03

Title: An Open Label, Multicenter, 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 identifier	LAL-CL03
Design	The study consisted of a screening period of up to 3 weeks, a treatment period of up to 4 years, and a follow-up visit at least 30 days after the last dose of investigational medicinal product (IMP). After confirmation of study eligibility based on screening assessments, subjects initiated weekly IV infusions with sebelipase alfa. All subjects who initiated treatment under the LAL-CL03 protocol received a starting dose of 0.35 mg/kg weekly (qw), and were escalated to a dose of 1 mg/kg qw once acceptable safety and tolerability had been demonstrated during at least 2 infusions at the dose of 0.35 mg/kg. One subject initiated treatment with sebelipase alfa under a Temporary Use Authorisation (Autorisation Temporaire d'Utilisation; ATU) prior to enrolling in LAL-CL03; this subject received a gradual dose escalation from 0.2 mg/kg to 1 mg/kg over a period of 4 weeks under the ATU and thereafter continued on a dose of 1 mg/kg qw and was transitioned into extension study LAL-CL05 (Week 40) and then into study LAL-CL03 (Week 85) at this dose Subjects who had a suboptimal clinical response after receiving at least 4 infusions at a dose of 1 mg/kg could be considered for a further dose escalation to 3 mg/kg qw, contingent upon acceptable safety and tolerability of preceding infusions. Subjects on long-term treatment (at least 96 weeks) who had been on a stable dose of sebelipase alfa for at least 24 weeks could
Design	be considered for a reduction in infusion frequency to every-other-week (qow) infusions of sebelipase alfa. Such subjects received sebelipase alfa at the same dose (per infusion) that they had been receiving on their stable qw dosing schedule. Any subject receiving qow dosing who subsequently met criteria for a suboptimal clinical response was to either revert to his/her stable qw dosing schedule or, if applicable, escalate in dose from 1 mg/kg qow to 3 mg/kg qow. Dose reductions were permitted in the event of poor tolerability. During the conduct of this study, emerging clinical data indicated that some subjects in the study were developing antibodies to sebelipase alfa, and thus could be developing neutralising antibodies with the potential to impact efficacy. In response to observations in 1 subject, the protocol was amended to allow a further dose escalation to 5 mg/kg qw in the specific situation where a subject receiving a dose of 3 mg/kg qw met the protocol definition for suboptimal response, and this suboptimal response was observed in association with the presence of neutralising antibodies. Dose escalation to 5 mg/kg and dose continuation (after the first 2 infusions of 5 mg/kg) were undertaken in consultation with the SC.
	Duration of main phase: Up to 4 years for each subject (data cut-off for this report: 3 years, one month and six days since initiation)

Hypothesis	Exploratory: survival in infants with Wolman disease on sebelipase alfa	
Treatments groups	Wolman disease infants 9 eligible subjects enrolled All subjects received sebelipase alfa, administered by IV infusion at a starting dose of 0.35 mg/kg (8 subjects) or 0.2 mg/kg (1 subject), and escalating to 1 mg/kg qw and 3 mg/kg qw, as applicable. One subject who had a continued suboptimal response in association with the presence of neutralising antibodies received a dose increase to 5 mg/kg qw. Dosing frequency could be reduced to qow for subjects who had been on treatment for at least 96 weeks and had been receiving a stable dose for at least 24 weeks. Dose reductions were permitted in the event of poor tolerability. Fourteen Synageva drug lots of sebelipase alfa were administered in this study.	
Endpoints and definitions	Primary endpoint	Proportion of subjects in the Primary Efficacy Set (PES) surviving to 12 months of age
	Secondary efficacy endpoints	Proportion of subjects surviving at 18 and 24 months of age Median age at death Changes from baseline in percentiles and/or z-scores for weight-for-age (WFA), weight-for-length or height (WFL/HFL), length or height-for-age (LFA/HFA), head circumference-for-age (HCFA), and mid-upper arm circumference-for-age (MUACFA) Dichotomous growth status indicators of underweight, wasting, and stunting Changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum ferritin Normalisation of hemoglobin levels without requirement for blood transfusion.
	Safety endpoints	Safety was evaluated based on the incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and infusion-associated reactions (IARs), as well as results of clinical laboratory results (chemistry, haematology, urinalysis, and anti-drug antibodies [ADAs]), vital sign measurements, physical examinations, electrocardiograms (ECGs), and information on use of concomitant medications/therapies.
	PK endpoints	Limited PK sampling was performed, as blood volume permitted, to measure sebelipase alfa concentrations within critical time windows.

Database lock	10 June 2014

Results and Analysis

Survival

Sebelipase alfa demonstrated a clinically meaningful improvement in survival in subjects with LAL deficiency presenting in infancy who had documented growth failure or other evidence of rapidly progressive disease within the first 6 months of life.

For the PES, the proportion of subjects surviving to 12 months of age was 67% (Figure 3.4.1, exact 95% CI = 29.93%, 92.51%). The ages of the surviving subjects at their last available assessment were 12.0, 15.7, 15.8, 20.4, 25.1, and 42.2 months, and thus the proportion of subjects in the PES surviving to 18 and 24 months of age were 33% (3 of 9 subjects) and 22% (2 of 9 subjects).

Growth

Growth improvements were observed for all 6 surviving subjects. For WFA percentile, 1 subject improved across 2 major centiles, 2 subjects improved across 3 major centiles, 1 subject improved across 4 major centiles, and 1 subject improved across 5 major centiles from baseline through the last assessment prior to data cut-off. Two of these subjects had substantive increases in WFA within the first 6 weeks and continuing throughout treatment, 1 subject having a more gradual increase in WFA throughout treatment, and 3 subjects showing an initial growth deceleration with increases in WFA beginning between Month 3 and 6. Data for other growth parameters (LFA, mid-upper arm circumference-for-age [MUACFA], head circumference-for-age [HCFA], body mass index-for-age [BMIFA], and WFL) supported the trends observed for WFA: 2 subjects had an increasing trend in all growth parameters from the onset of treatment, 3 subjects had an initial decreasing trend in all or most growth parameters, after which improvements were noted in all parameters, and 1 subject had a more gradual and fluctuating growth response but demonstrated an overall improvement in all parameters by the last assessment.

Developmental milestones

Development milestones, as assessed by the Denver II, were primarily normal for those subjects who were on treatment with sebelipase alfa for 24 weeks or longer. No subject tested as abnormal in any skill area at any time point, and "suspect" test results were reported in only a few instances in gross motor and language skills.

Effects on Serum Transaminases

Liver parameters improved in all 6 surviving subjects. Reductions in serum transaminases were evident by Week 1, when all subjects were receiving sebelipase alfa at a dose of ≤ 0.35 mg/kg, and decreased further by Week 4, 2 weeks after most subjects escalated to 1 mg/kg qw (median reduction from Baseline = -55.5 U/L for AST, n = 4 and -33.0 U/L for ALT, n = 5), and remained fairly stable thereafter. Normalisation of transaminase levels was achieved for 4 of the 6 subjects with elevated Baseline AST and all 4 subjects with elevated Baseline ALT, with normal levels achieved in these subjects between Week 1 and Week 5. Three subjects had transient elevations in serum transaminases shortly prior to the data cut-off, which were temporally associated with a switch from a qw to qow dosing regimen (1 subject) or were noted in association with a severe viral infection (1 subject) or a study ultrasound that was positive for gallstones (1 subject). Levels were generally stable (and remained normal to near-normal in subjects who had normalised) through the data cut-off.

Effects on Serum Ferritin

Serum ferritin decreased rapidly on treatment in all 6 surviving subjects. The median reduction in serum ferritin was -122.0 µg/L by Week 1 (n = 4) and -269.3 µg/L by Week 6 (n = 3). Ferritin levels normalised in all 4 subjects who had an elevated Baseline level; time to normalisation ranged from approximately 1 week to 13 weeks and, as might be expected, was longer for those subjects with a higher Baseline ferritin level.

Haematological Effects

Haematological abnormalities associated with LAL deficiency also improved during treatment with sebelipase alfa. Transfusion-free haemoglobin normalisation (also referred to as short-term TFHN) was achieved by 83.3% (5 of 6) of the surviving subjects, including all 3 subjects who had low haemoglobin levels at Baseline. The estimated median time to achieve short-term TFHN based on Kaplan-Meier analysis was 4.6 months, with a lower 95% confidence limit of 0.2 months (the upper confidence limit could not be estimated). Two (33.3%) of the 6 surviving subjects also achieved TFHN maintenance (also referred to as sustained early TFHN), which extended from Week 6 to the last available assessment in these subjects.

Table 1: Summary of efficacy for trial LAL-CL02

Title: A Multicenter, Randomized, Placebo-controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency (ARISE [Acid Lipase Replacement Investigating Safety and Efficacy])	
Study identifier	LAL-CL02
Design	This multicentre, randomised, placebo-controlled study was designed to evaluate the safety and efficacy of sebelipase alfa in patients with LAL deficiency. The study consisted of a screening period of up to 6 weeks, a 20-week double-blind treatment period, an open-label period of up to 130 weeks, and a follow-up phone call at least 4 weeks after the last dose of study drug. Subjects in the placebo group could crossover to receive sebelipase alfa upon entry into the open-label period. Subjects were randomised to treatment following completion of all screening assessments and confirmation of study eligibility. Randomisation was stratified by the following parameters: age at randomisation (< 12 years, ≥ 12 years); average screening ALT level (< 3 × ULN, ≥ 3 × ULN); and use of lipid-lowering medications (LLM) (yes, no). Efficacy and safety assessments were performed at regular intervals throughout the study. In addition, the PK of sebelipase alfa and effects on health-related quality of life (HRQOL) were characterised at selected time points. Blood and urine samples also were collected for an additional analysis of potential disease-related biomarkers in this population. An independent safety committee (SC) appointed by the Sponsor provided additional oversight of subject safety in this study through periodic and ad-hoc reviews of safety data.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	20 weeks double-blind 6 Weeks of screening + Maximum 130 Weeks in open-label period
Hypothesis	Superiority of sebelipase alfa ERT to placebo	
Treatments groups	Sebelipase alfa (double-blind)	N=36 Every-other-week (qow) IV infusions of sebelipase alfa at a dose of 1 mg/kg, for a total of 11 infusions over this 20-week period. No dose modifications were permitted during the double-blind treatment period. Subjects who demonstrated evidence of significant clinical progression on blinded study drug were permitted to discontinue from the double-blind treatment period and transition to open-label treatment with sebelipase alfa at a dose of 1 mg/kg qow. Subjects may also have been considered for a further dose escalation to 3 mg/kg qow in the event of inadequate clinical response during open-label treatment, as described below.
	Placebo (double-blind)	N=30 Placebo infusions were identical in volume (based on a subject's weight) and administered over the same duration as infusions of sebelipase alfa in the SA group.
	Open-label group	N=65 qow IV infusions of sebelipase alfa at a dose of 1 mg/kg, irrespective of their treatment allocation during the double-blind treatment period. Beginning at Week 24, subjects received sebelipase alfa infusions over approximately 1 hour. However, if the infusion was not well tolerated, the infusion rate could be decreased to the previously tolerated infusion rate. A subject may have received a total of up to 64 infusions over the maximum 130-week open-label period. A dose increase to 3 mg/kg qow was permitted in the event of an inadequate clinical response, and a dose reduction to 0.35 mg/kg qow was permitted in the event of poor tolerability. All dose adjustments were made at the discretion of the Investigator in consultation with the Sponsor.

Endpoints and definitions	Primary endpoint	Proportion of subjects who achieved ALT normalisation (i.e., ALT below the age-and gender-specific ULN provided by the central laboratory performing the assay) at the last visit in the double-blind treatment period.
	Secondary endpoints	Changes (improvement or normalisation rates, as applicable) from baseline to the end of the double-blind treatment period (Week 20): relative reduction in LDL-c relative reduction in non-HDL-c the proportion of subjects with an abnormal baseline AST (i.e., > ULN) who achieved AST normalisation, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay relative reduction in triglycerides relative increase in HDL-c; and, in the subset of subjects for whom the assessments were performed relative reduction in liver fat content the proportion of subjects who showed improvement in liver histopathology relative reduction in liver volume

	Supportive efficacy endpoints	Changes (or normalisation, as applicable) from baseline to the end of the double-blind treatment period (Week 20): proportion of subjects with abnormal baseline gamma glutamyltransferase (GGT) (i.e., > ULN) who achieved normalisation based on age- and gender-specific normal ranges provided by the central laboratory performing this assay absolute reductions in ALT, AST, and GGT relative reduction in spleen volume and fat content z-scores and percentiles for weight-for-age (WFA), and stature-for-age (SFA) (based on Centres for Disease Control and Prevention [CDC] child growth standards) in subjects ≤ 18 years of age on the date of informed consent absolute reductions in serum ferritin and serum chitotriosidase During the open-label period, durability of clinical response in subjects originally randomised to sebelipase alfa and treatment response in subjects originally randomised to placebo were investigated for efficacy endpoints similar to those described above. The effect of anti-drug antibodies (ADAs) on the efficacy of sebelipase alfa also was explored.
	Safety endpoints	incidence of adverse events (AEs), serious adverse events (SAEs), and IARs changes from baseline in 12-lead electrocardiograms (ECGs) and clinical laboratory tests (haematology, serum chemistry [including lipid panel], and urinalysis) changes in vital signs during and post-infusion, relative to pre-infusion values physical examination findings use of concomitant medications/therapies characterisation of ADAs including proportion antibody positive, time to antibody positivity, ADA titre by time point, peak ADA titre, and time to peak ADA titre. The effect of ADAs on the safety of sebelipase alfa also was explored, in particular, the relationship between ADA-positive subjects and the incidence of IARs.

	PK endpoints	Population and individual PK parameters are to be reported in a separate report. Parameters to be determined, based on samples collected in this study, may have included, as permitted by the data, clearance (CL) and volume (V) estimates along with secondary parameters of area under the concentration- time curve (AUC), maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$). The effect of ADAs on sebelipase alfa PK also was explored.
	Health-related QOL	Exploratory HRQOL measures included changes from baseline in scores for the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, Chronic Liver Disease Questionnaire (CLDQ), and/or Paediatric Quality of Life Inventory (PedsQLTM) Generic Core Scales, as appropriate to the age of the subject.
Database lock	30 May 2014	

Efficacy Results and Analysis

Baseline Disease Characteristics

All 66 subjects had a confirmed diagnosis of LAL deficiency, based on DBS LAL enzyme testing, at baseline. Genetic testing showed that overall, 85% of subjects had at least one copy of the previously described c.849G>A common exon 8 splice junction mutation (32% homozygotes, 53% compound heterozygotes); the remaining 10 subjects had other distinct mutations.

The median age at onset of the first LAL deficiency related abnormalities was reported to be 4 years overall, with a similar median age at onset of 5 and 4 years in the SA and placebo groups, respectively. Overall, 44% of subjects had a history or evidence of medically important chronic liver disease at baseline, including cirrhosis, portal hypertension, and/or coagulopathy.

As required by the entrance criteria, all subjects had an ALT > 1.5 × ULN at baseline. In the SA and placebo groups, mean baseline ALT values were 105.1 U/L and 99.0 U/L, respectively. All but 1 subject in the placebo group had elevated AST values at baseline; mean AST values were 86.6 U/L and 78.2 U/L in the SA and placebo groups, respectively. The mean GGT was similar in the SA group and placebo group at baseline (52.4 and 52.0 U/L, respectively); 36% of subjects in the SA group and 40% of subjects in the placebo group had elevated baseline GGT levels.

Baseline assessments of lipids demonstrated marked dyslipidaemia. Mean LDL-c values were 189.9 mg/dL (4.9 mmol/L) and 229.5 mg/dL (5.9 mmol/L) in the SA and placebo groups, respectively. Overall, more than half (58%) of subjects had LDL-c values in the very high range (> 190 mg/dL).

Hypertriglyceridaemia, defined as TG levels ≥ 200 mg/dL, was seen in 21% of subjects. Mean HDL-c values were 32.4 mg/dL (0.8 mmol/L) and 33.4 mg/dL (0.9 mmol/L) in the SA and placebo groups, respectively. Statistically significant differences between groups were seen with regard to cholesterol and non-HDL-c at baseline, with higher mean values seen in the placebo group than in the SA group. In the SA and placebo groups, mean baseline cholesterol values were 252.5 mg/dL (6.53 mmol/L) and 296.7 mg/dL (7.67 mmol/L), respectively (p=0.0341), and mean baseline non-HDL-c values were 220.5 mg/dL (5.7 mmol/L) and 263.8 mg/dL (6.8 mmol/L), respectively (p=0.0341).

Baseline liver pathology was available in 32 subjects in the FAS, including 19 subjects in the SA group and 13 subjects in the placebo group. As assessed by the blinded central reviewer, all (100%)

subjects with baseline biopsies had evidence of fibrosis. A total of 5 (26%) of 19 subjects in the SA group and 5 (38%) of 13 subjects in the placebo group with biopsy data available for analysis had Ishak fibrosis scores of 5 or 6, indicating either early or incomplete cirrhosis or probable or definite cirrhosis, respectively.

Multi-echo gradient-echo (MEGE) assessment of fat content was available in 35 subjects in the SA group and 26 subjects in the placebo group. At baseline, the mean liver fat content, as assessed by MEGE, was 8.5%, with similar mean liver fat content of 8.75% and 8.16% in the SA and placebo groups, respectively. Liver volume assessments by MRI were available in 36 subjects in the SA group and 28 subjects in the placebo group. The mean baseline liver volume, as assessed by MRI, was 1.46 multiples of normal (MN) overall, with similar mean liver volumes of 1.44 and 1.50 MN in the SA and placebo groups, respectively.

Efficacy:

Primary Endpoint:

ALT normalisation: A greater proportion of subjects in the SA group (31%) than in the placebo group (7%) achieved normalisation in ALT by the last time point in the double-blind period, a 24% difference between groups in favour of SA; the difference between groups was statistically significant (p=0.0271). All subjects in the SA group demonstrated a decrease in ALT; the mean decrease in ALT in the SA group was -57.9 U/L, representing a mean percent decrease from baseline of -53%. In contrast, the decrease from baseline to the last time point in the double-blind period in the placebo group was -6.7 U/L, representing a -6% mean percent decrease from baseline.

Secondary Endpoints:

LDL-c Reduction: a greater mean percent change from baseline in LDL-c was seen in the SA group than in the placebo group (-28.42% versus -6.25%, respectively), a -22.17% difference between groups in favour of SA; the difference between groups was statistically significant (p<0.0001).

Non-HDL-c Reduction: a greater mean percent reduction in non-HDL-c was seen in the SA group than in the placebo group (-27.97% versus -6.94%, respectively), a -21.04% difference between groups in favour of SA; the difference between groups was statistically significant (p<0.0001).

AST Normalisation: a greater proportion of subjects in the SA group (42%) than in the placebo group (3%) experienced normalisation in AST by the last time point in the double-blind period, a 39% difference between groups in favour of SA; the difference between groups was statistically significant (p=0.0003). The mean decrease in AST in the SA group was -41.9 U/L, representing a mean percent decrease from baseline of -44%. In contrast, the decrease from baseline to the last time point in the double-blind period in the placebo group was -6.3 U/L, representing a -7% mean percent decrease from baseline.

TG Reduction: a greater mean percent decrease from baseline to the last time point in the double-blind period in TG was seen in the SA group than in the placebo group (-25.45% versus -11.14%, respectively), a -14.30% difference between groups in favour of SA; the difference between groups was statistically significant (p=0.0375).

HDL-c Increase: a greater mean percent increase from baseline to the last time point in the double-blind period in HDL-c was seen in the SA group than in the placebo group (19.57% versus -0.29%, respectively), a 19.86% difference between groups in favour of SA; this difference between groups was statistically significant (p<0.0001).

Liver Fat Content Reduction: a greater mean percent decrease from baseline to the last time point in the double-blind period in liver fat content was seen in the SA group than in the placebo group (-31.98% versus -4.21%, respectively), a -27.77% difference between groups in favour of SA; this

difference between groups was statistically significant (p<0.0001).

Liver Histology Improvement: a greater proportion of subjects in the SA group (63%) than in the placebo group (40%) experienced improvement in liver histology (steatosis by morphometry) from baseline to the last time point in the double-blind period, as determined by central blinded read. This 23% difference between groups in favour of SA was not statistically significant (p=0.4216). As this result was not statistically significant, formal hypothesis testing stopped at this point in the sequence.

Liver Volume Reduction: a greater mean percent decrease from baseline in liver volume was seen in the SA group than in the placebo group at the last time point in the double-blind treatment period (-10.28% versus -2.66%, respectively), a -7.62% difference between groups in favour of SA. However, the SAP did not allow formal statistical testing of this endpoint.

Findings in the PP Set were similar to those in the FAS.

In summary, sebelipase alfa was statistically significantly more effective than placebo in improving a broad range of disease-related abnormalities, including normalisation of serum transaminases (ALT and AST), improvement in dyslipidemia (reductions in LDL-c, non-HDL-c, and TG, and increases in HDL-c), and reduction in liver fat content as assessed by MRI. Furthermore, sebelipase alfa treatment produced clear reductions in MRI-estimated liver volume during the 20-week double-blind treatment period. The positive effects of sebelipase alfa seen in sebelipase alfa-treated subjects were very consistent, with a highly similar pattern of response in the subjects treated initially with sebelipase alfa and in those who switched to sebelipase alfa in the open-label treatment period. Furthermore, evidence of the consistency of efficacy of sebelipase alfa was seen across the analysed study subgroups.

Extent of Exposure:

Thirty-five of 36 subjects in the SA group and 29 of 30 subjects in the placebo group received all 11 study drug infusions during the double-blind treatment period, as planned. One subject in the SA group received only 2 of 11 study drug infusions; this subject withdrew from the double-blind treatment period of the study after experiencing a severe atypical infusion-related reaction. (This subject may enter the open-label period upon rechallenge.) In the placebo group, 1 subject received 10 of 11 study drug infusions; this subject missed the planned study drug infusion at Week 8 because she had chickenpox and it was decided to hold study drug until the event resolved.

When data from the open-label period were considered, the maximum number of sebelipase alfa infusions received as of the cut-off for this report was 35. Overall, 35 subjects in the SA group received at least 12 study drug infusions, with 8 subjects receiving at least 20 study drug infusions through the cut-off for this report. In the placebo/SA group, exposure to sebelipase alfa had not reached the level seen in the SA group during the double-blind treatment period as of the cut-off for this report. Half (15) of subjects in the placebo/SA group had received at least 5 infusions during the open-label period as of the cut-off for this report.

Per protocol, infusions were completed over approximately 2 hours from Week 0 to Week 22, and were to be administered over approximately 1 hour starting at Week 24. As of the cut-off for this report, 40 subjects, 21 in the SA group and 19 in the placebo/SA group, received at least 1 sebelipase alfa infusion at over approximately 1 hour during the open-label period; the maximum number of infusions administered over approximately 1 hour for an individual subject was 21.

Clinical studies in special populations

No specific studies in renally impaired or elderly patients were undertaken. As infants were a core target group of one of the main studies the results are treated in the different sections pertaining to main studies and comparison between studies.

2.4.2. Supportive studies

2.4.2.1. Study LAL-CL01 and study LAL-CL-04

Methods/ treatments

Study LAL-CL01 was a completed Phase 1/2 open-label dose-escalation study in adult subjects with liver dysfunction due to LAL deficiency. Focus of these trials was the assessment of the safety, tolerability, PK, and PD of 3 dose levels of sebelipase alfa (0.35 mg/kg, 1 mg/kg, and 3 mg/kg).

Upon completing the 4 dose schedule in LAL-CL01 subjects had a treatment free period (which ranged from 9 to 28 weeks) after which they entered Study LAL-CL04, which is an ongoing Phase 1/2 open-label extension designed to assess the long-term safety, tolerability, and efficacy of sebelipase alfa at 2 dose levels (1 and 3 mg/kg qow).

Objectives

The **primary objective** was to evaluate the long-term safety and tolerability of sebelipase alfa in subjects with liver dysfunction due to Lysosomal Acid Lipase (LAL) Deficiency, while **secondary objectives** included the aim to evaluate the long-term efficacy of sebelipase alfa in subjects with liver dysfunction due to LAL deficiency.

Sample size

Nine adult subjects enrolled in LAL-CL01, of which the majority was male and all were of Caucasian ethnicity, and 8 of these also enrolled in the LAL-CL04 extension study.

Results

Subjects saw decreases in liver volume up to Week 104, which was the data cut-off for the LAL-CL04 study, and those who had MEGE data for liver fat content available also showed significant decreases at all timepoints examined for this parameter.

All subjects had **liver transaminases** above the normal range at first study enrolment, and showed rapid lowering of levels upon treatment start. In the non-treated phase between LAL-CL01 and LAL-CL04 ALT and AST rose again and subsequently dropped once more after treatment was resumed in LAL-CL04 with levels reaching approximate normal reference ranges at data cut-off.

Serum lipid levels increased during the first 4 weekly infusions of sebelipase alfa in LAL-CL01 and ten dropped again following discontinuation of therapy. This is thought to be consistent with mobilisation of pathological accumulations of lipids. Of note is that no AEs were associated with these transient increases in lipids. As expected with continued treatment with sebelipase alfa, the mean LDL and triglycerides decreased to below original Baseline levels at Week 12 and remained so through Week 104 on the qow dosing regimens. Furthermore, post-infusion increases in serum lipids similar in magnitude to those seen during the first 4 weeks of dosing in LAL-CL01 were not seen in the one-week post-infusion sample taken after approximately 6 months of treatment in LAL-CL04.

Over time, decreases were observed in LDL, total cholesterol, and triglycerides. Mean LDL decreased by 73 mg/dL (1.89 mmol/L; p=0.0156; 61%) at Week 52 and by 65 mg/dL (1.69 mmol/L; p=0.0313; 54%) at Week 104. Mean total cholesterol decreased by 71 mg/dL (1.84

mmol/L; p=0.0156; 39%) at Week 52 and by 66 mg/dL (1.71 mmol/L; p=0.0313; 34%) at Week 104. Mean triglycerides decreased by 72 mg/dL (0.81 mmol/L; p=0.0469; 36%) at Week 52 and by 68 mg/dL (0.76 mmol/L; p=0.0625; 31%) at Week 104. Additionally, an increase in HDL was observed. Mean HDL increased by 9 mg/dL (0.24 mmol/L; p=0.0156; 29%) at Week 52 and by 5 mg/dL (0.13 mmol/L; p=0.1250; 18%) at Week 104.

Mean **serum ferritin** decreased from LAL-CL01 Baseline to Week 104 (227 µg/ L to 139 µg/L, p=0.0313). Mean **high sensitivity C-reactive protein** (hs-CRP) also decreased from LAL-CL01 Baseline to Week 104 (0.23 mg/dL [2.3 mg/L] to 0.11 mg/dL [1.1 mg/L], p=0.1563).

Pathology reports of post-treatment liver biopsy assessments are currently available from 2 subjects. Although one must be careful about drawing **hepatic histopathology** conclusions from such limited data, there appeared to be a marked reduction in fat content and fibrosis in both of these subjects following sebelipase alfa treatment.

2.4.2.2. Study LAL-NH01

Study LAL-1-NH01 is a completed multinational, multicentre, retrospective natural history study of patients presenting with LAL deficiency before 2 years of age and diagnosed with LAL deficiency from 01 January 1985 to 30 September 2011, which aimed to:

- Characterize patient survival and key aspects of the clinical course of LAL deficiency/Wolman phenotype
- Serve as a historical reference for efficacy studies of enzyme replacement therapy (ERT) in patients with LAL deficiency/Wolman phenotype.

A feasibility questionnaire was sent to approximately 500 physicians, identified by review of medical literature and through referrals by other physicians receiving the questionnaire, in 44 countries. Specified demographic and clinical data from eligible patients were extracted through clinical chart review and entered on case report forms (CRFs) for further analysis. For any patient alive as of the last chart record reviewed, their physician was contacted prior to database lock to determine the patient's survival status.

Data were collected and listed for 36 eligible patients, but one patient turned out to be part of one of the studies conducted in support of this application. Thus ultimately the analysis set was made up of 35 eligible patients.

Patient **demographics** showed a predominantly Caucasian (48.6%) patient makeup with Asians (22.8%) making up the second largest contingent and characteristics in patients with early growth failure were similar to those of the overall eligible patient population.

Symptom onset was reported within the first month of life in 15 (42.9%) eligible patients, with only 2 subjects not exhibiting symptoms until 3 months of age.

Liver test analysis revealed that abnormalities in liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transferase [GGT], and/or total bilirubin) were also noted within the first few months of life in most patients.

Supportive interventions were received by 33 (94.3%) subjects, most commonly under the form of nutritional support (71.4%) or blood transfusions (62.9%). Steroid therapy was administered to only 5 (14.3%) patients. Other common interventions included plasma, platelets, albumin, vitamin K, antibiotics, diuretics, and morphine.

Hematopoietic stem cell transplantation (HSCT) as a **treatment with curative intent** was received by 10 (28.6%) eligible patients, at a median age of 5.45 months. One patient receiving a

HSCT at approximately 35 months also had a prior liver transplant at approximately 4 months. HSCT procedures were performed less frequently in patients with early growth failure (19.2%) compared with patients without early growth failure (55.6%).

Clinical chemistry and haematology testing revealed that abnormalities in ALT, AST, GGT, and total bilirubin were observed in 61.5%, 90.4%, 83.3%, and 52.4% of patients, respectively, and that all these parameters worsened over time in a subset of patients.

Serum lipid observations were as follows:

	Diagnosis	Death	Change from Diagnosis to Death
TC	2.99 mmol/L [115.4 mg/dL] (n=18)	3.49 mmol/L [134.7 mg/dL] (n=25)	0.47 mmol/L [18.1 mg/dL] (n=6)
TG	2.41 mmol/L [213.3 mg/dL] (n=16)	2.40 mmol/L [212.4 mg/dL] (n=23)	-0.20 mmol/L [17.7 mg/dL] (n=4)
HDL	0.36 mmol/L [13.9 mg/dL] (n=7)	0.36 mmol/L [13.9 mg/dL] (n=11)	-0.152 mmol/L (n=2) -5.87 mg/dL]
LDL	0.695 mmol/L [26.8 mg/dL] (n=2)	1.10 mmol/L [42.5 mg/dL] (n=5)	-0.01 mmol/L [0.39 mg/dL] (n=1)

Almost all patients had **abnormally low serum albumin** and **abnormally high serum ferritin** at diagnosis and death.

Physical examinations revealed that body weights were low at birth (or first measurement) for all subjects, and that rapid and marked decreases in WFA Z-scores and percentiles were observed over time in a majority of patients. Other findings on physical examination included hepatomegaly, splenomegaly and abdominal distension, as well as adrenal calcification and enlarged liver and spleen.

Histopathological findings indicating that a large amount of patients had fibrosis and/or steatosis.

Survival findings showed that 54.3% of patients died by 4 months of age, and 88.6% died by 9 months of age. The K-M estimate (95% CI) for probability of survival past 12 months of age was 0.114 (0.009, 0.220) in the overall eligible patient population.

Median age at **death** in treated (with HSCT and/or liver transplant) patients (8.6 months) was greater than that in untreated patients (3.0 months) and treatment was associated with a significantly longer time from birth to death in the K-M analyses for the overall eligible patient population (p=0.0008, log-rank test). While these results may indicate a modest effect of treatment, prudence of rash interpretation should be had as they may also reflect the fact that the treated subgroup could have been biased toward patients who survived long enough to receive such treatment, as evidenced by the fact that median age at transplant initiation (5.45 months) exceeded the median age at death in the study population (3.71 months).

Survival was poorer for patients with early growth failure (median age at death=3.46 months) and particularly so for those with early growth failure who were untreated, all of whom died before 8 months of age (median age at death=3.02 months). K-M estimates for probability of survival beyond 12 months of age were 0.038 (0.000, 0.112) for all patients with early growth failure and 0.000 (0.000, 0.000) for untreated patients with early growth failure.

2.4.3. Analysis / results performed across trials

No across-trial analysis was performed due to the fact that the main and supportive trials were too dissimilar across populations, methods and designs to allow this in a meaningful way.

Instead the Applicant opted for a comparison between trials, the results and findings of which are discussed later in this report.

Demographics

Parameter	Statistic	LAL-CL01/ LAL-CL04 (N=9)	LAL-CL02 (N=66)	LAL-CL03 (N=9)	Total SA Treated (N=84)	LAL-1-NH01 (N=21)[a,b]
Age of LAL Deficiency Symptom Onset (years)	n	9	66	8	83	21
	Mean (SD)	13.1 (11.19)	7.0 (7.12)	0.083 (0.12)	7.0 (7.82)	0.12 (0.09)
	Median	9.8	4.9	0.04	4.6	0.10
	Min, Max	0.8, 30.3	0.0, 42.4	0.0, 0.3	0.0, 42.4	0.0, 0.25
Age at Diagnosis (years)	n	9	61	9	79	21
	Mean (SD)	18.5 (17.02)	11.1 (9.33)	0.21 (0.15)	10.7 (10.79)	0.23 (0.08)
	Median	12.1	9.1	0.17	8.6	0.22
	Min, Max	4.1, 42.4	0.9, 53.6	0.0, 0.4	0.0, 53.6	0.11, 0.42
Age at First Dose						
< 2 years	n (% of N)	0	0	9 (100)	9 (10.7)	N/A
2 - 12 years	n (% of N)	0	24 (36.4)	0	24 (28.6)	N/A
> 12 years - < 18 years	n (% of N)	0	23 (34.8)	0	23 (27.4)	N/A
≥ 18 years	n (% of N)	9 (100)	19 (28.8)	0	28 (33.3)	N/A
Age at First Dose (years)	n	9	66	9	84	
	Mean (SD)	32.2 (10.54)	16.8 (10.92)	0.23 (0.13)	16.7 (12.6)	N/A
	Median	29.9	13.6	0.17	13.6	N/A
	Min, Max	19.9, 45.5	4.7, 59.3	0.8, 0.4	0.8, 59.3	N/A
Gender						
Male	n (% of N)	6 (66.7)	33 (50.0)	5 (55.6)	44 (52.4)	10 (47.6)
Female	n (% of N)	3 (33.3)	33 (50.0)	4 (44.4)	40 (47.6)	11 (52.4)
Race						
White	n (% of N)	9 (100)	55 (83.3)	4 (44.4)	68 (81.0)	6 (28.6)
Non-White	n (% of N)	0	11 (16.7)	5 (55.6)	16 (19.0)	15 (71.4)
Japanese	n (% of N)	0	2 (3.0)	0	2 (2.4)	N/A
Non-Japanese	n (% of N)	9 (100)	64 (97.0)	9 (100)	82 (97.6)	N/A
LIPA Mutations						
Homozygous Common	n (% of N)	1 (11.1)	21 (31.8)	0	22 (26.2)	N/A
Heterozygous Common	n (% of N)	8 (88.9)	35 (53.0)	0	43 (51.2)	N/A
Other[c]	n (% of N)	0	10 (15.2)	6 (66.7)	16 (19.0)	N/A
Not Provided	n (% of N)	0	0	3 (33.3)	3 (3.6)	N/A

Baseline characteristics

LAL-CL03

All 9 subjects enrolled in Study LAL-CL03 had confirmed LAL deficiency and LIPA genetic testing indicated distinct mutations were identified for each of the 6 subjects with none having the previously described c.849G>A common exon 8 splice junction mutation, which is commonly associated with LAL deficiency presenting in children and adults.

In Study LAL-CL03, age at symptom onset ranged from 0 months (birth) to 5.0 months of age, and age at diagnosis ranged from 0 months (birth) to 5.8 months of age, compared to 42.9% of patients reporting symptom onset within the first month of life and all patients exhibiting symptoms by 4 months of age in study LAL-1-NH01.

Initial signs and symptoms of LAL deficiency reported in both Study LAL-CL03 and Study LAL-1-NH01 included hepatosplenomegaly, abdominal distension, vomiting, diarrhoea, adrenal calcification, and failure to thrive.

Marked abnormalities in liver biochemical parameters were observed at Baseline in all subjects with AST elevated in all 9 subjects (median=125 U/L) and ALT was elevated in 7 (median=145 U/L). Elevations in GGT, total bilirubin, and ALP were also reported. Eight of the 9 subjects had a finding of hepatomegaly and/or splenomegaly on Baseline physical examination. In comparison,

abnormalities in liver function tests (AST, ALT, GGT, and/or total bilirubin) were also noted within the first few months of life in most patients in the historical control cohort from Study LAL-1-NH01.

In Study LAL-CL03, serum lipid abnormalities were observed at Baseline in most subjects with data available, consistent with the serum lipid abnormalities observed in the historical control cohort from Study LAL-1-NH01 and the literature, where consistently low HDL-c but often normal LDL-c and total cholesterol are observed.

LAL-CL02

Median age at disease onset was 4.0 years and across all 66 subjects.

Genetic testing showed that overall, 56 (85%) subjects had at least one copy of the previously described c.849G>A common exon 8 splice junction mutation (21 [32%] homozygotes, 35 [53%] compound heterozygotes); the remaining 10 (15%) subjects had distinct mutations other than common variants identified.

There were no differences in medical histories between ERT and placebo groups.

Baseline liver pathology was evaluated in 32 of the 66 subjects, with all having biopsy evidence of fibrosis (19 in the sebelipase alfa group, 13 in the placebo group). Ten (31%) of these 32 subjects (5 in each treatment group) had either early or incomplete cirrhosis or probable or definite cirrhosis with less than half (4 of 10) having a documented medical history of cirrhosis. All but 1 subject had biopsy evidence of microvesicular steatosis at Baseline.

Despite over one-third of subjects receiving LLMs (26 of 66; 39%) Baseline assessments of lipids demonstrated marked dyslipidaemia, with a greater degree of dyslipidaemia seen in the placebo group than in the sebelipase alfa group.

LAL-CL01/LAL-CL04

Medical history findings were consistent with those expected in this patient population, and those seen in Study LAL-CL02. Seven subjects had a medical history of hepatomegaly and/or splenomegaly and 1 subject had prior biopsy evidence of hepatic fibrosis.

Infant survival

LAL-CL03

In the historical control cohort from Study LAL-1-NH01, none of the 21 infants survived beyond 8 months of age. In contrast, 6 of 9 sebelipase alfa-treated infants in Study LAL-CL03 survived beyond 12 months (67% at 12 months of age; 95% CI: 29.9%, 92.5%)

For the 3 subjects who died in Study LAL-CL03 before data cut-off, the age at death (median age of 2.92 months, range: 2.8 to 4.3 months) was consistent with the median age at death of 3.0 months (range: 1.4 to 7.1 months) for the historical control cohort from Study LAL-1-NH01.

LAL-CL02

Not applicable.

LAL-CL01/LAL-CL04

Not applicable.

Transaminase levels

LAL-CL03

Reductions in ALT were observed as early as Week 1 in some of these subjects, when all subjects were receiving sebelipase alfa at a dose of ≤ 0.35 mg/kg, and were apparent in all 5 subjects by Week 4 of treatment, 2 weeks after most subjects escalated to 1 mg/kg qw.

All 7 subjects with post-Baseline data also showed rapid and marked reductions in AST following initiation of treatment with sebelipase alfa, which were already observed by Week 1 in the majority (6 of 7) of subjects at a dose of ≤0.35 mg/kg, and further reductions were observed by 2 weeks after most subjects escalated to 1 mg/kg qw and the median AST levels remained stable from Week 4 through Week 60.

Reductions in GGT and bilirubin were observed following treatment with sebelipase alfa which by Week 4 represented median percent changes of -13% and -21%, respectively. Further marked decreases in GGT were observed through Week 12 (median change=-79%, n=5) and were fairly stable thereafter through Week 164. Modest and gradual decreases in total bilirubin were observed through Week 84 (median change=-40%).

In contrast, no normalizations were noted in the historical control group for either of these parameters.

LAL-CL02

Treatment with sebelipase alfa led to normalisation of ALT levels in a significantly greater proportion of subjects compared placebo (p=0.0271). At the end of the double-blind treatment period, 31% (11 of 36) of subjects in the sebelipase alfa group compared with 7% (2 of 30) of subjects in the placebo group achieved normalisation in ALT.

Following the transition to sebelipase alfa treatment from placebo during the open-label period for placebo-arm subjects, a rapid decline in ALT levels was observed with a mean percent decrease in ALT of 27% by Week 2 and 46% by Week 14. Normalisation was achieved by 22% of subjects by Week 2 and 44% by Week 14, similar to the decrease observed in subjects who initially received sebelipase alfa treatment during the double-blind treatment period.

Treatment with sebelipase alfa led to normalisation of AST levels in a significantly higher proportion of subjects treated with sebelipase alfa compared with placebo (p=0.0003). At the end of the double-blind treatment period, 42% (15 of 36 subjects) of subjects in the sebelipase alfa group compared with 3% (1 of 30 subjects) in the placebo group achieved normalisation in AST

Following the transition from placebo to sebelipase alfa treatment during the open-label period, a rapid decline in AST levels was observed with mean percent decreases ranging from 20% to 39% from Weeks 2 to 14 in these subjects with 15% achieving AST normalisation by Week 2 and 38% by Week 14; a decrease similar to the decrease observed in subjects who initially received sebelipase alfa treatment during the double-blind treatment period.

Findings in this study also echoed those of LAL-CL03 with rapid and significant reductions in GGT, total bilirubin, and ALP following initiation of treatment with sebelipase alfa in the double-blind treatment period.

LAL-CL01/LAL-CL04

Mean ALT levels during LAL-CL01 and LAL-CL04 rapidly declined after initiation of treatment with sebelipase alfa over the full range of doses. After the treatment-free interval between dosing in LAL-CL01 and LAL-CL04 (ranging from 9 to 28 weeks), ALT was increased at the LAL-CL04 Baseline relative to the end of treatment value in LAL-CL01.

The reversibility of response upon discontinuation of treatment supports that transaminase reductions were related to treatment; re-initiation of treatment in LAL-CL04 produced a similar rapid decline in ALT.

Mean AST levels during LAL-CL01 and LAL-CL04 rapidly declined after initiation of treatment with sebelipase alfa over the full range of doses. After the treatment-free interval between dosing in LAL-CL01 and LAL-CL04 (ranging from 9 to 28 weeks), AST was increased at the LAL-CL04 Baseline relative to the end of treatment value in LAL-CL01.

The reversibility of response upon discontinuation of treatment supports that transaminase reductions were related to treatment; re-initiation of treatment in Study LAL-CL04 produced a similar rapid decline in AST. The improvements were maintained after the transition from qw to qow dosing

Changes in GGT and ALP were consistent with those reported in Study LAL-CL02, with reductions in both parameters observed following treatment with sebelipase alfa, and these results, supported by the findings from the open-label extension period of Study LAL-CL02 demonstrate a sustained effect of sebelipase alfa on liver-related biochemical parameters over a longer duration of treatment.

Liver fat, volume & histopathology

LAL-CL03

Improvements in hepatomegaly were observed with sebelipase alfa treatment. On physical examination, improvement in liver size was observed for all 6 subjects surviving beyond Week 4 and shifts to a non-palpable liver were observed for 3 of 4 subjects with available data by Week 36.

LAL-CL02

Significant improvements in hepatomegaly were observed in subjects treated with sebelipase alfa in with a significant difference of -7.62% (p=0.0068), in favour of the sebelipase alfa arm, apparent between treatment groups. Note however that formal statistical testing of this endpoint was not done in this study.

Improvement in liver histopathology from Baseline to the last time point in the double-blind period was reported in a greater proportion of subjects in the sebelipase alfa group than in the placebo group (63% versus 40%; respectively), though this difference was not significant (p=0.4216) (Important clinical differences between groups were noted however, see AR.).

LAL-CL01/LAL-CL04

Reductions in hepatic fat and liver volume were observed following the initiation of sebelipase alfa treatment in Study LAL-CL04. Reductions in liver fat content were seen within 10/12 weeks of initiation of treatment across all doses, with further improvements through the last available time point.

Pathology reports suggested that histopathological improvements were observed following extended treatment with sebelipase alfa in steatosis and fibrosis in these cases.

Dyslipidaemia improvement

LAL-CL03

Despite potential confounding factors, LDL-c levels were shown to decrease in the majority (5 of 6) of surviving subjects following initiation of sebelipase alfa treatment and normalised in 2 of 2 subjects who had an elevated LDL-c at Baseline or the first available assessment.

Transient increase in LDL-c, total cholesterol and triglycerides were seen at Week 1 of treatment consistent with the cellular fat mobilization mechanism of action of sebelipase alfa.

LAL-CL02

Treatment with sebelipase alfa led to a statistically significant greater mean percent change in LDL-c levels from Baseline to the end of the double-blind treatment period (-28%) compared with subjects who received placebo, and results for non-HDL-c (-28% versus -7%, respectively; p<0.0001) and triglycerides (-25% versus -11%, respectively; p=0.0375) were similar. The marked decreases in LDL-c were associated with statistically significant increases in HDL-c levels in favour of sebelipase alfa (20% versus -0.3%; p<0.0001).

Following transition of placebo-treated subjects to open-label treatment with sebelipase alfa in the open-label extension (Figure 7), a similar transient increase with subsequent rapid decline in LDL-c was observed as was an improvement in HDL-c. Importantly, among the subjects randomised to sebelipase alfa, further reductions in LDL-c were observed during the open-label extension.

LAL-CL01/LAL-CL04

More substantial increases were noted for cholesterol and triglycerides during the initial 4-week treatment period and this was again observed following the initial 4 weekly infusions in Study LAL-CL04 as subjects who entered the extension study had been off treatment with sebelipase alfa ranging from 9 to 28 weeks. These increases were likely higher in Studies LAL-CL01/LAL-CL04 than those observed in Study LAL-CL02 due either to the more frequent dosing interval or more frequent assessments conducted in the earlier studies. By Week 104, all 7 subjects in Study LAL-CL04 with data available at the time of the data cut-off showed decreases from their original Study LAL-CL01 Baseline values in LDL-c and most had increases in HDL-c and decreases in triglycerides.

Of note, as was observed with transaminase levels, when subjects went off treatment at the end of Study LAL-CL01 (interval between dosing of 9 to 28 weeks), LDL-c levels increased and HDL-c levels decreased from the lowest and highest levels, respectively, within 4 weeks after the last dose of sebelipase alfa in Study LAL-CL01 during the period between studies. These observations support the utility of these biochemical parameters in the monitoring of the clinical effects of sebelipase alfa and highlight the requirement for continuous treatment with sebelipase alfa.

Growth and weight improvement

LAL-CL03

Marked and rapid improvements in WFA percentiles following initiation of sebelipase alfa treatment were observed for all 6 subjects who survived beyond Week 4. Half of them achieved WFA near or above the 25th centile, 1 achieved WFA above the 90th centile, and 1 maintained WFA above the 75th centile. The final subject had increases in WFA but remained under the 10th centile.

In contrast, in the historical control cohort from LAL-1-NH01, rapid and marked decreases in WFA percentiles were observed over time.

Moderate improvements in LFA/HFA percentiles following initiation of sebelipase alfa treatment in were observed. Although half of the subjects who survived beyond Week 4 had fluctuating LFA/HFA percentiles they nevertheless showed an overall improvement during treatment with sebelipase alfa. The other subjects initially decreased in LFA/HFA, but returned to Baseline level eventually.

In contrast, in the historical control cohort from LAL-1-NH01, rapid and marked decreases in LFA percentiles were observed over time.

Mid-Upper Arm Circumference-for-Age, Head Circumference-for- Age, BMI-for-Age, and Weight-for-Length (or Height) all followed the above trend of improvement.

LAL-CL02

Improvement in growth was not a secondary endpoint in Study LAL-CL02, but some anthropometric measurements were taken.

Review of change from Baseline to Week 20 of the double-blind treatment period revealed small mean increases in weight from Baseline in the sebelipase alfa and placebo groups. A continued increase from Baseline in weight was observed during the open-label period in subjects initially treated with sebelipase alfa and a mean increase from Baseline of 1.8 kg was observed at Week 14, in subjects who transitioned from placebo to sebelipase alfa during the open-label period. Given that no analysis was foreseen on these parameters in the protocol, no decisions can be drawn from these findings.

Baseline height measurements were obtained in all subjects and follow-up height measurements in subjects ≤18 years of age, and review of change from Baseline revealed small mean increases from in both the sebelipase alfa and placebo groups which is expected in a population with this age structure. Consistent with the mean change seen in the subjects initially treated with sebelipase alfa in the double-blind period, a mean increase from Baseline was observed in subjects who transitioned from placebo to sebelipase alfa during the open-label period and in subjects initially treated with sebelipase alfa.

Insights into the effects of treatment on height will require longer-term follow-up of growth using centile charts.

Inflammation markers and haematological parameters

LAL-CL03

Rapid and marked reductions in serum ferritin were observed following initiation of sebelipase alfa treatment, with reductions apparent by Week 1 and further observations through Week 6, the latter after which ferritin remained fairly stable through Week 60.

Improvements in haematological parameters (i.e., TFHN levels) were observed in infants with rapidly progressive disease. Of the 6 subjects surviving beyond Week 4, 5 achieved TFHN normalisation prior to the data cut-off (haemoglobin levels consistently above the age-adjusted LLN over a minimum period of 4 weeks, with no transfusions during this period or for 2 weeks prior to the first haemoglobin measurement in the period)

In 2 other subjects, TFHN maintenance was also achieved (transfusion-free at Week 6 and had no haemoglobin levels below the age-adjusted LLN beginning at Week 8 and continuing for at least 13 weeks).

In contrast, in the historical control cohort from Study LAL-1-NH01, blood transfusions were administered to 62.9% of patients in the study, and no change in haemoglobin levels were observed from the time of diagnosis to death.

LAL-CL02

Marked reductions in serum ferritin were observed in Study LAL-CL02 following initiation of sebelipase alfa treatment. At the last visit in the double-blind treatment period, decreases from Baseline were seen in the sebelipase alfa and placebo groups, with the difference between groups being statistically significant in favour of sebelipase alfa. The reason for the decrease in ferritin in the placebo group is unknown.

Decrease in serum ferritin continued during the open-label period, and these results support the findings from Study LAL-CL04, demonstrating a sustained effect of sebelipase alfa on serum ferritin reduction over a longer duration of treatment.

LAL-CL01/LAL-CL04

Though Baseline serum ferritin levels were normal in 8 of 9 study subjects in LAL-CL01, mean reductions in serum ferritin were observed from Baseline up until to study LAL-CL04 Week 104, demonstrating that the sebelipase alfa-mediated reduction on serum ferritin is maintained over long-term treatment.

This decrease and the magnitude the decrease in serum ferritin were independent of dose, and these findings are consistent with the reduction reported in LAL-CL02.

Spleen fat and Health-related QOL

LAL-CL03

Improvements in splenomegaly were apparent with sebelipase alfa treatment as on physical examination, improvement in spleen size was observed in all 5 subjects who had a palpable spleen at Baseline. Shifts to a non-palpable spleen were observed for 2 of 4 subjects with available data by Week 20, and for 3 subjects with available data by Week 36. Additionally, marked reductions were observed for 4 subjects who had spleens that extended 4 to 8 cm beyond the costal margin at Baseline, and spleens for all 4 subjects were non-palpable by the last assessment.

On abdominal imaging (ultrasound and MRI), improvement in spleen size was observed for all 5 subjects with Baseline and post-Baseline data. After the initial improvement, spleen sizes were stable or continued to decrease over time, with the exception of 1 subject who had a worsening splenomegaly that coincided with a switch to qow dosing.

Normal development milestones and dietary improvements were achieved in infants on long-term sebelipase alfa treatment.

LAL-CL02

Similarly as above, significant improvements in splenomegaly were observed in subjects treated with sebelipase alfa in this study. A significant mean absolute decrease from Baseline to the last time point in the double-blind period in spleen volume was observed in subjects treated with sebelipase alfa compared with an increase of in subjects treated with placebo group.

Consistent with the reductions in spleen volume, a mean absolute decrease from Baseline to the last time point in the double-blind period in spleen fat content was observed for subjects who received sebelipase alfa compared with the increase observed for placebo, but this difference was not statistically significant.

In children and adults, though there was some consistency in the HRQoL measurements in the subjects with low scores, there was no obvious treatment effect overall in fatigue or quality of life

LAL-CL01/LAL-CL04

Although increased spleen lipid content was anticipated, summaries of the spleen fat content were not created in Studies LAL-CL01/LAL-CL04 as the low values, lack of information on fat content in normal spleens, and the absence of a placebo comparator, made any effect of sebelipase alfa treatment difficult to interpret.

No QOL endpoints were examined in this study.

Long-term efficacy

In total 6 of the 9 subjects enrolled in LAL-CL03 were still alive at data cut-off, with the oldest child being 42.2 months of age and the youngest being 12 months of age. The longest exposure duration was +/- 38 months. In contrast, none of the untreated subjects that were part of the historical control cohort in LAL-1-NH01 lived past the age of 8 months.

Not only long-term survival, but also improved growth and normal development milestones were achieved in infants on long-term sebelipase alfa treatment, as well as improvements in serum transaminase levels, haematological parameters, serum lipid levels, serum ferritin, and hepatosplenomegaly.

Long-term efficacy was evaluated in 8 adults who completed their Week 104 assessment in Study LAL-CL04 and 65 subjects who continued to the open-label period of Study LAL-CL02, including 5 subjects in the sebelipase alfa/sebelipase alfa treatment group who completed their Week 36 assessment.

Initiation of sebelipase alfa treatment produced a rapid decline in transaminase levels, with notable decreases occurring in the majority of subjects within 2 weeks. Overall improvements and normalisation of serum transaminase levels were sustained through Week 104 of Study LAL-CL04 and through Week 36 of Study LAL-CL02.

All 7 subjects who received the full set of infusions in Study LAL-CL04 through Week 104 showed decreases in mean LDL-c and triglycerides to levels below original Baseline levels, and most subjects showed increases in HDL-c. Decreases in LDL-c and triglycerides, and increases in HDL-c, were noted at Week 12 of Study LAL-CL04 and continued through Week 104 on the qow dosing regimens. These early improvements in lipid profiles after 12 weeks on ERT with sebelipase alfa improved even further between Week 12 and Week 104, with further reductions in total cholesterol, LDL-c, and triglycerides, and further increases in HDL-c.

Similarly, further reductions in LDL-C continued during the open-label extension period in Study LAL-CL02, with a maximum decrease from Baseline around 44% at Week 36. Sustained improvement in HDL-c, triglycerides, and non-HDL-C levels were also seen, with a maximum mean percent increase from Baseline around 41% seen at Week 36.

Other benefits of ERT with sebelipase alfa were also demonstrated in LAL-CL04 with patients showing further reduction in fat fraction in the liver, reduction in liver volumes, and improvements in liver histopathology.

Immunogenicity

In Study LAL-CL03, 4 subjects were ADA positive during at least one assessment, defined as having a positive screening ELISA that was confirmed by depletion ELISA. Most subjects who developed ADAs did so within the first 2 months of exposure. At the time of initial ADA positivity, 3 subjects were receiving a dose of 1 mg/kg qw and 1 was receiving a dose of 3 mg/kg qw. Persistence of ADA positivity was observed in 3 subjects; 1 had a single positive result and thereafter tested negative. All 3 subjects who had multiple positive ADA assessments showed decreases from maximum titre with continued dosing, with 2 of these 3 having a negative ADA result at their last assessment prior to data cut-off. Two subjects who were ADA positive tested positive for *in vitro* neutralising antibodies that inhibited both LAL enzyme activity and LAL cellular uptake, one of whom was ADA negative at the last assessment.

A medical review of the clinical response data for the 4 subjects who tested ADA positive suggested that the presence of neutralising antibodies in one subject could have been a contributing factor, along with other comorbid conditions, in the subject's suboptimal rate of growth; other clinical outcome measures in this subject do not appear to have been affected by the development of ADAs. The other 3 subjects testing positive for ADAs, one of whom also developed neutralising antibodies, showed no evidence of a potential loss of response in any clinical outcome measures coincident with the development of ADAs.

In Study LAL-CL02, 35 of the 36 subjects who received sebelipase alfa in the double-blind period were evaluated for ADAs. Five (14%) subjects had at least one positive ADA test. Those subjects

who developed ADAs did so within the first 3 months of exposure and none of the 5 subjects developed neutralizing antibodies at any time, with the exception of partial inhibition of cell uptake just above the assay cut point in one subject at Week 12. As samples from this subject were negative for inhibition of cell uptake at all other time points (including Weeks 20 and 28), this may represent an isolated false positive result. In general, ADA titres were low and not sustained. Two subjects were positive at only a single time point and none of the 5 subjects with positive ADA titres continued to be ADA positive at their last time point prior to data cut-off. Review of efficacy results among the 5 ADA-positive subjects showed that all 5 experienced a decrease from Baseline to the last time point in the double-blind period in ALT, AST, and LDL-c. Thus, evidence of the effectiveness of sebelipase alfa was seen among ADA-positive subjects.

In Study LAL-CL01, all samples from the 9 subjects enrolled were negative for ADAs as were all samples from 7 of 8 subjects in Study LAL-CL04. One subject in Study LAL-CL04 had 1 result that was above the pre-determined positivity cut-off for ADAs. This finding occurred at a single isolated assessment at Week 4, and did not coincide with any notable change in serum transaminases or lipids.

2.4.4. Discussion on clinical efficacy

LAL deficiency in both its forms (rapidly progressing in infants and 'normal' progressing in adults) is a designated orphan disease, which severely limits the potential pool of patients on which can be drawn to populate the trials. This is especially true in infants with the rapidly progressing form of the disease, whom usually do not live past their 6th month of age, which further lowers the already low availability of potential subjects in this patient group.

Design and conduct of clinical studies

The Applicant submitted data of 4 studies in support of the efficacy part of the dossier; two pivotal trials of which one in infants with Wolman disease (LAL-CL03) and one in children and adults with LAL deficiency (LAL-CL02). Data of two additional trials was used in support of the observations made in the pivotal trials; one was a natural history study of Wolman disease in infants (LAL-1-NH01) and the other was a dual PK/PD/safety study in adults (LAL-CL01/04) that consisted of a dose escalation study (CL01) followed by an extension study (LAL-CL04) for subjects whom completed the course in the former.

In regards to Wolman's disease infants, the Applicant opted for a combined phase 2/3 open-label trial without a comparison arm. This design choice is considered acceptable as there is currently no effective treatment for infants suffering from this disease, and they usually die a few months after birth.

The Applicant attempted to rectify the very low number of infant subjects in the LAL-CL03 trial by doing a natural history study whereby collecting historic records and measurements for Wolman disease victims from the 1980's onward.

This method is considered acceptable in order to try and mitigate to some extent the issue of extremely small study populations, though some caution is necessary as state of the arts on measuring methods and data retention may evolve over time and may cause older data to have a lesser informative weight then newer data.

The pivotal trial in children and adults was a more traditional Phase III trial consisting of a double-blind period whereby subjects were randomized to either receive sebelipase alfa treatment or placebo.

Given that LAL deficiency in subjects with the normal onset variety can be marginally supported by dietary measures and is not as lethal as the Wolman disease form but mainly manifest in lowered quality of life, allowing placebo treatment for a limited time is fully acceptable. Moreover, after the double-blind study there was an open-label extension period in which previously placebo-treated patients were switched to ERT treatment (initial qw dosing that was switched to qow after 4 weeks) while former sebelipase alfa treated patients continued on from the double blind phase, in a qow schedule.

Since non-infant patients usually survive for a longer time then infants with Wolman disease, there was a larger pool of patients. Nevertheless, with the disease being orphan and the prevalence very rare about 66 patients went through the trial procedures, thus limiting the statistical power of the outcomes.

In a similar fashion to the LAL-CL03 and LAL-1- NH01, the Applicant used the results from the PI/PII LAL-CL01/CL04 studies to support the outcomes seen in LAL-CL02.

In summary, all studies designed for efficacy analysis were of different designs and harbouring populations with different dispositions. Thus intra-study or pooled analysis would be a futile exercise from a statistical point of view, and as such a simple comparison between studies to see whether the effects seen in each trial were mirrored in other trials, is done, considering that this would indicate that any beneficial effect seen would very likely be due to sebelipase alfa treatment.

This approach is acceptable, although observations and conclusions drawn from such an intra-study comparison lack the absolute certainty that a more formal statistical comparison would achieve due to the inherent statistical analysis limitations in the former, the intrinsic nature of the orphan disease precludes the possibility of using traditional statistical analyses.

In the current dossier long-term efficacy data are lacking. Both pivotal trials as well as LAL-CL04 were still ongoing or in follow-up at the moment of data cut-off. The natural history study LAL-1-NH01 also lacks long term data, which is non-surprising given the nature of the subjects that it included (Wolman disease infants whom usually pass away within the first 6 month of life) while LAL-CL01 had a duration of only 4 weeks. However, due to the high medical need it is acceptable to obtain this information post approval and the applicant has committed to long-term monitoring of efficacy and safety in the post-authorization setting, which will help to fill in this knowledge gap in the coming years.

This procedure is assessed under accelerated assessment due to the lack of effective treatment and the high mortality of the disease in infants. This is considered appropriate, and the overall data submitted considered comprehensive for a full marketing authorisation, nevertheless long-term efficacy and safety follow up will be necessary post approval with monitoring after commercialisation.

Efficacy data and additional analyses

Generally the results observed in the pivotal trials were positive, with significant improvements in survival for infants, in molecular markers of LAL deficiency and in makers such as hepato-histology, growth, liver size and QOL.

Transaminases such as ALT and AST, as well as serum lipids and free cholesterols increased or decreased (along the type of marker) to near normal levels with treatment relative to Baseline; and these improvements were seen in all ERT treatment populations across the different trials.

Likewise other markers saw similar improvements, and a majority of infants lived to or past the age of 12 months (compared to 6 months in the natural history study), thus demonstrating a significant benefit in survival.

Despite the limitations above mentioned (statistical limitations, limited number of patients), the efficacy results are mirrored across trials (contrasting to the lack of efficiency of non-ERT treatments in the natural history study). This is very reassuring and indicates that sebelipase alfa ERT actively improves the negative effects of LAL deficiency over the whole of the disease spectrum.

Additionally, the applicant has provided efficacy data in patients with LAL deficiency in all age groups, namely infants, children and adults, thus in effect, a comprehensive efficacy documentation is provided for this orphan disease.

In conclusion, sebelipase alfa treatment gave rise to impressive results on the main efficacy endpoints. Nevertheless, despite these very positive results, there are also some areas which remain unclear.

Firstly, as mentioned in the previous section, there is currently no long-term efficacy data available beyond 36 months. Given that this ERT treatment will be a lifelong treatment, as the underlying gene defects are not corrected, the data submitted remain limited in regard to long-term use. This will be addressed through the ongoing clinical trials and the registry where collection of long term efficacy data (liver function) will be captured.

There is also some uncertainty in regards to long-term immunogenic developments. Patients may or may not develop resistance to the ERT treatment on a longer term basis or heterozygote subjects whom still have a basal level of endogenous enzyme might develop cross-reactive ABs in reaction to the exogenous recombinant enzyme.

Furthermore, there have been cases of ADA positivity among subjects in the LAL-CL02 and LAL-CL03 trials. In LAL-CL02, in adults and children, ADA development was rare (less than 10%) and without obvious impact on efficacy (transient effect while no ADA positivity was reported in the LAL-CL01/CL04 trial).

In the LAL-CL03 infant study, of the 6 infants that lived to or past the age of 12 months, four (>50% of subjects) developed ADA positive titres and two (thus 30% of subjects) patients developed neutralizing ABs, of which one showed a negative effect on growth improvement (although other markers seemed unaffected). A definite judgement of loss of efficacy is not possible at present, however, this is a point of concern, thus further monitoring over time in the post authorisation setting. It is considered important to monitor immunogenicity in the post approval setting to collect data to provide further insight on this matter. This is further discussed in the safety part of this report, together with the updated data provided at D120 of the procedure.

Additionally, in the infant trial almost 50% of the participating patients died despite treatment, which raises concern. Review of the deceased subject's autopsies and medical histories showed that numerous medical co-morbidities were present which could each be a possible reason for their deaths. It is thus impossible to implicate LAL-enzyme treatment with any degree of certainty.

On the other hand, the majority of patients lived to at least 12 months of age, which is a clear improvement in term of survival compared to untreated patients as exhibited in the natural history study results.

Due to the limited number of available subjects definite conclusions related to possible lack of efficacy in certain patients, there is a need to continue gathering long term efficacy data in the post authorisation setting. In this context the ongoing study in infants less than 8 months (LAL CL-08) is considered a key study to further characterise long term efficacy in infants with Wolman disease.

Lastly, the rationale for the final recommended dose was further discussed during the procedure due to concerns expressed earlier in the report. In the end, the CHMP agreed with the Applicant

clarification provided during assessment, that the non-clinical aspects and safety margins could support rationale for selecting the 1 mg/kg qow dose as a posology showing adequate efficacy in the LAL-CL02 trial in children and adults.

In the Wolman infants' trial, most subjects were at 3mg/kg qw at data cut-off. The Applicant considered that a treatment with 1 mg/g qw would be enough, whereas questions were initially raised to the applicant whether starting on 3 m/kg qw and down titrating if good response could be a better approach based on rapid deterioration in physical state of Wolman patients. Further rationale provided by the applicant, justified the recommendation for 1 mg/kg qw as starting dose based on safety related to the rapids free lipid spike seen at treatment start, and the fact that despite the rapidly progressing nature of Wolman syndrome, there would be enough time to up-titrate to higher doses if efficacy would be unsatisfactory. This is considered acceptable by the CHMP and adequately addressed in the SmPC in the posology section.

There were no renally impaired patients amongst the trial subjects, thus influence of dose, clearance and other parameters on efficacy endpoints could not be assessed. Since sebelipase alfa is a recombinant human LAL enzyme of relatively high-MW (55 kDa), renal excretion is not expected to play an important role in its elimination. Therefore, variability in renal function would not have a relevant effect on the exposure to sebelipase alfa, as also indicated by covariate analysis during development of the population PK model for sebelipase alfa.

2.4.5. Conclusions on clinical efficacy

The treatment with sebelipase has shown to be efficacious in the treatment of LAL deficiency, with very positive results seen in Wolman-infants in term of survival.

LAL deficiency is a serious and potential life-threatening disease without an effective treatment and the data provided in this application despite their limitations are considered adequate.

The Applicant provided efficacy data in all age groups of patients with LAL deficiency justifying an indication in patients of all age. The efficacy data support a full Marketing authorisation approval in term of complete data package, although collection of long term efficacy and safety data will be done in the post authorisation setting through the disease registry and with the ongoing study in infants (LAL-CL-08) .

2.5. Clinical safety

Clinical safety was evaluated in a total of 6 studies, with 4 (LAL-CL01/04 in adults, LAL-CL02 in adults and children and LAL-CL03 in infants with Wolman disease), while the two remaining studies LAL-CL06 in adults and children and LAL-CL08 in infants with Wolman disease only contributed data about deaths, SAEs, withdrawals due to TEAEs and moderate or severe IARs. The latter two studies safety data were provided at D120 of the procedure.

In the D120 safety update provided during the procedure, a total of 106 subjects with LAL deficiency have received treatment with sebelipase alfa, including 14 infants (<2 years), 57 children (24 ≥2years and <12 years, 23 ≥12 years and <18 years), and 33 adults.

A pooled safety assessment was conducted to look at safety signals that were not otherwise evident in the individual clinical studies. However, this approach had limitations due to differences in the rate of disease progression according to age, in study designs and populations and due to the low number of subjects available inherent with orphan disease.

Included in this updated pooled safety set were patients from study LAL-CL06, but the following should be noted:

- 2 Subjects from the LAL-CL06 study were not included in the total for subjects ongoing treatment because these subjects were rescreened and included in the study after initially being marked as screen failures. Therefore, the number of subjects treated with sebelipase alfa is recorded in the database as 17 and not 19.

- Adverse events for which the first date of active dose or the event start date were missing were included in the subject listing of adverse events. However, they were not flagged as TEAEs, and were therefore not included in the tables of TEAEs. Two of the 19 subjects dosed in LAL-CL06 were affected in this way.

Subjects with known egg hypersensitivity were excluded from the clinical studies.

Patient exposure

The exposure in subjects in the safety data set is summarized in table 3 below.

The extent of exposure across all trials was:

< 04 weeks:	104 subjects
≥ 04-12 weeks:	94 subjects
≥ 12-26 weeks:	88 subjects
≥ 26-38 weeks:	80 subjects
≥ 38-52 weeks:	66 subjects
≥ 52-78 weeks:	48 subjects
≥ 87–104 weeks:	16 subjects
≥ 104-130 weeks:	9 subjects
≥ 130-156 weeks:	9 subjects
≥ 156-182 weeks:	7 subjects
≥ 182 weeks:	1 subject

The majority of patients exposed in the 6 trials were Caucasian and the number of non-Caucasians was still too low as to allow drawing conclusions.

The majority of subjects had either homo- or heterozygous c.849G>A common exon 8 splice junction mutation, with the latter making up slightly over half of the pooled safety set, while 16 were classified under the 'other mutation' state. Of these 16 subjects more than one third were infants treated in the LAL-CL03 trial, by matter of which the median treatment duration of 'other mutation' state patients was generally lower, and this mutation group had a higher administration of 3mg/kg qw dosing regimens.

Nevertheless, even in the in the current safety update the data are currently too sparse as to allow assessment of exposure stratified according to mutation status.

Subjects with known egg hypersensitivity were excluded from the clinical studies.

Adverse events

Overall, 84% (89/106) of sebelipase alfa-treated subjects reported a **TEAE**, with the majority being judged not related to sebelipase alfa treatment and mild or moderate in severity. In total 31 (29%) subjects experienced treatment-related (as judged by the investigators) TEAEs.

Nineteen subjects (17.9%) reported **treatment-emergent SAEs**, the majority of which were also not considered related to sebelipase alfa treatment, except for four. A total of 16 subjects (15.1%) reported events assessed by the Investigators as infusion associated reactions (IAR).

Infusion associated reactions were defined as any TEAE that occurred during or within 4 hours of completion of the infusion that were considered by the Investigator to be related to study treatment.

In LAL-CL03 4 infants presented with mild IARs. One subject had severe IARs which however occurred concurrently with significant non-treatment-related infections. All IARs were successfully managed by infusion interruption, infusion rate reduction, conventional treatment with antipyretics and antihistamines, and/or other supportive treatment, and no cases of anaphylaxis were noted. There were also no treatment discontinuations due to IARs (or other TEAEs).

In LAL-CL02, 4 sebelipase alfa treated subjects experienced an IAR, of which 3 had only mild events, but one had a serious IAR.

In LAL-CL01/CL04 two subjects, whom were siblings, experienced the majority of IARs, which were generally mild of nature. One IAR by one of the subjects was considered a hypersensitivity-type reaction, but the person was able to continue treatment once symptoms had subsided.

An analysis of all TEAEs regardless of causality was performed to identify potential immune-mediated **hypersensitivity** reactions, including anaphylaxis. Events identified by the SMQ analysis were analysed in the context of other information and the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network 2006 criteria for anaphylaxis were applied to identify cases of suspected anaphylaxis, with a comprehensive review of a subject's clinical course. The placebo-controlled clinical study LAL-CL02 also was used to help to evaluate potential relatedness of these events.

Hypersensitivity reactions**,** generally mild to moderate in severity, proved to be more common in infants and proved to be manageable by decreasing the infusion rate, temporarily stopping the infusion, or administering antihistamines and/or antipyretics. Reported signs and symptoms occurring in 2 or more subjects were gastrointestinal disorders, general disorders (pyrexia/body temperature increased/hyperthermia, chills) and skin reaction, as well as tachycardia, pallor and laryngeal oedema. The majority of events occurred during or within 4 hours of completion of the infusion and no subject had a permanent dose reduction due to poor tolerability.

Table 3: exposure in safety context

	LAL-CL01	LAL-CL04	LAL-CL02	LAL-CL03	LAL-CL006	LAL-CL08	Pooled safety set
design	dose-escalating	open-label	RCT + open-label	open-label	open-label	open-label	
age (years)	18-65	18-65	≥ 4	< 6 months	> 8 months	< 8 months	
Inclusion criteria	hepatomegaly or ALT or AST ≥1.5 ULN	Extension LAL-CL01	ALT ≥1.5 ULN	growth failure	Clinical disease presentations not prior studied, subjects < 4 yo not included in LAL-CL03, subjects with severe liver disease, subjects with a previous liver or hematopoietic stem cell transplant, and subjects with an atypical or underappreciated presentation of LAL deficiency.	Infants less than 8 months of age with rapidly progressive LAL deficiency.	
Study duration	4 week	on-going	RCT: OL: on-going	on-going	on-going	on-going	
***Nb of subjects*:**	**9**	**8**	**66**	**9**	**17**	**5**	**106**
0.35 mg/kg [qw]	3		-	8	-	-	11
1 mg/kg [qow]	5		66	-	17	-	88
1 mg/kg [qw]	3		-	7	-	5	15
3 mg/kg [qow]	3		-	1	-	-	5
3 mg/kg [qw]	3		1	6	-	2	11
5 mg/kg [qw]	-		-	1	-	1	2

Nb of infusions:	**68 447**	**735**	**462**			**1,712 (100%)**
0.35 mg/kg [qw]	24	-	14			38 (10.4%)
1 mg/kg [qow]	343	1786	-	89		2218 (83%)
1 mg/kg [qw]	20	-	141		54	215 (14.2%)
3 mg/kg [qow]	215	2	17			234 (4.7%)
3 mg/kg [qw]	24	-	417		35	476(10.4%)
5 mg/kg [qw]	0	-	41		15	56 (1.9%)
Other	-	-	4			4 (0.9%)

In the D120 safety update, one subject with temporally associated component signs and/or symptoms that met the NIAID/FAAN 2006 criteria for **anaphylaxis** was identified in Study LAL-CL08, with symptoms occurring within approximately 15 minutes from the start of the 6th infusion of sebelipase alfa at a dose of 1 mg/kg qw. Skin-prick testing with sebelipase alfa concluded with negative results and with premedication and a lower initial infusion rate, this subject continues to receive sebelipase alfa.

In the D120 updated safety report updates for potential **hypersensitivity** reactions that occurred in the original Pooled Safety Set since the analysis cut-off dates, in addition to data obtained from recently initiated studies LAL-CL06 and LAL-CL08. Five subjects were removed from the listing as they experienced singular events which were assessed as either unlikely or not related to treatment. The updated analysis updates the number of potential hypersensitivity reactions to 119 events in 21 subjects.

Overall, in the pooled safety set provided at D120, 21 subjects (19.8%), representing 5 new cases since the initial safety report cut-off, experienced signs and symptoms either consistent with or potentially related to a hypersensitivity reactions. This number breaks down to 9 of 14 infants (64.3%) and 12 of 92 children and adults (13.0%).

Out of the 16 subjects included in the original submission, most of the patients showed resolution of the events, though only 2 of these subjects continue to experience hypersensitivity events, both infants from LAL-CL03.

Of the 5 cases reported in the answer to the D120, 2 were assessed as serious; one is a 4 month-old male infant in LAL-CL08 whom recovered after adequate treatment and continued Kanuma treatment. The other case involved a 44-year old male in LAL-CL06, whom had a severe **anaphylactic** reaction judged as related to treatment, but continued Kanuma administration under a desensitization protocol.

During the late breaking period of the D120 update one more subject in study LAL-CL02 was reported to have an event consistent with **anaphylaxis** which is currently under assessment. The patient was on a 1 mg/kg, IV, qow dose schedule when symptoms occurred, starting 10 minutes after routine infusion. All the events were assessed to be related to study drug by the Investigator, and this subject has paused treatment with sebelipase alfa pending further evaluation.

No evidence for cumulative toxicity presented amongst the various trials.

Serious adverse events and deaths

Across all trials of the pooled safety assessment, 3 **deaths** were reported in the sebelipase alfa clinical programme and all three occurred in the LAL-CL03 Wolman infant trial. All fatal events were assessed as unrelated to sebelipase alfa treatment by the Investigators, and an overview is given in the following table:

Deaths Occurring in the Sebelipase Alfa Clinical Programme

Study	Subject Number	Cause of Death (MedDRA PT)	Last Sebelipase Alfa Dose[a]	Time Since First Dose	Time Since Last Dose Prior to Death	Relationship to Treatment
LAL-CL03	01-001	Hepatic failure	0.35 mg/kg qw	--[b]	5 days	Not related
LAL-CL03	06-003	Peritoneal haemorrhage	0.35 mg/kg qw	--[b]	6 days	Not related
LAL-CL03	11-001	Cardiac arrest	1 mg/kg qw	25 days	6 days	Unlikely related

Source: ISS Table 1.3.5, LAL-CL03 CSR Section 14.3.3.
MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; qw=once weekly.
Note: Deaths are presented as of the database cut-off date of 27 Jun 2014.
[a] Last dose of sebelipase alfa prior to event.
[b] Subject received only one dose of study drug prior to death.

In addition one subject in LAL-CL03 died at 15 months of age (but after data cut-off), and cause of death was not yet determined at dossier submission.

In the D120 report the number of deaths has been updated to 6, in order to include the three late-breaking reports received after the initial MAA safety data cut-off. All 6 deaths occurred in infants (≤2 years of age) with rapidly progressive disease, and all deaths were assessed by the Investigator as unrelated or unlikely related to sebelipase alfa treatment.

Serious adverse events, the majority of which were considered unrelated to treatment, were reported in 19 (17.9%) of the 106 subjects and were most frequent in Wolman infants as these compromised 8 of the subjects presenting with one or more SAE(s). In 4 infants, catheter site or device-related infection were reported early in treatment (within 8 months) likely due to compromised state of these infants at study entry. Two subjects (1 each in studies LAL-CL02 and LAL-CL03) reported treatment-related SAEs, which were also considered potential hypersensitivity reactions.

In adults and infants all SAEs occurred in subjects on sebelipase alfa treatment, except for a Road traffic accident occurring to one of the subjects who was at that time part of the placebo group in the double-blind phase. On subject in the double-blind sebelipase group experienced an SAE that was considered an IAR after the second study drug infusion, after which treatment was discontinued for the remainder of the double-blind study phase although the subject in question could enter the open-label phase after negative rechallenge. Finally, one subject in the placebo/sebelipase alfa group experienced an SAE during the open-label period but this was considered unrelated to study drug.

In LAL-CL04 one subject had multiple SAEs, all of which were IARs. They occurred with a single infusion on Week 12 (3 mg/kg qw) and resolved the same day following infusion interruption and administration of antihistamine, antipyretic, and IV sodium chloride.

In the recently initiated Wolman infant study LAL-CL08 2 subjects already had treatment-related SAEs which were also considered potential hypersensitivity reactions.

In the D120 safety update 28 new serious events were reported, of which 27 occurred in infants. Half of the newly reported serious TEAEs were considered moderate in intensity, 12 as severe and 1 as mild (compared to all being considered severe in the original safety report.)

Two events led to deaths (already reported in the previous report's late breaking information section), 10 events had resolved at data cut-off. The majority of newly reported serious events were not related to treatment, with only 4 in 2 subjects being judged so and which concerned the anaphylaxis cases mentioned earlier.

Overall, despite the additional deaths reported, the updated D120 safety data provided during assessment did not change the initial safety profile.

Laboratory findings

No safety signals were observed based on a thorough evaluation of clinical laboratory data. Initial treatment with sebelipase alfa is associated with a transient and reversible increase in blood cholesterol and triglycerides consistent with mobilisation of accumulated lysosomal lipid from the tissues as a result of correcting the pathophysiology of reduced lysosomal acid lipase activity. The increase in lipids was not associated with any clinical sequelae. From baseline to the last assessment, total cholesterol, LDL-C, and triglyceride values decreased and HDL-C values increased.

A thorough review of haematology, renal function, liver function, and electrolytes, including descriptive statistics over time, shift analyses, and assessment of clinically significant changes from Baseline, showed no deleterious effect of sebelipase alfa on any of these parameters.

Treatment with sebelipase alfa is associated with an improvement in both hepatic function and dyslipidaemia. Reductions in serum transaminase levels were observed and, after an initial transient increase, reductions in LDL-c, non-HDL-c, and triglycerides, with an increase in HDL-c were noted.

Safety in special populations

There were no clinically meaningful differences noted in the safety profile of sebelipase alfa based on gender, race, or use of LLMs.

The incidence of related TEAEs and SAEs was higher in the <2 year old age group which included infants with rapidly progressive LAL deficiency, but review of clinical laboratory data and vital signs data did not suggest any meaningful differences across age group.

Clinical studies did not include subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

As analyses of TEAEs by mutation category are confounded by study and population, no meaningful conclusions can be drawn for safety parameters by mutation status.

It has to be noted however that just like all other safety endpoints, statistically sound conclusions are not possible given the small study populations and heterogeneous study designs.

Findings for TEAEs by age provided in the Day 120 Safety Update were consistent with the initial safety data provided.

Immunological events

In the D120 safety update, overall 12 of the 106 subjects (thus 2 more compared to the initial data submitted) were tested ADA positive during at least 1 assessment with six of them testing positive for ADAs at more than 1 time point.

The proportion of subjects ADA positive at more than 1 time point (N=8, 66.7%) was more common among infants compared with children and adults and the median time to first ADA positive result increased to approximately 70.5 days compared to 57 in the initial report. All of these subjects were able to continue treatment without interruption. The age group with the highest proportion of ADA positive subjects was infants <2 years of age (35.7% positive).

Given the small numbers involved, direct comparison of the AE profile between ADA positive and ADA negative subjects across AEs was limited and no clear relationship between the presence of ADAs and IARs was apparent. Furthermore, the TEAE profile seen among ADA-positive subjects

was consistent with that in the study population as a whole, and no ADA-positive subject died or reported a TEAE that led to study drug discontinuation.

Of note in the initial data, there was a relatively high incidence of anti-drug antibodies, 4 (57%) of the 7 subjects for whom testing was performed (2 other subjects died prior to the first ADA assessment on treatment), in the Wolman infant LAL-CL03 trial. Persistence of ADA positivity (>1 assessment) was observed for 3 subjects, 1 of whom remained ADA positive through the data cut-off date and 2 who had ADA negative results at the last assessment prior to the data cut-off date. Moreover, 2 ADA-positive subjects also tested positive for neutralising antibodies that inhibited both LAL enzyme activity and LAL cellular uptake. Serum tryptase in one of these two subjects was below the normal range in the 1 subject tested to date.

In the D120 safety update, overall five subjects had tested positive for neutralizing antibodies. Two subjects in Study LAL-CL02 tested positive for neutralizing antibodies to cellular uptake but not to enzyme activity, and 2 subjects in Study LAL-CL03 and 1 subject in Study LAL-CL08 tested positive for neutralizing antibodies to both enzyme activity and cellular uptake. However, the presence of neutralizing antibodies was not anticipated to impact the safety profile of sebelipase alfa.

While differences in the frequency of TEAEs by ADA status were noted, including a higher frequency of serious TEAEs and treatment-related TEAEs in ADA-positive subjects compared with ADA-negative subjects, interpretation of these findings is limited due to the small number of subjects who were ADA positive (N=12) and the fluctuations in ADA positivity in these subjects over time, as well as by the higher proportion of infants in the ADA-positive group (5 of 12 subjects [41.7%]) compared with the ADA-negative group (9 of 104 subjects [8.7%])

Safety related to drug-drug interactions and other interactions

Overall, a review of TEAE incidence, clinical laboratory, and vital signs data did not suggest any meaningful differences by LLM use based on review of the data from Study LAL-CL02 during which subjects who were on LLMs were to remain on a stable dose of LLM through at least the first 32 weeks of treatment.

Discontinuation due to AES

One subject in study **LAL-CL02** was discontinued during the double-blind period after experiencing IARs after the first and second infusions of sebelipase alfa; the event was reported as a treatment-related SAE. The subject may enter the open-label period upon rechallenge.

One infant in study **LAL-CL03** was discontinued from treatment after the first infusion due to bradycardia that was assessed as unrelated to study treatment; the subject died later that day of hepatic failure prior to the next scheduled infusion.

2.5.1. Discussion on clinical safety

The Applicant provided further safety data in the D120 procedure leading to a total of 106 subjects with LAL deficiency have received treatment with sebelipase alfa, including 14 infants (<2 years), 57 children (24 ≥2years and <12 years, 23 ≥12 years and <18 years), and 33 adults.

The pooled safety assessment is limited due to the orphan disease thus a small number of subjects included in studies, differences in disease progression according to age, the relatively short period of follow up (in relation to the expected duration of treatment) and the design of studies, only one study being placebo-controlled.

The expected safety concerns, linked to enzyme replacement therapy which were hypersensitivity, transient hyperlipidemia and ADAs, have been confirmed in the updated safety data provided.

The clinical significance of transient hyperlipidemia is limited and longer term results are in favour of clinical improvement.

Hypersensitivity, anaphylactic reactions and Infusion Adverse Reactions were observed in the vast majority of patients. Nine of 14 (64%) infants and 12 of 92 (13%) children and adults patients experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction.

Three patients of 106 (3%) patients treated with KANUMA, including 1 of 14 (7%) infants and 2 of 92 (2%) children and adults, in clinical studies experienced signs and symptoms consistent with anaphylaxis.

Events related to hypersensitivity reactions, anaphylaxis is more frequent in infants and should be further monitored in different age groups and on the long term. Similarly, the identification of two subjects with neutralising antibodies is questioning and the possible explanations remain at present unclear and need to be monitored in the post authorisation setting.

The sudden free lipid surge, presumably liver-stored lipids that are suddenly released in bulk, that is seen at treatment start remains to be further characterised. Although this effect is transient this may negatively affect patients with cardiovascular co morbidities. At present this is a theoretical issue.

The proportion of subjects ADA positive at more than 1 time point was more common among infants compared with children and adults and the median time to first ADA positive result increased to approximately 70.5 days compared to 57 in the initial report. All of these subjects were able to continue treatment without interruption. The age group with the highest proportion of ADA positive subjects was infants <2 years of age (35.7% positive).

The occurrence of ADA should therefore be monitored in the post authorisation setting in infants and in older population. A warning has also been introduced in the SmPC.

In the clinical trials there were cases of bradycardia noted, but given the limited populations and the significant amount of co-morbidities seen in the affected subjects it remains unclear whether these observations might be indicative of a CV risk signal or not, and further monitoring is thus recommended through the registry.

Since no pregnant subjects were amongst the study populations the effect on clinical safety for both mother and foetus are not known at this time.

2.5.2. Conclusions on clinical safety

In general the treatment has proven to be safe and serious issues were rare. The safety exposure remains limited due to the orphan disease, especially in Wolman infants.

However, it is considered that the safety data provided for this application (initial submission and D120 safety update) constitute a comprehensive safety package justifying a full marketing authorisation as data are provided on all ages groups in various stage of the disease or not.

Nevertheless there is a need to further monitor the long term safety in the post authorisation setting in relation to hypersensitivity reactions, anaphylaxis and ADAs in all patients. This will be done through a disease registry of patients with Lysosomal Acid Lipase Deficiency.

Additionally the ongoing clinical study in infants (LAL-CL06) is considered key to benefit risk to further monitor the efficacy and safety profile in infants with Wolman disease.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice with the following changes:

- Addition in the Pharmacovigilance plan of the following studies:

- Clinical study LAL-CL06 (category 3) to assess the safety and efficacy in a paediatric population 2-4 years of age and ADA development impacting response to drug

- Clinical study LAL-CL08 (category 1) to assess the safety and efficacy and ADA development impacting response to drug

These studies were requested to provide more accurate information on the role of the anti-drug antibodies on the safety and efficacy of the product. In fact, the clinical trials ensure more systematic and scheduled data collection on ADA development, whereas in the registry healthcare professional might collect such information only on the basis of the requirements contained in the product information.

- Additional risk minimisation measure (i.e. educational material for healthcare professionals) aimed to:

- Reinforce the information on the risk of hypersensitivity including anaphylaxis and ADA development impacting response to drug

- Encourage healthcare professionals to enrol patients in the prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase (LAL) Deficiency to monitor for efficacy and safety of Kanuma (LAL deficiency Registry)

The applicant implemented the changes in the RMP as requested by the CHMP.

The CHMP endorsed the Risk Management Plan version 1 submitted on 24 June 2015 with the following content:

Safety concerns

Important identified risks	Hypersensitivity reactions including anaphylaxis
Important potential risks	ADA development impacting response to drug Use in patients with egg allergy
Missing information	Safety and efficacy in patients older than 65 years of age Safety and efficacy in paediatric population 2-4 years of age Use in pregnant and lactating women Long-term safety and efficacy data

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
LAL-CL06, category 3	Efficacy and safety; PK	Safety and efficacy in a paediatric population 2-4 years of age ADA development impacting response to drug	Ongoing	June 2017
LAL-CL08, category 1	Efficacy and safety; PK	Long-term safety and efficacy data ADA development impacting response to drug	Ongoing	December 2018
Non-interventional, imposed PASS, category 1 An Observational Disease and Clinical Outcomes Registry of Patients with Lysosomal Acid Lipase (LAL) Deficiency (Wolman Disease	The objective of the LAL eficiency Registry is to use uniform methodology to collect longitudinal data over an extended period to provide information to: Further understand the disease, its	Hypersensitivity reactions including anaphylaxis ADA development impacting response to drug Safety and efficacy in patients older than 65 years of age Safety and efficacy	Planned	Interim reports will be aligned with PSUR submissions. The registry is scheduled to run 10 years; the final report will be submitted 12 months after completion of the registry period.

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
and Cholesteryl Ester Storage Disease) and Carriers of the Disorder	progression and any associated complication. Evaluate the long-term efficacy and safety of sebelipase alfa. Evaluate the long-term effectiveness of other potential therapeutic and supportive interventions. Improve care through evidence-based patient management. Understand the relationship between LAL deficiency and access to care.	in a paediatric population 2-4 years of age Use in pregnant or lactating women Long-term safety and efficacy data		

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Hypersensitivity reactions including anaphylaxis	Special warnings and precautions for use relevant for hypersensitivity reactions including anaphylaxis are summarised in section 4.4. Undesirable effects related to hypersensitivity reactions including anaphylaxis are listed in section 4.8.	Educational materials reinforcing the risk of hypersensitivity including anaphylaxis as described in the SmPC to be provided to prescribers. This will provide consideration for antibody testing to be facilitated by the MAH.
IMPORTANT POTENTIAL RISKS		
ADA development impacting response to drug	A special warning to test for the presence of antibodies in cases of severe infusion reactions or lack or loss of effect is described in section 4.4. Described in section 4.8 with the additional information about the undesirable effects.	Educational materials reinforcing the potential risk of ADA development impacting response to drug to be provided to prescribers. This will provide consideration for antibody testing to be facilitated by the MAH.
Use in patients with egg allergy	**Table 1.** Section 2. Qualitative and quantitative composition. Described in Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use	None
MISSING INFORMATION		
Safety and efficacy in patients older than 65 years of age	Section 4.2 Posology and method of administration informs about the missing data. The absence of data is also described in section 5.2 Pharmacokinetic properties.	None
Safety and efficacy in paediatric population 2-4 years of age	The absence of data is also described in Section 5.2 Pharmacokinetic properties	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in pregnant and lactating women	Lack of the clinical data during pregnancy and lactation is stated in section 4.6 Fertility, pregnancy and lactation. Preclinical safety data pertinent for the use in this population are summarised in section 5.3.	None
Long-term safety and efficacy data	KANUMA is only to be administered by healthcare professionals experienced in the management of patients with LAL deficiency, other metabolic disorders, or chronic liver diseases.	None

2.8. Product information

2.8.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

The Applicant submitted four studies to assess efficacy and safety of sebelipase alfa ERT in treatment of LAL deficiency, both in typical exon 8 splice-junction mutation c.849G>A patients (mainly children and adults) and Wolman disease sufferers (infants with the rapidly progressing form of LAL deficiency, not living past the age of 6 months),

- LAL-CL01/04; a dose-escalation and associated extension study in adults
- LAL-CL02: A PII/PIII placebo controlled study in adults and children
- LAL-CL03: A PII study in infants with Wolman disease

As there was no ethical possibility to have a placebo-controlled trial in Wolman disease, the Applicant also ran a natural history study by collecting historical data on prior Wolman sufferers (LAL-1-NH01) in order to provide supportive arguments that sebelipase alfa has a positive efficacy on the disease.

Generally the results observed in the pivotal trials were positive, with significant improvements in survival for infants, in molecular markers of LAL deficiency and in makers such as hepato-histology, growth, liver size and QOL.

The molecular markers for efficacy across all trials included transaminases and serum lipids, all of which were expected to decrease as treatment took effect. This was indeed observed in all trials and in the majority of subjects receiving ERT, to reach near normal levels with treatment relative to baseline. Additionally, reversibility of the effects on the molecular markers was apparent when treatment was stopped as seen in study LAL-CL02 and in subjects enrolled in LAL-CL01 and its extension phase LAL-CL04.

Due to the inherent nature of the disease intra-study analysis was limited to side-by-side comparisons between trials, the same trends and observations were seen in efficacy outcomes between the studies.

Data from adults and children from study LAL-CL02, (liver volume, histopathology and spleen fat content analysis) showed marked improvements compared to their status at study enrolment.

Additional confirmation on the efficacy of sebelipase alfa as ERT is provided from the open-label phase in LAL-CL02 where participants receiving placebo during the double blind phase were switched to active treatment. The efficacy seen in these patients was similar to the efficacy shown in subjects receiving the active treatment arm during the former phase.

In infants with Wolman disease enrolled in LAL-CL03 similar improvements were seen, but more impressive was the improvement in survival of infants with LAL deficiency for which no treatment was available up until now. In this study 6 of the 9 subjects attained the primary efficacy endpoint of surviving to 12 months of age, with one child living to almost three years of age at data cut-off.

Furthermore, the majority of patients saw marked improvements in their growth indicators, which is also of clinical relevance, as Wolman disease is associated with stunted growth and failure to thrive. Other beneficial efficacy effects seen throughout the various trials are marked improvements in various QOL indicators, as well as laboratory values.

The results seen in infants with Wolman disease are of clinical importance is corroborated by the results of the natural history study, in which Wolman patients in general die before the age of 6 months, even when experimental and inherently high-risk treatments like hematopoietic stem cell transplantation are attempted.

Uncertainty in the knowledge about the beneficial effects

LAL deficiency is a rare disease, thus the efficacy data provided is rather limited in quantity and duration.

In this respect, dosing decisions were based on the limited data set. Thus the starting dose in the infants trial was selected based on the established minimally effective dose in nonclinical studies (0.35 mg/kg qw), to be up-titrated to 1 mg/kg in order to allow rapid further dose escalation if the response would be suboptimal.

In infants with Wolman disease a 1 mg/kg qw dosing is currently recommended. However, most children in the LAL-CL03 trial were on a 3 mg/kg qw dose at data cut-off. Nevertheless, it was finally considered to recommend 1 mg/kg qw dose, with possibility of up titration to a 3 mg/kg qw dosing, when necessary based on clinical response. This dose can also be de-escalated to 1 mg/kg qw once the child is stable or if adverse events would occur.

Due to the high medial need of an effective treatment, an accelerated procedure, was granted while trials are ongoing. The study LAL-CL06 in infants with Wolman disease will provide further insight in the long term efficacy and related posology.

Due to the limited population numbers inherent to the orphan disease, coupled with the fact that the underlying genetic cause is not yet fully understood (particularly in the aspect of whether

different mutations might have disease characteristic differences), there is a need to continue gathering long term efficacy information in all patients, particularly in infants.

In Wolman infants, around 30% (n=3) of the subjects did not reach the primary efficacy endpoint of living to or past 12 months of age. The causes of death were considered not directly due to the ERT, as two of the subjects' deaths implicated possible liver function. Given that LAL deficiency does often lead to liver issues and failure, it remains an open question whether these deaths might have possibly been due to lack of sufficient efficacy. Autopsy and medical data revealed however that the patients had severe comorbidities that were more likely to be implicated in the subjects' deaths.

There is a lack of certainty is the immunogenic response of the body to the ERT treatment and the possible effects on efficacy. In LAL-CL02 5 of the 33 subjects developed ADAs in response to treatment, with one subject also testing positive for cellular uptake neutralizing antibodies. Nevertheless, none of the subjects showed signs of diminished efficacy, but given the extremely limited amount of subjects it is not possible to draw definite conclusions on the impact of the immunogenic responses.

In children about half of the subjects developed persistent ADAs, with two subjects developing neutralizing antibodies. In general subjects continued to show efficacy at doses of 3 mg/kg, except for one of the subjects with neutralizing ABs whom needed an up-titration to 5 mg/kg due to signs of growth retardation.

Finally, there is also limited data in children especially between 2 and 4 years of age, however the study LAL-CL06 ongoing has completed enrolment and will provide further efficacy data in children in the post authorisation setting.

In summary, long-term efficacy and long-term impact of factors such as immunogenic responses, impact on the underlying gene mutation origin of the disease remains to be further characterised inthe post-approval setting.

Risks

Unfavourable effects

The safety profile is based on a total of 106 subjects with LAL deficiency that have received treatment with sebelipase alfa, including 14 infants (<2 years), 57 children (24 ≥2years and <12 years, 23 ≥12 years and <18 years), and 33 adults.

The safety exposure remains limited due to the orphan disease, especially in Wolman infants.

In general the treatment has proven to be safe and serious safety issues were rare or manageable.

A number of reactions to sebelipase alfa were observed, among which a transient hyperlipidaemia, which occurred across all trials after starting treatment and which is more than likely a result of the mobilisation of, accumulated cellular fat content.

Hypersensitivity, anaphylactic reactions and Infusion Adverse Reactions were also observed in the vast majority of patients. Nine of 14 (64%) infants and 12 of 92 (13%) children and adults patients experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction.

In clinical studies, three patients of 106 (3%) patients treated, including 1 of 14 (7%) infants and 2 of 92 (2%) children and adults experienced signs and symptoms consistent with anaphylaxis.

ADA positive tests were observed in all age groups. The proportion of patients with ADA positive was more common among infants compared with children and adults and the median time to first ADA positive result increased to approximately 70.5 days. All subjects were able to continue

treatment without interruption. The age group with the highest proportion of ADA positive subjects was infants < 2 years of age (35.7% positive).

No apparent trend was observed with most of the AEs being mild to moderate and transient or manageable with adequate care.

The incidence was higher in but no differences across age groups were noted in laboratory data nor vital signs.

Three subjects died before data cut-off, all infants in LAL-CL03, but none of the deaths was judged as being directly related to treatment related adverse events.

Uncertainty in the knowledge about the unfavourable effects

The number of patients across the trials from the safety analysis remains very low and that long-term safety data relative to a lifelong treatment is also available at this moment.

Therefore it is currently not possible to ascertain effects of mutation status and other demographic factors such as ethnicity on safety parameters.

Similarly, the effects of immunogenic responses to recombinant enzyme infusion in regards to safety and PK and especially on long term basis are currently unknown.

No specific studies have been performed to evaluate the pharmacokinetics of sebelipase in patients with decreased renal function. Because sebelipase alfa is a recombinant human LAL enzyme, renal excretion is not expected to represent major elimination route.

No drug-drug PK interaction studies have been undertaken, but patients were allowed to continue using LLM treatments during their participation and no impact on neither efficacy nor safety was observed.

In the clinical trials there were cases of bradycardia, however given the limited populations and the significant amount of co-morbidities seen in the affected subjects it remains unclear whether these observations might be indicative of a CV risk signal or not, and further monitoring is thus recommended through the registry.

Since no pregnant subjects were amongst the study populations the effect on clinical safety for both mother and foetus are not known at this time.

Overall, there is a need to further monitor the long term safety in the post authorisation setting in relation to hypersensitivity reactions, anaphylaxis and antidrug antibodies in all patients. This will be done through a disease registry of patients with Lysosomal Acid Lipase Deficiency.

Additionally the ongoing clinical study in infants (LAL-CL06) is considered key to benefit risk to further monitor the efficacy and safety profile in infants with Wolman disease.

Balance

Importance of favourable and unfavourable effects

There is currently no known effective treatment for the debilitating and severely QOL impacting effects of LAL deficiency, especially for patients with the rapid progressing form of the disease (also known as Wolman disease). These patients have a life expectancy of less than 6 months of age therefore there is a clear and urgent need for an effective and safe treatment for patients with LAL deficiency.

Benefit-risk balance

Due to the inherent nature of this orphan disease the number of eligible subjects for clinical trials, is reflected in the low number of subjects and limited data provided for efficacy and safety

assessment. The urgent medical need for treatment, together with promising results, was granted an accelerated assessment by the CHMP.

It is considered that the efficacy and safety data provided constitute a comprehensive safety package justifying a full marketing authorisation as information are provided on all ages groups and in various stage of the disease.

In conclusion, sebelipase alfa treatment gave rise to positive results on the main efficacy endpoints, consistent across different trials, with impressive results in survival in infants with Wolman disease.

In general the treatment has proven to be safe and serious issues were rare. The safety exposure remains limited due to the orphan disease, especially in Wolman infants.

Nevertheless, there is a need to further monitor the long term efficacy and safety in the post authorisation setting in particular assessment of liver function (efficacy), hypersensitivity reactions, anaphylaxis and antidrug antibodies (safety) in all patients. This will be done through a disease registry of patients with Lysosomal Acid Lipase Deficiency.

Additionally the ongoing clinical study in infants (LAL-CL06) is considered key to benefit risk to further characterise the long term efficacy and safety profile in infants with Wolman disease.

Thus the combination of the urgent medical need for treatment and the positive efficacy results observed, together with post-approval study monitoring of long term efficacy and safety, allows concluding that the data package is sufficient to demonstrate a positive benefit-risk balance is in patients with LAL deficiency in all age groups.

Conclusions

The overall Benefit risk of Kanuma is positive in patients of all ages diagnosed with LAL deficiency.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Kanuma for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Kanuma in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material is aimed to encourage healthcare professionals to enrol patients in the prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase (LAL) Deficiency to monitor for efficacy and safety of Kanuma (LAL deficiency Registry), with particular regard to hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies (ADA) development impacting response to drug.

The MAH shall ensure that in each Member State where Kanuma is marketed, all healthcare professionals who are expected to use Kanuma have access to the educational material. The educational material should contain:

- Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- Warning and precautions on the the risk of hypersensitivity including anaphylaxis or ADA development, with particular reference to symptoms, time to onset and severity.
- Information on how to manage patients experiencing severe hypersensitivity reactions including anaphylaxis.
- Details on how to monitor for potential ADA formation following initiation of treatment with Kanuma, particularly in patients on Kanuma who experience clinically important hypersensitivity reactions or potential loss of clinical response.
- Information to healthcare professionals that it is the responsibility of the MAH to provide the test for the monitoring of ADA positive patients including the modalities for requesting the test.
- Information on the ongoing LAL deficiency Registry, including the importance of enrolling patients, also those not treated with Kanuma, and the modalities for participation.

Obligation to conduct post-authorisation measures

The MAH shall complete, the measures described below:

Description	Due date
Non-interventional post-authorisation safety study (PASS) : LAL deficiency Registry: Non-interventional, multicentre, prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase Deficiency to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy (normalisation of hepatic function) and safety of Kanuma (in particular hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies development potentially impacting response to drug) according to agreed protocol.	Interim reports expected yearly within PSURs Final study report expected in Jan 2027

Study LAL-CL08: an open-label, Phase 2 study in infants with rapidly progressive LAL deficiency to explore long-term safety and efficacy data. The efficacy objectives are assessment of hepatic function over time up to 3 years and survival at 12 months. The safety objectives should focus to hypersensitivity reactions, particularly anti-drug antibodies development impacting response to drug.	Final study report expected in December 2018

4.1. Proposed list of post-authorisation measures

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

Not applicable.

New Active Substance Status

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

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0179/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.