15 October 2020
EMA/CHMP/637875/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kanuma

International non-proprietary name: sebelipase alfa

Procedure No. EMEA/H/C/004004/II/0026/G

Note

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

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Status of this report and steps taken for the assessment		
Current step[1]	**Description**	**Planned date**
☐	Start of procedure	27 January 2020
☐	CHMP Rapporteur Assessment Report	25 February 2020
☐	PRAC Rapporteur Assessment Report	28 February 2020
☐	PRAC members comments	04 March 2020
☐	Updated PRAC Rapporteur Assessment Report	05 March 2020
☐	PRAC endorsed relevant sections of the assessment report	12 March 2020
☐	CHMP members comments	16 March 2020
☐	Updated CHMP Rapporteur Assessment Report	19 March 2020
☐	Request for Supplementary Information	26 March 2020
☐	Start of procedure	25 May 2020
☐	CHMP Rapporteur Assessment Report	23 June 2020
☐	PRAC Rapporteur Assessment Report	26 June 2020
☐	PRAC members comments	01 July 2020
☐	Updated PRAC Rapporteur Assessment Report	02 July 2020
☐	PRAC endorsed relevant sections of the assessment report	09 July 2020
☐	CHMP members comments	13 July 2020
☐	Updated CHMP Rapporteur Assessment Report	16 July 2020
☐	Request for Supplementary Information	23 July 2020
☐	Submission	14 August 2020
☐	Start of procedure	17 August 2020
☐	CHMP Rapporteur Assessment Report	21 September 2020
☐	CHMP members comments	5 October 2020
☐	Updated CHMP Rapporteur Assessment Report	8 October 2020
☒	Opinion	15 October 2020

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

List of Abbreviations

ACFA	arm circumference-for-age
ADA	antidrug antibody
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BMIFA	body mass index-for-age
BMT	bone marrow transplant
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CSR	clinical study report
EAP	expanded access protocol
EOS	end of study
ERT	enzyme replacement therapy
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
GGT	gamma glutamyltransferase
H&E	hematoxylin and eosin
HCFA	head circumference-for-age
HDL-C	high density lipoprotein cholesterol
HFA	height-for-age
HSCT	hematopoietic stem cell transplant
ISE	integrated summary of efficacy
ISS	integrated summary of safety
LAL	lysosomal acid lipase
LDL-C	low density lipoprotein cholesterol
LAL-D	lysosomal acid lipase deficiency
LFA	length-for-age
LIPA	Lipase A, lysosomal acid
LLM	lipid-lowering medication

LLN	lower limit of normal
MAH	Marketing Authorisation Holder
M6P	mannose-6-phosphate
MEGE	Multi-echo gradient echo
MEGE-MRI	multi-echo gradient echo magnetic resonance imaging
MMR	macrophage mannose receptors
MN	multiples of normal
MRI	magnetic resonance imaging
PBMCs	peripheral blood mononuclear cells
PBO/SA	treatment group designation for patients originally randomized to receive placebo in Study LAL-CL02
PedsQL	Pediatric Quality of Life Inventory
PPN/TPN	peripheral or total parenteral nutrition
PY	patient-year
qow	once every other week
qw	once weekly
SA/SA	treatment group designation for patients originally randomized to receive sebelipase alfa in Study LAL-CL02
SAP	statistical analysis plan
SD	standard deviation
SFA	stature-for-age
TFHN	transfusion-free hemoglobin normalization
UK	United Kingdom
UK-MELD	United Kingdom Model for End-Stage Liver Disease
ULN	upper limit of normal
WFA	weight-for-age
WFH	weight-for-height
WFL	weight-for-length
WGD	whole-gene deletion
WHO	World Health Organization

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 17 December 2019 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Grouping consisting of the following variations:
- Update of sections 4.2, 4.4, 4.8, 5.1, 5.2, 6.6 of the Summary of Product Characteristics (SmPC) in order to update the clinical information based on the pooled safety and efficacy analysis of already submitted studies (Studies LAL-CL04, LAL-CL03, LAL-CL06, LAL-CL08 and LAL-CL02) and updated population pharmacokinetic analyses in children and adults. The Package Leaflet has been amended accordingly. The RMP version 4 has also been submitted. Annex II is also updated to remove the specific obligation related to the provision of study LAL-CL08.
- Submission of the final report from study LAL-EA01 An open-label study with sebelipase alfa (1 mg/kg every other week for up to 78 weeks or until drug commercialization) in United States (US) patients who did not otherwise qualify for an active sebelipase alfa trial (expanded access protocol)

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

At the time of submission of the application, the PIP P/0173/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0173/2015.

2. Overall conclusion and impact on the benefit/risk balance

The current variation provided an integrated analysis of the clinical data from 6 post-authorisation studies as well as the final data from an expanded access programme in the United States (US) for patients not eligible for clinical trial participation.

Overall the clinical efficacy and safety outcomes from both analyses did not diverge from the observations and conclusion on efficacy and safety made during the initial Marketing Authorisation assessment or the analyses of the individual studies that made up the data aggregate of the integrated analysis.

Based on observations in the integrated analysis the marketing authorisation holder (MAH) proposed to alter the approved posology to allow dose escalation from 1 mg/kg qow (once every other week) to 3 mg/kg qow (once weekly) in children and adults in function of clinical response. This proposal was based on the fact that in the aggregated data there was a patient year exposure at the dose level of 3 mg/kg qow that was equal to about 25% of the total exposure of patients on the standard dose of 1 mg/kg

qow. This represents a relatively fairly large exposure to the former dose that was mostly due to non-optimal responses to the basic dose. Analysis of safety per dose level also did not reveal any difference in risk profile, within the confirmative caveats of the limited patient numbers, and as such this change to the posology is supported.

Likewise, the MAH proposed a change to the posology in infants as to allow dose escalation from 1 to 5 mg/kg qw depending on clinical response. This change is based on observations in the Pooled Safety Set 2 (studies of infants who developed growth failure or other evidence of a rapidly progressive course of LAL-D, ie studies LAL-CL03 and LAL-CL08) where 7 of 19 patients needed escalation to 5 mg/kg qw to maintain adequate response (1 patient needed even further escalation to 7.5 mg/kg qw), and for which no negative safety impact was noted. This change of posology is difficult to accept based on available data solely though, given the very low number of involved patients (7 of 19 total) and the fact that 3 of these were dual WGD (whole gene deletion) patients which do not fit the 'normal' phenotype of the majority of patients in the study and likely have a far worse disease severity. Thus the body of data to allow such a posology change is too thin for evidence-based confirmative acceptance. However, it is also known that the clinical reality of infants with early-onset lysosomal acid lipase deficiency (LAL-D) is such that they are generally more seriously burdened with more severe consequences and a far higher mortality rate. Thus based on the clinical reality it could be acceptable to allow dose escalation in severely stricken infants.

In response to this concern the Applicant proposed a reworded dosing guidance for LAL-D infant treatment, which establishes clearly when an up titration to 5 mg/kg could take place, but leaves further up- or down-titration more open to the threating expert's insight and the patient's needs and response to treatment. Given the clinical reality that responses to replacement-therapies are often very individually bound and that treatment will be initiated by experts in metabolic diseases this more open approach to guidance can be accepted.

Finally, and as already discussed in both the LAL-CL08 assessment and the renewal procedures, three patients were uncovered to have a dual WGD in the form of a homozygous deletion affecting both alleles of the genes *LIPA* and Cholesterol 25-Hydroxylase. These patients were characterised by a high neutralzing immunogenic response that affected efficacy, requiring dose escalations and immunomodulatory treatment/bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) to control their disease. Given that a retrospective analysis to discover more potential cases is not necessary due to lack of genetic typing data in the other trials, data on this specific type of the LAL-D syndrome is of such scarcity that any impact, if at all, on the benefit/risk is impossible to determine at the moment. A new safety signal was however included in the latest PSUR (Data Lock Point: 28 August 2019), and thus more data may potentially be forthcoming in the future.

Regarding pharmacokinetics (PK), a substantial number of PK samples were disqualified due to data integrity issues. The corrective and prevention action plan taken to address this issue has been described. In general, this is deemed acceptable in terms of GCP and is expected to prevent a similar problem in the future. Furthermore, all issues raised during Health Authority inspections carried out during the same periods as Kanuma studies were addressed by the CRO.

The population pharmacokinetic (POPPK) model submitted in the original marketing authorisation application (MAA) has been updated and incorporated 25% more PK data than in the original regulatory application model. A Pop-PK/PD model to provide further information on the relation between plasma levels of sebelipase alfa and pharmacodynamic (PD) outcomes has been developed. The population pharmacokinetic and PK/PD analyses have been conducted to support the proposed posology and pharmacokinetic characteristics of sebelipase alpha in sections 4.2 and 5.2 of the SmPC. The data from the patients in the lower age subgroups are not considered very informative given the limited number

of patients in the different age subgroups (5 versus 2 versuss 6 in the 3 age subgroups for patients <2, 2 to 6 and 4 to <6 years old, respectively). In addition, in the absence of PK exposure comparison between the adults and the different age groups, it cannot be concluded that the POPPK data are supportive of the recommended starting dose. Regarding the PK/PD modelling exercise, it has been clarified that there has been no attempt to quantitatively characterize the link between the 2 biomarkers selected (ALT and LDL-C) and the actual meaningful clinical response. This drastically decreased the value of the PK/PD exercise, which does not have any interest to inform the dose in this context. Given the fact that the dose is intended to be adjusted based on clinical benefit-risk assessment, this issue is not pursued.

Overall, the results of the integrated analysis of the studies and the US Extended Access programme data did not raise any new issues in regards to safety nor efficacy. All the relevant paediatric data have been reflected in the Product Information of Kanuma.

The benefit-risk balance of Kanuma remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Grouping consisting of the following variations:
- Update of sections 4.2, 4.4, 4.8, 5.1, 5.2. 6.6 of the Summary of Product Characteristics (SmPC) in order to update the clinical information based on the pooled safety and efficacy analysis of already submitted studies (Studies LAL-CL04, LAL-CL03, LAL-CL06, LAL-CL08 and LAL-CL02) and updated population pharmacokinetics analyses in children and adults. The Package Leaflet has been amended accordingly. The RMP version 4.1 has also been submitted. Annex II is also updated to remove the specific obligation related to the provision of study LAL-CL08.
- Submission of the final report from study LAL-EA01 An open-label study with sebelipase alfa (1 mg/kg every other week for up to 78 weeks or until drug commercialization) in United States (US) patients who did not otherwise qualify for an active sebelipase alfa trial (expanded access protocol)

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

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 overtime up to 3 years and survival at 12 months. The safety objectives should focus on hypersensitivity reactions, particularly anti-drug antibodies development impacting response to drug.	Final study report expected in July 2019

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to Scientific Discussion 'Product Name-H-C-004004-II-0026/G

Annex: Rapporteur's assessment comments on the type II variation

1. Introduction

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic chicken (Gallus gallus), with the same amino acid sequence as the native human enzyme. Purified sebelipase alfa is a glycoprotein with a molecular weight of approximately 55 kD with 6 N-linked glycosylation sites. Structural and compositional analyses demonstrate that sebelipase alfa glycans consist of predominately N-acetylglucosamine and mannose terminated N-linked structures, which target proteins to the macrophage mannose receptors (MMR; also known as N-acetylglucosamine/mannose receptors), as well as mannose 6 phosphate (M6P) moieties, which target proteins to the M6P receptors. 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 MMR or M6P receptors.

Sebelipase alfa has been developed for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D). LAL-D is an ultra-rare and life-threatening autosomal recessive monogenic disorder caused by a marked decrease in LAL activity. Lysosomal acid lipase plays a key role in the metabolism and degradation of lipids, predominantly cholesteryl esters and triglycerides, and the marked reduction or absence of its activity in patients with LAL-D leads to lysosomal accumulation of these lipids in various tissues and cell types throughout the body. 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. Sebelipase alfa is intended to directly address the root cause of disease by replacing the missing or deficient enzyme, thereby resulting in reduction of the accumulated substrates and restoration of normal lipid metabolism.

Although LAL-D is a single disease, patients present and progress along a phenotypic continuum similar to other lysosomal storage disorders and inborn errors of metabolism. For LAL-D, this disease spectrum ranges from a presentation in infants that is rapidly progressive (historically called Wolman disease) to a presentation that manifests clinically in childhood, adolescence, or, less frequently, in adulthood in which the rate of disease progression is more variable (historically referred to as cholesterol ester storage disease). Irrespective of where a patient is on the disease spectrum, LAL-D is associated with significant burden of disease and a shortened life expectancy.

Sebelipase alfa drug product is supplied as a sterile concentrate for intravenous (IV) infusion (single-use vial) and should be diluted in 0.9% sodium chloride injection before administration. According to the MAH, the sebelipase alfa formulation used in clinical studies is the formulation that was initially proposed and was subsequently approved for marketing; therefore, no biopharmaceutic bridging studies were conducted. Some changes were made to the drug substance manufacturing process during development. No significant changes have been made to the overall process since initiation of pivotal clinical development, although some additional controls and process optimization were implemented for the current commercial process. These process changes were developed and implemented to ensure batch-to-batch consistency of the quality, safety, and potency of the drug substance, as well as to augment viral reduction capacity of the purification process.

Sebelipase alfa was approved in the European Union (EU) on 28 Aug 2015 for long-term ERT in patients of all ages with LAL-D. At MAA, it was recommended that the Sponsor provide final sample analysis reports upon completion of the Studies LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08, provide an update of the population pharmacokinetic (PK) model, and develop a PK/pharmacodynamic (PD) model to explore the impact of weight-based dosing on PD biomarkers. Additionally, during the assessment of the sebelipase alfa periodic safety update report #3 (covering the reporting period from 29 Aug 2016 to 28 Feb 2017), the Pharmacovigilance Risk Assessment Committee (PRAC) recommended inclusion of quantitative data in the sebelipase alfa product information (including the actual number of patients experiencing anti-drug antibodies [ADAs] and IARs) at time of finalization of ongoing/planned studies (EMA/PRAC/625005/2017).

The MAH proposes to change the sections 4.2, 4.4, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 6.6 of the EU SmPC in order to update clinical information based on the pooled safety and efficacy analysis of completed studies LAL-CL04, LAL-CL03, LAL-CL06, LAL-CL08 and LAL-CL02 (results from 19 infants, 69 children < 2 to >18 years of age and 37 adults) and updated population pharmacokinetic analyses in children and adults. The Package Leaflet has been amended accordingly. These changes are proposed in alignment with the Company Core Data Sheet (CCDS) version 3.0 dated 26 Nov 2019. The RMP version 4.0 has also been submitted.

Of note, due to data integrity and long-term stability issues identified following approval, some of the data from the original regulatory application were excluded from the new Pop-PK analyses. Despite exclusion of these data, the new (final) Pop-PK model incorporated 25% more PK data than did the original model.

The Pop-PK/pharmacodynamic (PD) models developed for alanine aminotransferase (ALT) and LDL-C per EMA request was also submitted.

Additionally, 6 patients with LAL-D received sebelipase alfa in completed Study LAL-EA01, an expanded access protocol implemented in the US. Patients who were enrolled under this protocol did not meet the entry criteria for any of the other studies in the sebelipase alfa clinical program. The pooled analyses did not include data from Study LAL-EA01, and as such, the results of this study are not included in the label update proposal. A narrative for this study is provided and the Final CSR is submitted in the present application.

2. Clinical Pharmacology aspects

2.1. Methods – analysis of data submitted

2.1.1. Study design

The clinical studies supporting the clinical pharmacology of sebelipase alfa in patients with LAL-D are summarized in the table below. The primary clinical pharmacology data in support of sebelipase alfa for the long-term treatment of patients with LAL-D are derived from the 6 completed clinical studies, including 2 studies conducted in infants (Study LAL-CL03 and Study LAL-CL08), 2 studies conducted in children and adults (Study LAL-CL02 and Study LAL-CL06), and Study LAL-CL01 and its extension, Study LAL-CL04, conducted in adults.

A POPPK analysis using data from 75 patients included in studies LAL-CL06, LAL-CL04, LAL-CL02 and LAL-CL03 was carried out. Some PK data from the original submission were excluded from the Pop-PK analyses due to a data integrity issue (DII) and some samples having been analyzed beyond the long-term stability of the assay. This impacted all PK samples from Study LAL-CL01. In addition, PK and PD data from study LAL-CL08 were not included due to errors in dosing records.

Furthermore, a Pop-PK/pharmacodynamic (PD) model to link plasma levels of sebelipase alfa with PD outcomes, ie, changes from baseline in ALT concentrations and in LDL-C concentrations was developed. Use the Pop-PK/PD model to explore the impact of body weight-based dosing on PD parameters.

Table 1 - Overview of Sebelipase Alfa Clinical Studies and modelling studies Contributing Data to the Summary of Clinical Pharmacology

Study Identifier: (Population)	Clinical Study Reports (Date of Report)	Study Description Sebelipase alpha dose	Number of Patients Treated	Type of Data Included: Duration of Data Coverage	PK information	PD information
LAL-CL01 (Adults with liver dysfunction due to LAL-D)	Final CSRa (04 Jun 2012); Final CSR Version 2.0 (24 Oct 2019)	Phase 1/2, open-label, multicenter, multidose study to evaluate the safety, tolerability, and PK for up to 4 weeks 0.35 mg/kg, 1 mg/kg, and 3 mg/kg. In each cohort, pts received infusions of sebelipase alfa on Days 0, 7, 14, and 21	Sebelipase alfa: 9	PK, PD, and ADA: up to Week 4	No reportable sample results (see below)	Liver panel : predose on Days 0, 1, 7, 14, and 21 as well as on Days 28, 35, and 52. Lipid panel: on Day 0 as well as on Days 28, 35, and 52, the latter 2 timepoints for Cohorts 2 and 3 only.
LAL-CL04 (Adults with liver dysfunction due to LAL-D who completed Study LAL-CL01)	Week 104 CSRa (17 Jun 2014; data for 7 of 8 pts through Week 104); Final CSR (20 Mar 2018)	Phase 2, open-label, multicenter, extension study to evaluate long-term safety, efficacy, tolerability, PK, and PD for up to 260 weeks Once weekly dose of sebelipase alfa equivalent to the dose administered during the fourth infusion in study LAL-CL01. After the 4th infusion in study LAL-CL04, all subjects were administered sebelipase alfa every other week at 1 or 3 mg/kg as an IV infusion over 2 h	Sebelipase alfa: 8	PK: up to Week 104; PD and ADA: up to Week 260	Rich sampling at Week 24, 52 and 104 immediately pre-dose (within 30 min of dosing) and at 10(±1), 15(±1), 20(±1), 40(±2), 60(±2) and 90(±2) min during the infusion, at the end of the infusion (approximately 120 min) and at 5(±1), 10(±1), 20(±1), 30(±1), 40(±2), 60(±2) and 120(±2) min after completion of the infusion	Liver panel: screening (Day -14 to -1) and predose at Week 1, 4, 8, 12, 16, 20, 24, 25, 32, 38, 52, 66, 78, 90, and 104 as well as at the End-of-Study Visit.
LAL-CL02 (Children and adults with LAL-D)	Double-Blind Period CSRa (04 Sep 2014); Final CSR (22 May 2019; includes open-label data)	Phase 3, double-blind, placebo-controlled, multicentre study to evaluate safety, tolerability, PK, and PD for 20 weeks followed by an open-label extension for up to 234 weeks 1 mg/kg administered every other week as an IV infusion over 2 h. Following completion of the 20-week double-blind treatment period, subjects will begin open-label treatment at a dose of 1 mg/kg during the	Total: 66 SA/SA: 36 PBO/SA: 30	PK: up to Week 56; PD and ADA: up to Week 256	< 18 years of age: 4 samples at Baseline (Week 0) and Week 22 taken any time during the infusion, and 0-30, 30-60 and 60-120 min after the completion of the infusion. At week 56: samples taken at EOI, 0 to 1hr and 1 to 2hr after completion of infusion ≥ 18 years of age: 12 samples at Baseline (Week 0) + 10 samples at Week 22. Taken within 30 minutes prior to the infusion, at 15 (±5) [not Week 10], 30 (±5), 60 (±5) [not Week 10] min following the	Liver and lipid panels: screening (Day -45 to -7), and double-blind treatment period (predose on Week 0, 2, 4, 6, 10, 14, 18, 20, 20, 22, 24, 26, 28, 32, 36, 40, 42, 46, 50, and then once every 12 weeks through end of the study, as well as at the End-of-Study Visit.).

		extension period.			beginning of the infusion and at the end of the infusion (±5), 5 (±2), 10 (±2), 15 (±2), 30 (±2), 45 (±2), 60 (±2) and 120 (±2) min after the completion of the infusion.	
LAL-CL06 (Children and adults with LAL-D)	Week 96 CSR (12 Sep 2018); Week 144 CSR (30 Oct 2018)	Phase 2 open-label, single-arm, multicenter study to evaluate efficacy, safety, tolerability, PK, and PD for up to 144 weeks All pts initiated treatment with sebelipase alfa at a dose of 1 mg/kg through IV administration every other week. Dose escalations up to 3 mg/kg once weekly (qw) was allowed based on pt response to treatment (e.g., inadequate clinical response, significant clinical progression) after a minimum time on the previous dose.	Sebelipase alfa: 31	PK: up to Week 48; PD and ADA: up to Week 144	**Patients <18 years.** PK samples (during infusion: 0hr to end of infusion; after completion of infusion : within 0-30 min, 30-60 min, and 1-2 h time windows) were taken at baseline, Week 24, Week 48, and on the first day of any dose increase. **Patients ≥18 years.** At Week 0, PK samples were collected at predose (within 30 min of infusion), 15 (±5) min, 30 (±5) min, 1 (±5) h and EOI (±5). After completion of the infusion, PK samples were collected at 5 (±5) min, 10 (±5) min, 15 (±5) min, 30 (±5) min, 45 (±5) min, 30 (±5) min, 45 (±5) min, 1 h (±5), and 2 h (±5). At Week 24, PK samples were collected at predose (within 30 min of infusion), 15 (±5) min, 30 (±5) min and EOI (±5). After completion of the infusion, PK samples were collected at 5 (±5) min, 10 (±5) min, 15 (±5) min, 30 (±5) min, 45 (±5) min, 30 (±5) min, 45 (±5) min, 1 h (±5), and 2 h (±5). At Week 48, PK samples were collected at EOI (±5) and within 0-1 h and 1-2 h after then EOI. After a dose increase, PK samples were collected using the same scheme as Week 0, with an additional blood sample at 1-2 h after the EOI.	Liver and lipid panels: screening (Day -45 to 0) and treatment (predose on Day 0 and every 4 weeks ±1 week until Week 12, and then every 12 weeks ±1 week thereafter).

LAL-CL03 (Infants with growth failure due to LAL-D)	Primary Analysis CSR[a] (04 Sep 2014); Final CSR (01 Nov 2018)	Phase 2/3, dose escalation, multicenter study to evaluate efficacy, safety, tolerability, PK, and PD for up to 262 weeks Once weekly dose of 0.35 mg/kg, administered as an IV infusion over 2 hours. Dose escalation to 1 mg/kg once weekly occurred in all subjects (subject to tolerability) with dose escalations permitted to 3 mg/kg in subjects that had a suboptimal response. Dose escalation to 5mg/kg qw.	Sebelipase alfa: 9	PK: up to Week 72; PD and ADA: up to Week 252	All subjects: 2 samples taken 0 to 1 h after the start of the infusion, and between 1 h after the start of the infusion and the end of the infusion (i.e. when the infusion bag has been emptied, but prior to the sodium chloride flush) at week 0, week 22 and week 72. Subjects whom blood collection volume thresholds had not been exceeded: 0 to 0.5 h after completion of the infusion, 0.5 to 1 h after completion of the infusion and 1 to 2 h after completion of the infusion at week 0, week 22 and week 72.	Liver and lipid panels :pre-infusion at Weeks 0 (Day 0, initial infusion), 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 32, 40, 48, and then once every 12 weeks through the End-of-Study Visit including for early withdrawal from the study.
LAL-CL08 (Infants with Rapidly progressing LAL-D)	Final CSR (04 Apr 2019)	Phase 2 open-label, single-arm, repeat-dose, multicenter study to evaluate safety, tolerability, immunogenicity, and PK for up to 3 years IV infusions alfa at a dose of 1 mg/kg qw. Dose escalation to 3 mg/kg qw. Further dose escalation to 5 mg/kg qw after at least 4 infusions at a dose of 3 mg/kg qw. A further dose escalation to 7.5 mg/kg qw can be considered in UK.	Sebelipase alfa: 10	PK: up to Week 48; PD and ADA: up to Week 156	All subjects: 1 sample taken between 0 h and the end of infusion (i.e. when the infusion bag has been emptied, but prior to the sodium chloride flush) at week 0 and week 22. Subjects whom blood collection volume thresholds had not been exceeded: 0 to 0.5 h after completion of the infusion and 0.5 to 1 h after completion of the infusion at week 0 and week 22.	Liver and lipid panels: pre-infusion at Weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and then once every 8 weeks and 12 weeks through the end of the study, as well as at the End-of-Study Visit.
Population PK Analysis and the PK-PD analysis	The objectives of the Population PK Analysis and the PK-PD analysis using data from studies LAL-CL06, LAL-CL04, LAL-CL02 and LAL-CL03 were: 1. Following addition of new clinical data, develop a new Pop-PK model and assess the impact of the following: a. Body size on PK parameters. b. Age and enzyme maturation on PK parameters. c. BLQ data on the Pop-PK model to potentially under predict low concentrations, using multiple imputation methods. d. Infusion rate and duration on PK parameters, using a sensitivity analysis. e. Under-exposing infants and younger children when using body weight-based dosing on PK parameters. 2. Develop a Pop-PK/PD model to provide further information on the relation between plasma levels of sebelipase alfa and PD outcomes, i.e., changes from baseline in ALT concentrations and in LDL-C concentrations. Use the Pop-PK/PD model to explore the impact of body weight-based dosing on PD parameters.					

[a] Included in the original regulatory application.

Abbreviations: ADA = antidrug antibody; CSR = Clinical Study Report; EOI = end of infusion; IV = intravenous; LAL-D = lysosomal acid lipase deficiency; PBO/SA = placebo during Double-blind Period and sebelipase alfa during Open-label Period; PD = pharmacodynamics; PK = pharmacokinetics; pts= patients; SA/SA = sebelipase alfa during Double-blind and Open-label Periods.

2.1.2. Bioanalytical method

Sebelipase alfa serum concentration data were analyzed by CRO using a validated bioanalytical method. The same method ELISA-0558, an enzyme activity-based assay, has been used in the analysis of samples from all studies during the clinical development of sebelipase alfa. The range of quantification for the method is 3.125 to 100 ng/mL. However, a data integrity issue (DII) occurred, which led to the disqualification of some results. In brief, the DII involved the overwriting of original raw instrument data for multiple analytical runs. Investigation into the data overwrites revealed the collection of raw instrument data multiple times per individual analytical run. Original raw instrument data were erased in this process and, therefore, were unavailable for evaluation or study reconstruction. No documentation was generated to describe these actions, and no cause for the actions could be determined. For these reasons, the data generated in these analytical runs were invalidated by Alexion. At the time of data disqualification these samples were beyond the validated long-term storage stability and could not be reanalyzed and were, therefore, unreportable. In addition, there was insufficient long-term stability to cover storage periods of some samples.

The scope of impacted samples across the clinical studies of sebelipase alfa for the treatment of LAL-D due to the DII or long-term stability issue is presented in the table below.

Table 2 - Summary of Non-reportable Sample Results Due to Data Integrity and Long-term Stability Issues

Clinical Study	Bioanalytical Report	Non-reportable[a]/Total PK Samples
LAL-CL01	8299-266	270/270
LAL-CL02	8291-767	291/973
LAL-CL03	8291-768	21/47
LAL-CL04	8291-766	106/342
LAL-CL06	8299-224	278/456
LAL-CL08	8308-665	13/34

[a] Does not include samples non-reportable for analytical reasons. (eg, insufficient sample volume).
Abbreviation: PK = pharmacokinetic(s).
Source: Module 2.7.1 Table 5

Assessment of the responses to the 1st request for supplementary information in procedure EMA/H/C/4004/P46 08 and related to the bioanalytical method used to quantify sebelipase alpha:

Question 1

As recommended by the CHMP at time of the MA grant, the final report of the parallelism study should be submitted to complete the current validation report of the method for the determination of sebelipase in human serum using enzymatic activity assay (Method No. ELISA-0558) and the Applicant is asked to discuss this aspect in particular for the infant population included in the study LAL-CL08.

Summary of the MAH's response

Parallelism evaluations performed at the time of the original Marketing Authorization were carried out using samples from Studies LAL-CL02, LAL-CL03 and LAL-CL04 (LAL-CL01). Samples were grouped by patient age categories as follows: Group 1 (1-12 years old), Group 2 (> 12-18 years old) and Group 3 (> 18 years old). Corresponding parallelism results (8285-709 Final Validation Report Addendum 1 – see below) demonstrate the absence of a significant matrix effect in the general patient population with

lysosomal acid lipase deficiency (LAL-D), suggesting that the bioanalytical assay would also be tolerant to matrix from patients < 1 year of age. Patients < 1 year of age do exhibit the most severe forms of LAL-D, defined by significant heterogeneity in disease manifestation which leads to a large variability of patient blood chemistry (Jones, et al. Orphanet Journal of Rare Diseases, 2017, 12:25). Due to this variability, it is difficult to generally speculate if the assessment of parallelism would be different for patients < 1 year of age. Ten patients < 1 year old have been included in Study LAL-CL08. No samples from patients aged < 1 year old who were enrolled in Study LAL-CL08 remain within validated storage stability. No other samples from patients < 1 year old who were enrolled in sebelipase alfa clinical studies are available within validated stability. Therefore, the assessment is not feasible at this time.

Group 1 Pool 1

Parallelism

Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
60	90176.699	> ULOQ	> ULOQ
120	52140.414	60.295	7235.400
240	29944.500	30.340	7281.600
480	15857.447	14.166	6799.680
960	8706.434	6.619	6354.240
1,920	4781.248	< LLOQ	< LLOQ
3,840	2803.575	< LLOQ	< LLOQ
7,680	1988.577	NA	NA
		Mean	6917.730
		Stdev	433.886
		%CV	6.3

Group 1 Pool 2

Parallelism

Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
60	99560.594	> ULOQ	> ULOQ
120	58706.402	70.450	8454.000
240	33352.451	34.552	8292.480
480	18714.615	17.298	8303.040
960	9611.918	7.553	7250.880
1,920	5553.876	3.406	6539.520
3,840	3162.162	< LLOQ	< LLOQ
7,680	2089.343	NA	NA
		Mean	7767.984
		Stdev	837.932
		%CV	10.8

Group 1 Pool 3

Parallelism

Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
3	91232.348	> ULOQ	> ULOQ
6	53367.817	62.128	372.768
12	32968.003	34.071	408.852
24	17955.331	16.459	395.016
48	9610.148	7.551	362.448
96	5240.809	3.090	296.640
192	3073.641	< LLOQ	< LLOQ
384	2046.585	NA	NA
		Mean	367.145
		Stdev	43.419
		%CV	11.8

Underlined = CV>25%

Group 2 Pool 1			
Parallelism			
Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
6	88568.551	> ULOQ	> ULOQ
12	51760.766	62.911	754.932
24	31437.435	35.034	840.816
48	17468.602	17.352	832.896
96	9382.654	7.791	747.936
192	5054.127	< LLOQ	< LLOQ
384	3093.636	< LLOQ	< LLOQ
768	2086.883	NA	NA
		Mean	794.145
		Stdev	49.507
		%CV	6.2

Group 2 Pool 2			
Parallelism			
Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
6	92163.618	> ULOQ	> ULOQ
12	57518.176	71.248	854.976
24	35676.018	40.643	975.432
48	19098.509	19.345	928.560
96	10531.688	9.111	874.656
192	5645.830	3.613	693.696
384	3308.809	< LLOQ	< LLOQ
768	2275.289	< LLOQ	< LLOQ
		Mean	865.464
		Stdev	106.973
		%CV	12.4

Group 2 Pool 3			
Parallelism			
Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
3	116880.070	> ULOQ	> ULOQ
6	74311.734	96.672	580.032
12	47744.754	57.210	686.520
24	27203.950	29.537	708.888
48	15198.182	14.609	701.232
96	7968.317	6.186	593.856
192	4507.533	< LLOQ	< LLOQ
384	2714.067	< LLOQ	< LLOQ
		Mean	654.106
		Stdev	62.027
		%CV	9.5

Group 3 Pool 1			
Parallelism			
Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
6	80738.125	97.911	587.466
12	50220.231	53.717	644.604
24	28085.457	26.994	647.856
48	14929.706	12.737	611.376
96	8831.727	6.458	619.968
192	4925.270	< LLOQ	< LLOQ
384	3006.848	< LLOQ	< LLOQ
768	2152.372	NA	NA
		Mean	622.254
		Stdev	24.944
		%CV	4.0

Group 3 Pool 2			
Parallelism			
Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
3	107444.696	> ULOQ	> ULOQ
6	71083.719	82.844	497.064
12	45769.303	48.027	576.324
24	26587.431	25.314	607.536
48	13902.121	11.666	559.968
96	7793.067	5.404	518.784
192	4460.585	< LLOQ	< LLOQ
384	2919.203	< LLOQ	< LLOQ
		Mean	551.935
		Stdev	44.330
		%CV	8.0

Group 3 Pool 3			
Parallelism			
Dilution Factor	Mean Response (OD)	Mean Observed Conc. (ng/mL)	Mean Conc. Corrected for Dilution (ng/mL)
3	96024.989	> ULOQ	> ULOQ
6	60869.895	68.065	408.390
12	36268.260	36.443	437.316
24	20371.934	18.510	444.240
48	11739.848	9.432	452.736
96	6826.080	4.427	424.992
192	3947.248	< LLOQ	< LLOQ
384	2672.778	< LLOQ	< LLOQ
		Mean	433.535
		Stdev	17.341
		%CV	4.0

Assessment of the MAH's response

As requested, the final results of the parallelism study for the method for the determination of sebelipase in human serum using enzymatic activity assay (Method No. ELISA-0558) were provided by the MAH. According to the addendum 1 of the validation report 8285-709, parallelism for this study was tested in both pediatric and adult populations using study samples from LAL-CL02, LAL-CL03 and LAL-CL01/LAL-CL04. Clinical samples were identified from three age groups (1-12, >12-18, and >18 years) and confirmed as ADA negative. Of note, an additional age group (<1 years) was initially identified for the parallelism study however due to there being no patient samples (due to blood volume limitations and sparse sampling in the clinical studies) in this age group it was removed from the study analysis. A total of 3 study samples of similar PK concentration were mixed together to

*create a pool in each age group. A total of 3 separate pools will be created for testing each age group resulting in a total of 9 pools. Each pool was diluted using 2 fold dilutions in 33.3% human serum diluent, after minimum required dilution (MRD) at 1/3 dilution in Assay Buffer, imitating study sample dilutions. At least 1 dilution will be >ULOQ dilution will be <LLOQ, and at least 3 dilutions will fall within the range of the assay. The Guideline on bioanalytical methods (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) recommends the use of study sample instead of pooled samples. Since 3 independently pooled samples using 3 individual patient samples per pool and the %CV results were found to be ≤ 12.4 %, the parallelism of the method is deemed sufficiently demonstrated.*

Regarding the patients aged < 1 years old, uncertainties on the impact of the patient matrix on the PK assay remain based on the current data. But no samples within validated sample stability remain available. Therefore, the MAH cannot conduct further assessment of the parallelism of the bioanalytical method. But taking into account the acceptable ISR results from studies LAL-CL03 and LAL-CL08 including infants analysis with a pass rate of 78% for reportable PK samples (11/14; i.e. 29.8% (14/47) of the total number of samples with reportable results for both studies - see before) and the orphan status of the disease and the unmet medical need of the disease, this issue is not pursued.

Conclusion

Not pursued

Question 2

The validation data supporting the long-term stability range of 507 days for sebelipase alpha should be provided.

Summary of the MAH's response

The long-term storage stability of Kanuma in serum up to 507 days has been documented in an addendum to the validation report (8285-709 Final Validation Report Addendum 1). In 2 independent analyses 2/3 of long-term stability quality control samples at each level met acceptance criteria as presented in Table 1.

Table 1: Long-term Storage Stability of Kanuma at 507 Days

18 Month -70ºC

	LQC		HQC	
Nominal Concentration (ng/mL)	**14.063**		**225.000**	
Time Interval	**18 Months Repeat 1**		**18 Months Repeat 1**	
Actual Time	**507 Days**		**507 Days**	
Storage Condition	**Nominal -70°C**		**Nominal -70°C**	
	Result	**%Bias**	**Result**	**%Bias**
Replicate Pair 1	11.886	-15.5	217.599	-3.3
Replicate Pair 2	12.379	-12.0	214.937	-4.5
Replicate Pair 3	13.207	-6.1	212.830	-5.4
n	3		3	
Mean	12.491		215.122	
Stdev	0.668		2.390	
%Bias	-11.2		-4.4	

18 Month -70ºC

	LQC		HQC	
Nominal Concentration (ng/mL)	**14.063**		**225.000**	
Time Interval	**18 Months Repeat 2**		**18 Months Repeat 2**	
Actual Time	**507 Days**		**507 Days**	
Storage Condition	**Nominal -70°C**		**Nominal -70°C**	
	Result	**%Bias**	**Result**	**%Bias**
Replicate Pair 1	12.232	-13.0	219.599	-2.4
Replicate Pair 2	12.383	-11.9	223.557	-0.6
Replicate Pair 3	14.560	3.5	**14.772**	**-93.4**
n	3		3	
Mean	13.058		152.643	
Stdev	1.303		119.416	
%Bias	-7.1		-32.2	

Assessment of the MAH's response

*The MAH has provided the requested validation results to support the long-term stability of the collected samples (the addendum 1 of the 8285-709 Final Validation Report). The following acceptance criteria were described in the method validation protocol provided at MAA submission (study number 8285-709): stability is acceptable if the measured concentrations of the analyte in ≥ 67% of all stability samples, with ≥ 50% at each level, meet the following criteria: accuracy (expressed as % Bias): ± 25% ; precision (expressed as %CV): CV≤20%. The Applicant has reported that the stability was proven acceptable for up to 507 days at -60ºC to -80ºC temperature (Study Number 8285-709, Method Validation Report Addendum No. 1). The acceptance criteria selected by the Applicant were not in line with the current principles of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) expecting that the mean concentration of QC samples at each level should be within up to ±20% of the nominal concentration. However, as the wider acceptance criteria were prospectively defined and were met, this issue is not pursued.*

Conclusion

Not pursued

Overall Rapporteur's comments on bioanalytical method and study sample analysis

All the samples were analysed with the same bioanalytical method and by the same central laboratory as in the original dossier at MAA submission.

A number of issues were raised regarding the bioanalytical method used for the determination of sebelipase alpha in serum for PK analysis at MAA submission regarding the specificity, selectivity in lipaemic serum samples and higher variability than usually accepted. Further data were provided on the

parallelism of the method in the post-approval procedures EMEA/H/C/004004/II/0019, EMA/H/C/4004/P46 05 and EMA/H/C/4004/P46 06. It was deemed sufficiently demonstrated for all groups of age except for the patients aged < 1 year old for whose uncertainties remain since no sample within validated storage stability remained for further analysis. Further validation data supporting the long-term stability range of 18 months for sebelipase alpha were also provided post-approval. Acceptable demonstration for longer periods of storage has failed (3 years and 2 months at -70°C, validation report 8285-709-AM2). However, the final ISR analysis across all six studies (CL01, CL02, CL03, CL04, CL06, and CL08) passed with an average pass rate of 85.7% (total 167 samples; data reported in procedure EMA/H/C/4004/P46 05, bioanalytical report 8308-665) based on predefined acceptance criteria (results within +/- 30% differences to their respective primary results). The updated overall ISR pass rate is 4+16+62+28+7/4+22+76+30+10 (CL03, CL06, CL02, CL04, CL08 – all PK study samples from study CL01 are non-reportable) = 117/142 = 82.4%, which is acceptable. The number of samples with reportable results tested in ISR represents 12.4% (142/1143) of the total number of samples with reportable results across the 6 clinical studies. If the studies including infants are taken separately (LAL-CL03 and LAL-CL08), a pass rate of 78% (11/14) was observed for ISR (taking only in account the PK samples with reportable results). This represents 29.8% (14/47) of the total number of PK samples with reportable results.

Overall, it is concluded that the pending bioanalytical issues regarding the specificity, selectivity in lipeamic serum, the higher variability than commonly accepted and missing parallelism data for patients aged < 1 year old would not have an impact on the positive benefit/risk balance for children of > 4 years old (see Rapporteur's comment section 6.2.6 for children of lowest age groups) taking into account the following points:

- the overall ISR analysis for reportable PK samples and additional parallelism data showed acceptable results;

- the orphan status of the disease and the unmet medical need of the disease.

Regarding the study sample analysis, it is observed that at least 287 samples from 4 clinical studies (studies LAL-CL02, LAL-CL03, LAL-CL06 and LAL-CL08) were impacted by data integrity issues, i.e. 19% of the total number of samples for these 4 studies (287/1510) or 14% out of all PK samples collected in the six clinical studies with PK sampling (287/2122). The sponsor proposes to report these results as 'non reportable'. The disqualification of this substantial number of results raises concerns about the validity of the entire set of PK data reported and may warrant an inspection. The MAH is required to justify that the conclusions drawn on the pharmacokinetics of sebelipase can be considered reliable.

In total 979 study samples have presented a non-reportable result for a total of 2122 PK samples (49%). This represents a substantial number of samples. But the MAH has emphasized that the final population PK model incorporated 25% more PK data than in the original regulatory application model, i.e. the final POPPK model was conducted on 714 samples (on 880 considered PK samples) compared with 570 samples in the original regulatory application. The reasons for not including 116 reportable samples in the POPPK analysis were: pre- or post-dose blank, a measurable concentration before the first dose, TAD>10 and not BLQ, missing sampling time and amount of previous dose imputed (table 4 and table 10.1.4. PK/PD modelling and simulation report). The MAH is requested to clarify why a total of 1122 study samples with reportable results (as calculated based on Table 5 Module 2.7.1 and excluding the samples excluded from LAL-CL01 due to data integrity issues and from study LAL-CL08 due to errors in dosing records) has not been considered for inclusion in the POPPK analysis. In addition, the exclusion criteria 'TAD>10' should be clarified.

Only the valid data should be included in the POPPK model, but it essential that all available and valid data be included in the analysis dataset unless adequately justified.

2.1.3. PK parameters

Pharmacokinetic parameters for sebelipase alfa in serum were assessed using non-compartmental analysis for some individual studies : LAL-CL04 and LAL-CL06. Serum sebelipase alfa concentrations for samples with reportable values were determined for all studies.

A Pop-PK model-based analysis of pooled data was conducted. The final analyses were conducted on pooled PK and ADA data from the 6 studies described above. All PK and PD observations with missing dose records were removed as justified. Missing values for a baseline covariate were amended using a single imputation approach whereby the missing value was substituted by an imputed value as follows:

- For continuous covariates, the median study-specific value from all patients was used.
- For categorical covariates, the mode of the observed values, possibly after stratifying on other observed covariates (eg, sex and study), was used.

The imputed values were used only for fitting the model and are not presented in tables or summaries. Where the proportion of missing values was high (ie, > 15%), the covariate was dropped from the analysis altogether.

A Pop-PK analysis was previously performed for the original regulatory application using a 1-compartment model-based on data collected from 49 patients in 4 ongoing clinical studies. The input was originally described by a complex dual-input model to allow for variability in infusion rate during the recorded infusion time due to the flush. The model in the original regulatory application (hereafter referred to as the original Pop-PK model) included the effect of body surface area (BSA) on CL and volume of distribution in the central compartment (Vc). In addition, the model included the effect of dose (≥ 3 mg/kg) on CL and Vc as well as inter-occasion variability (IOV) on CL. This original Pop-PK model was associated with biased predictions of low concentrations (Sebelipase Alfa PK/PD Report Section 10.2.1), which was mainly observed during the terminal phase (Sebelipase Alfa PK/PD Report Section 10.2.2).

Following incorporation of all new PK and ADA data, a 2-compartment model with linear elimination was used as a starting point for assessing the concentration-time profiles of sebelipase alfa based on the Pop-PK Analysis Dataset (75 patients). This base Pop-PK model included the effect of body weight as opposed to BSA because dosing of sebelipase alfa was body weight-based (mg/kg) in the contributing studies and because of the high correlation between BSA and body weight (Spearman correlation = 0.995, Sebelipase Alfa PK/PD Report Section 10.2.3). Exponents for the effect of body weight were estimated using an allometric model. The IV flush component was removed and a single zero-order infusion component was implemented. The effect of dose (3 mg/kg) on CL was estimated using a power model. A shared ETA between CL and intercompartmental clearance (Q) was included in the model.

The Pop-PK model development for sebelipase alfa consisted of testing the following (Sebelipase Alfa PK/PD Report Section 5.3.2):

- Two-compartment model to describe the relationship between serum concentration and time following IV administration of sebelipase alfa.
- An empirical allometric model accounting for body weight impact (used to determine each dose) on CL and Vc parameters was used. Exponents for the effect of time-varying body weight on CL and Vc were estimated.

- A variance component characterizing inter-individual variability (IIV) in model parameters.
- Modeling of unexplained residual variability using additive, proportional, or additive and proportional models.
- Any covariates identified in the model building process.

Pop-PK models tested were in the following form:

$C_{ij} = C(D_i, t_{ij}, \theta_i) \cdot (1 + \varepsilon_{p,ij}) + \varepsilon_{a,ij}$	**Equation 1**
$\theta_i = (\theta_{i1}, \dots, \theta_{ip})$	**Equation 2**

Where Cij is the concentration at the j^{th} collection time t_{ij} for patient i; D_i represents dosing history for patient i; θi is the vector of p PK parameters for patient i; and $\varepsilon_{p,ij}$ and $\varepsilon_{a,ij}$ are the proportional and additive random residual error terms, respectively, associated with j^{th} concentration for patient i. Terms ε_p and ε_a are normally distributed with mean 0 and variances σ_p^2 and σ_a^2, respectively.

The IIV was modeled using exponential random-effect models with the following form:

$\theta_{in} = (\theta_{TV,n} e^{(\eta_{in})})$	**Equation 3**
$(\eta_{1,\dots,}\eta_p) = MVN(0, \Omega)$	**Equation 4**

Where θ_{in} is the value of the n^{th} PK parameter of the i^{th} individual; $\theta_{TV,n}$ is the typical value of the n^{th} PK parameter in the population; and η_{in} is the random inter-individual deviation from the typical value $\theta_{TV,n}$ for patient i. Inter-individual random effects ($\eta_1, \dots, \eta_p$), also known as ETAs, are multivariate normally (MVN) distributed with mean 0 and estimated variance ω^2 included in the variance-covariance OMEGA (Ω) matrix.

The final decision to retain a potential covariate in the model was based on scientific or clinical interest, mechanistic plausibility, a priori knowledge about covariate effects, correlation with other potential covariates considered for evaluation in the model, adequate sample size for a categorical subgroup, and the greatest correlation with random effects of PK parameters.

Details on model evaluation, estimation shrinkage, performance, and robustness are provided in Sebelipase Alfa PK/PD Report Sections 5.3.4 through 5.3.6. Individual Bayesian estimates of PK parameters were used to predict rich concentration-time profiles of sebelipase alfa from which the PK parameters were derived as described in Sebelipase Alfa PK/PD Report Section 5.3.7.

A sensitivity analysis was conducted to assess the effects of dose on CL, with and without the data from 3 patients who received the higher dose of 3 mg/kg (Sebelipase Alfa PK/PD Report Section 6.2.3). Given the large parameter uncertainty likely due to the data from only 3 individuals, and the little difference observed in the sensitivity analysis, the final model was estimated without including the data from these 3 patients.

Rapporteur's comments

The methods described by the applicant for the new model building and evaluation are overall considered state of the art. However, in view of the identified issues with data integrity and related data exclusion, the applicant is asked to provide the distribution of the data used for POPPK modelling by age group and to discuss whether there were enough data in the different age subgroups (<2, 2-4, 4-6, 6-12, and 12-18 y.o) to allow adequate PK characterization in the different age groups.

Moreover, the applicant should justify why they did not use fixed allometric scaling exponents for CL and volume of distribution parameters and compare the predictive performances with estimated parameters.

This would be of utmost importance in case the data in the younger age children are not sufficiently represented in the dataset.

2.1.4. Immunogenicity

To examine the potential for immunogenicity, the incidence of anti-sebelipase alfa antidrug antibodies (ADA) was monitored with the validated method ELISA-0556 containing three tiers of testing: (1) Screening assay, which identifies initial positive or negative samples, (2) Confirmatory assay, which assesses specificity of the positive screen samples, and (3) Titration assay which estimates the level of antibody for the confirmed positive samples. Any samples confirmed as ADA-positive were then further subject to testing for neutralizing antidrug antibody (NAb) activity by inhibition of enzyme activity (ELISA-0566) and inhibition of cellular uptake (CELL-0042). Immunogenicity samples were collected before the administration of sebelipase alpha. The numbers of patients who were had positive ADA titers and the duration of exposure before first appearance of a positive ADA titer are presented.

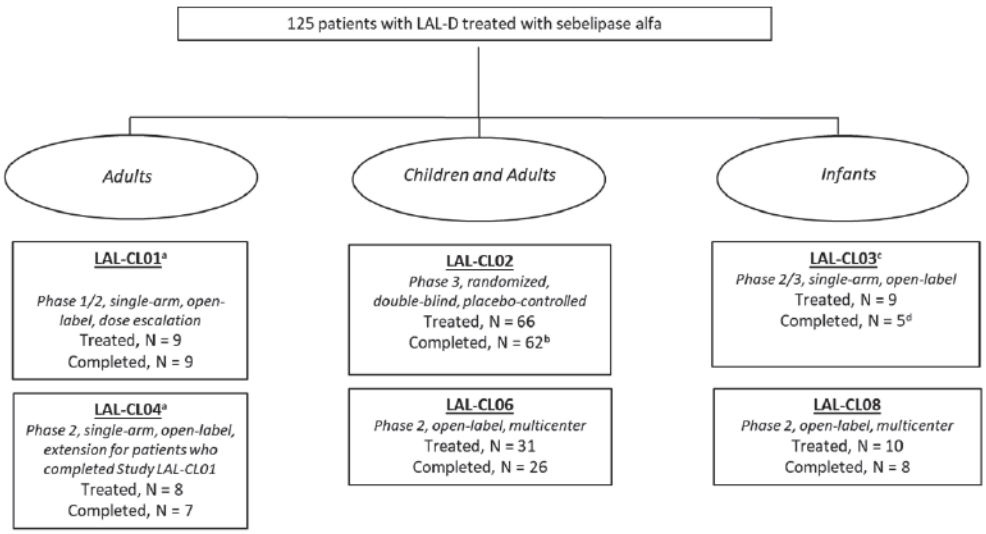
Rapporteur's comments

All the samples were analysed with the same immunogenicity assays as in the original dossier at MAA submission.

Concerning the immunogenicity assays, the Applicant is requested to determine the cut-points of the target populations using the pre-treatment samples from the completed studies LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08 to confirm the assay cut points determined with samples from healthy drug-naïve subjects. A statistical comparison is expected.

2.2. Results

2.2.1. Study patients



[a] All except 1 patient in Study LAL-CL01 were enrolled in extension Study LAL-CL04.
[b] Patients were considered to have completed Study LAL-CL02 if they completed the Open-label Extension or Expanded Period or moved to commercially available drug:2 patients were lost-to-follow-up and 2 patients withdrew consent.
[c] Study LAL-CL05 (an open-label extension study of sebelipase alfa in children with LAL-D) was terminated. Data from the 1 patient enrolled in Study LAL-CL05 were subsequently merged with the data from Study LAL-CL03. Therefore, data from Study LAL-CL05 are not presented separately from those for Study LAL-CL03.
[d] In Study LAL-CL03, 4 patients were considered early terminated due to death.
Abbreviations: LAL-D = lysosomal acid lipase deficiency; N = number of patients in a specified subgroup.

Figure 1 – Sebelipase alpha programme

Descriptive statistics of baseline characteristics of patients included in the POPPK analysis (i.e., subjects who received at least 1 dose of sebelipase alfa with at least 1 measurable concentration) in each study and overall are presented in the table below.

Table 3 – Baseline characteristics of PK Population included in POPPK analysis

Characteristics	LAL-CL02 (N=35)	LAL-CL03 (N=5)	LAL-CL04 (N=8)	LAL-CL06 (N=27)	Overall (N=75)
Age (years)					
Mean (SD)	16.7 (10.9)	0.308 (0.185)	31.4 (10.5)	15.6 (14.6)	16.8 (13.5)
Median	13.5	0.350	29.4	11.6	13.1
[Min, Max]	[4.71, 55.2]	[0.0900, 0.480]	[20.4, 45.9]	[2.96, 54.8]	[0.0900, 55.2]
Body Weight (kg)					
Mean (SD)	48.6 (20.3)	5.39 (1.73)	76.0 (13.2)	37.3 (27.4)	44.6 (26.6)
Median	52.3	5.70	75.9	30.5	37.9
[Min, Max]	[17.9, 88.1]	[3.36, 7.91]	[56.0, 94.6]	[12.4, 130]	[3.36, 130]
Height (cm)					
Mean (SD)	150 (21.0)	59.0 (7.56)	172 (7.56)	132 (27.0)	140 (33.1)
Median	150	60.0	171	134	146
[Min, Max]	[102, 190]	[50.5, 67.4]	[161, 184]	[89.2, 170]	[50.5, 190]
Body Mass Index (kg/m^2)					
Mean (SD)	20.4 (4.15)	15.1 (1.77)	25.7 (3.42)	19.1 (7.16)	20.1 (5.71)
Median	19.2	15.7	26.0	16.4	18.5
[Min, Max]	[15.0, 28.2]	[13.2, 17.4]	[19.9, 31.3]	[13.9, 48.5]	[13.2, 48.5]
Body Surface Area (m^2)					
Mean (SD)	1.41 (0.389)	0.282 (0.0635)	1.88 (0.187)	1.13 (0.475)	1.28 (0.524)
Median	1.46	0.293	1.90	1.06	1.24
[Min, Max]	[0.700, 2.16]	[0.207, 0.366]	[1.63, 2.18]	[0.554, 2.27]	[0.207, 2.27]
Sex					
Female	17 (48.6%)	2 (40.0%)	2 (25.0%)	10 (37.0%)	31 (41.3%)
Male	18 (51.4%)	3 (60.0%)	6 (75.0%)	17 (63.0%)	44 (58.7%)
Age Categories					
< 2 years	0 (0%)	5 (100%)	0 (0%)	0 (0%)	5 (6.7%)
2 to 5 years	1 (2.9%)	0 (0%)	0 (0%)	6 (22.2%)	7 (9.3%)
6 to 11 years	13 (37.1%)	0 (0%)	0 (0%)	9 (33.3%)	22 (29.3%)
12 to 17 years	9 (25.7%)	0 (0%)	0 (0%)	6 (22.2%)	15 (20.0%)
≥ 18 years (Adults)	12 (34.3%)	0 (0%)	8 (100%)	6 (22.2%)	26 (34.7%)
Race					
White	27 (77.1%)	1 (20.0%)	8 (100%)	23 (85.2%)	59 (78.7%)
Black or African American	1 (2.9%)	1 (20.0%)	0 (0%)	0 (0%)	2 (2.7%)
Asian	3 (8.6%)	0 (0%)	0 (0%)	0 (0%)	3 (4.0%)
Any Other Race*	4 (11.4%)	0 (0%)	0 (0%)	4 (14.8%)	8 (10.7%)
Not reported	0 (0%)	3 (60.0%)	0 (0%)	0 (0%)	3 (4.0%)
Ethnicity					
Not Hispanic or Latino	29 (82.9%)	2 (40.0%)	8 (100%)	22 (81.5%)	61 (81.3%)
Hispanic or Latino	6 (17.1%)	0 (0%)	0 (0%)	5 (18.5%)	11 (14.7%)
Not reported	0 (0%)	3 (60.0%)	0 (0%)	0 (0%)	3 (4.0%)

* Includes multiple or unknown race.
Abbreviations: SD = standard deviation.

A total of 75 and 40 patients were included in the population PK analysis of sebelipase alfa and PK/PD analysis of ALT and LDL, respectively.

Table 4 - Number of Patients and Samples Available for the population PK and PK/PD Analysis

Study Identifier (Population)	Endpoint	PK	ALT	LDL
LAL-CL02 (Children and adults with LAL-D)	Number of patients	35	35	35
	Number of samples analyzed	360	599	606
LAL-CL03 (Infants with growth failure due to LAL-D)	Number of patients	5	5	5
	Number of samples analyzed	21	62	36
LAL-CL04 (Adults with liver dysfunction due to LAL-D who completed Study LAL-CL01)	Number of patients	8	0	0
	Number of samples analyzed	191	0	0
LAL-CL06 (Infants, children, and adults with LAL-D)	Number of patients	27	0	0
	Number of samples analyzed	142	0	0
Total	Number of patients	75	40	40
	Number of samples analyzed	714	661	642

Abbreviations: ALT = Alanine aminotransferase; LDL = Low-density lipoprotein; PK = Pharmacokinetic.

Of a total of 880 samples, 138 (15.7%) presented BLQ concentrations on treatment. Overall, a total of 714 (81.1%) samples were included in the population PK analysis (see the table below).

Table 5 – Summary of dataset available for the population PK analysis

Study	Number of Patients	Total # of Sebelipase Alfa PK Samples	Pre-dose BLQ	Post-dose BLQ	Excluded[a]	Included in Population PK Analysis
LAL-CL02	35 (46.7%)	444 (50.5%)	8	68	8	360 (40.9%)
LAL-CL03	5 (6.7%)	28 (3.2%)	0	7	0	21 (2.4%)
LAL-CL04	8 (10.7%)	235 (26.7%)	0	43	1	191 (21.7%)
LAL-CL06	27 (36.0%)	173 (19.7%)	4	20	7	142 (16.1%)
Total	**75 (100.0%)**	**880 (100.00%)**	**12 (1.36%)**	**138 (15.7%)**	**16 (1.82%)**	**714 (81.1%)**

Note: the above table includes 93 samples collected in the following 3 patients who received high dose of 3 mg/kg in study LAL-CL04: 01-002 (41 years, male, 94.6 kg, 02-002 (20 years, female, 68.7 kg) and 06-001 (21 years, male, 82.0 kg). These 3 patients were removed from the population PK analysis after performing a sensitivity analysis (refer to Section 6.2.3).
[a] A total of 16 (1.82%) samples were removed from the analysis (refer to Appendix 2, Section 10.1.4).
Abbreviations: BLQ = below the limit of quantitation

2.2.2. Sebelipase alpha concentrations

Study LAL-CL01 : All PK samples were evaluated outside of validated assay stability and, therefore, were disqualified.

Study LAL-CL04 : 106/342 PK samples had unreportable results. See the table below summarizing the PK parameter impact as a result of these unreportable samples.

Table 6 - Impacted PK Parameter Summary (Study LAL-CL04)

Sebelipase Alfa Treatment	Number of Patients Impacted (%)	PK Impact
1 mg/kg qow	5 of 5 (100%)	Week 24 - results unreportable
3 mg/kg qow	2 of 3 (67%)	

Abbreviations: PK = pharmacokinetics; qow = every other week.
Source: LAL-CL04 Final CSR Tables 14.2.5.1 through 14.2.5.5

Study LAL-CL02 : Serum sebelipase alfa concentrations for samples with reportable values were included as appropriate in the final Pop-PK model that was developed using all available data.

Study LAL-CL06 : 283/456 PK samples had unreportable results. Impact on the PK parameter profiles is summarized in the table below.

Table 7 - Summary of Patients With PK Samples Impacted by Data Integrity and Long-Term Storage Issues (Study LAL-CL06)

Age Group	Visit	Patients With PK Results Impacted, n of N (%)
2 to < 4 years	Week 0	5 of 6 (83.3)
	Week 24	2 of 6 (33.3)
	Week 48	2 of 6 (33.3)
4 to < 18 years	Week 0	14 of 16 (87.5)
	Week 24	5 of 16 (31.3)
	Week 48	2 of 16 (12.5)
≥ 18 years	Week 0	3 of 9 (33.3)
	Week 24	5 of 9 (55.6)
	Week 48	5 of 9 (55.6)

Abbreviation: PK = pharmacokinetics.
Source: LAL-CL06 Week 96 CSR Listing 16.2.11.3

Study LAL-CL03, study LAL-CL08 : Serum sebelipase alfa concentrations for samples with reportable values were included as appropriate in the final Pop-PK model that was developed using all available data.

2.2.3. PK results from individual studies

Study LAL-CL01 : No reportable PK data and no data included in the Pop-PK analyses.

Study LAL-CL04 : The median (range) PK parameters for sebelipase alfa are summarized by dose for Week 24, Week 52, and Week 104 in the table below. Pharmacokinetic parameters were not available for 7 of the 8 patients at Week 24. At Week 104, Patient 06-001 had a measurable predose concentration that represented 34% of maximum observed concentration (Cmax). This predose concentration was not used for PK parameter calculation as it was considered an outlier. There was no evidence of accumulation following qow administration. Serum exposure to sebelipase alfa increased in a more than dose-proportional manner (up to 15-fold) over the 3-fold increase in dose from 1 to 3 mg/kg.

Table 8 - *Summary of Median (Range) Plasma Pharmacokinetic Parameters - Complete Analysis (Study LAL-CL04 PK Analysis Set)*

Parameter	Median (Range)					
	1 mg/kg qow[a]			3 mg/kg qow[a]		
	Week 24 (N = 0)[a]	Week 52 (N = 4)[a, b]	Week 104 (N = 5)	Week 24 (N = 1)[a]	Week 52 (N = 3)	Week 104 (N = 3)
C_{max} (ng/mL)	ND	1093 (628, 1276)	595 (498, 1048)	15552	14560 (9729, 29114)	5274 (5132, 12696)
t_{max} (h)	ND	0.50 (0.33, 1.03)	1.50 (0.67, 2.70)	2.25	1.50 (1.00, 2.25)	1.50 (1.50, 2.17)
$AUC_{0\text{-last}}$ (ng × h/mL)[c]	ND	1689 (1096, 2087)	1257 (1006, 1731)	27951	21765 (17270, 44425)	9165 (8768, 18385)
AUC0-inf (ng × h/mL)	ND	1693 (1099, 2090)	1306d (1013, 1736)	NC	21768 (17273, 44432)	9171 (8770, 18397)
t1/2 (h)	ND	0.127 (0.09, 0.16)	0.261d (0.16, 0.48)	NC	0.105 (0.10, 0.21)	0.193 (0.09, 0.26)
CLe (mL/h/kg)	ND	600 (479, 913)	795 (578, 994)	107	138 (67.5, 174)	327 (163, 342)
Vz e (mL/kg)	ND	80.9 (60.5, 89.0)	184d (126, 354)	NC	14.5 (14.1, 18.1)	42.5 (32.1, 63.0)

[a] PK parameters were not available for 7 of the 8 patients at Week 24 and for 1 patient at Week 52, as blood samples for measurement of sebelipase alfa concentration were not analyzed within the defined period of sample stability for the PK assay.
[b] Patient 03-001 missed the Week 52 visit.
[c] Area under the concentration-time curve from time zero to last quantifiable measurement is referred to interchangeably as $AUC_{0\text{-last}}$ and $AUC_{0\text{-t}}$ within the statistical source tables in the LAL-CL04 Final CSR.
[d] N = 4
[e] Apparent clearance and volume of distribution were both corrected for body weight and appear in the statistical source tables as CL/Wgt and V_z/Wgt.
Abbreviations: $AUC_{0\text{-last}}$ = area under the concentration-time curve from time zero to last quantifiable measurement; $AUC_{0\text{-inf}}$ = area under the concentration-time curve from time zero extrapolated to infinity; CL = apparent clearance; C_{max} = maximum observed concentration; h = hour; N = maximum number of patients; NC = not calculated; ND = no data; PK = pharmacokinetic; qow = every other week; $t_{1/2}$ = terminal elimination half-life; t_{max} = time to maximum concentration; V_z = volume of distribution.
Source: LAL-CL04 Final CSR Tables 14.2.5.1 through 14.2.5.5

Study LAL-CL02 : For Study LAL-CL02, noncompartmental PK parameters for sebelipase alfa were not generated.

Study LAL-CL06 : The median (range) PK parameters for sebelipase alfa are summarized by age group and dose in the tables below. As a result of the unreportable PK data, limited PK data are available at doses other than 1 mg/kg. As a result of the unreportable PK data, the dose-proportionality of sebelipase alfa across the range of studied doses could not be assessed. Additionally, PK parameters derived from the terminal elimination slope of the concentration-time curve (t½, AUC∞, CL, and Vz) could not be calculated in most cases and were only available for 2 patients > 18 years of age. There was no evidence of accumulation following qow administration.

Table 9 - Median (Range) PK Parameters Following Administration of Sebelipase Alfa Every Other Week in Patients Aged 2 to < 4 Years - Complete Analysis (Study LAL-CL06 PK Analysis Set)

Parameter (Unit)	Median (Range)			
	Week 0	Week 24	Week 48	
	1 mg/kg (N = 1)	1 mg/kg (N = 4)	1 mg/kg (N = 3)	3 mg/kg (N = 1)
C_{max} (ng/mL)	233.491	413.363 (245.61, 585.07)	95.461 (17.81, 216.71)	79.735
C_{max}/dose ([ng/mL]/[mg/kg])	233.491	413.363 (245.61, 585.07)	95.461 (17.81, 216.71)	26.578
t_{max} (h)	0.667	1.542 (0.12, 2.50)	1.433 (1.08, 2.83)	2.517
AUC_t (h × ng/mL)	325.503	748.979 (349.97, 961.59)	89.424 (25.23, 214.50)	162.439
AUC_t/dose ([h × ng/mL]/[mg/kg])	325.503	748.979 (349.97, 961.59)	89.424 (25.23, 214.50)	54.146
AUC_∞ (h × ng/mL)	NC	NC	NC	NC
AUC_∞/dose ([h × ng/mL]/[mg/kg])	NC	NC	NC	NC
$t_{½}$ (h)	NC	NC	NC	NC
CL (L/h/kg)	NC	NC	NC	NC
V_z (L/kg)	NC	NC	NC	NC

Abbreviations: AUC_∞ = area under the concentration-time curve from time zero extrapolated to infinity; AUC_∞/dose = dose-corrected area under the concentration-time curve from time zero extrapolated to infinity; AUC_t = area under the concentration-time curve from time zero to last quantifiable measurement; AUC_t/dose = dose-corrected area under the concentration-time curve from time zero to last quantifiable measurement; CL = apparent clearance; C_{max} = maximum observed concentration; C_{max}/dose = dose-corrected maximum observed concentration; h = hour; NC = not calculated; PK = pharmacokinetic; $t_{½}$ = terminal elimination half-life; t_{max} = time to maximum concentration; V_z = volume of distribution.

Source: LAL-CL06 Week 96 CSR Table 14.2.24.1.3

Table 10 - Median (Range) PK Parameters Following Administration of Sebelipase Alfa Every Other Week in Patients Aged 4 to < 18 Years - Complete Analysis (Study LAL-CL06 PK Analysis Set)

Parameter (Unit)	Median (Range)			
	Week 0	Week 24	Week 48	
	1 mg/kg (N = 2)	1 mg/kg (N = 11)	1 mg/kg (N = 12)	3 mg/kg (N = 2)
C_{max} (ng/mL)	55.907 (29.46, 82.36)	786.122 (424.93, 6426.17)	179.883 (52.59, 2129.92)	11585.435 (2517.54, 20653.33)
C_{max}/dose ([ng/mL]/[mg/kg])	55.907 (29.46, 82.36)	786.122 (424.93, 6426.17)	179.883 (52.59, 2129.92)	3861.811 (839.18, 6884.44)
t_{max} (h)	2.542 (2.42, 2.67)	0.950 (0.50, 2.18)	1.250 (0.58, 2.07)	0.750 (0.50, 1.00)
AUC_t (h × ng/mL)	69.396 (39.27, 99.52)	1377.480 (308.94, 4284.33)	188.314 (72.74, 1695.87)	9987.203 (3307.22, 16667.19)
AUC_t/dose ([h × ng/mL]/[mg/kg])	69.396 (39.27, 99.52)	1377.480 (308.94, 4284.33)	188.314 (72.74, 1695.87)	3329.068 (1102.41, 5555.73)
AUC_∞ (h × ng/mL)	NC	NC	NC	NC
AUC_∞/dose ([h × ng/mL]/[mg/kg])	NC	NC	NC	NC
$t_{½}$ (h)	NC	NC	NC	NC
CL (L/h/kg)	NC	NC	NC	NC
V_z (L/kg)	NC	NC	NC	NC

Abbreviations: AUC_∞ = area under the concentration-time curve from time zero extrapolated to infinity; AUC_∞/dose = dose-corrected area under the concentration-time curve from time zero extrapolated to infinity; AUC_t = area under the concentration-time curve from time zero to last quantifiable measurement; AUC_t/dose = dose-corrected area under the concentration-time curve from time zero to last quantifiable measurement; CL = apparent clearance; C_{max} = maximum observed concentration; C_{max}/dose = dose-corrected maximum observed concentration; h = hour; NC = not calculated; PK = pharmacokinetic; $t_{½}$ = terminal elimination half-life; t_{max} = time to maximum concentration; V_z = volume of distribution.

Source: LAL-CL06 Week 96 CSR Table 14.2.24.2.3

Table 11 - Median (Range) PK Parameters Following Administration of Sebelipase Alfa Every Other Week in Patients Aged ≥ 18 Years - Complete Analysis (Study LAL-CL06 PK Analysis Set)

Parameter (Unit)	Median (Range)				
	Week 0	Week 24	Week 48		
	1 mg/kg (N = 6)	1 mg/kg (N = 4)	0.35 mg/kg (N = 1)	1 mg/kg (N = 2)	3 mg/kg (N = 1)
C_{max} (ng/mL)	211.288 (61.25, 1078.98)	545.116 (173.91, 879.30)	74.340	2464.247 (233.69, 4694.81)	517.576
C_{max}/dose ([ng/mL]/[mg/kg])	211.288 (61.25, 1078.98)	545.116 (173.91, 879.30)	212.400	2464.247 (233.69, 4694.81)	172.525
t_{max} (h)	2.225 (2.02, 2.77)	1.958 (0.50, 2.05)	4.750	1.625 (1.00, 2.25)	2.267
AUC_t (h × ng/mL)	346.331 (104.69, 1211.08)	975.092 (267.19, 1802.57)	176.558	2759.568 (391.22, 5127.91)	356.007
AUC_t/dose ([h × ng/mL]/[mg/kg])	346.331 (104.69, 1211.08)	975.092 (267.19, 1802.57)	504.450	2759.568 (391.22, 5127.91)	118.669

Table 12 - Median (Range) PK Parameters Following Administration of Sebelipase Alfa Every Other Week in Patients Aged ≥ 18 Years - Complete Analysis (Study LAL-CL06 PK Analysis Set)

	Median (Range)				
	Week 0	Week 24	Week 48		
Parameter (Unit)	1 mg/kg (N = 6)	1 mg/kg (N = 4)	0.35 mg/kg (N = 1)	1 mg/kg (N = 2)	3 mg/kg (N = 1)
AUC_∞ (h × ng/mL)	282.965[a] (112.93, 453.00)	1128.498[a] (874.78, 1382.22)	NC	NC	NC
AUC_∞/dose ([h × ng/mL]/[mg/kg])	282.965[a] (112.93, 453.00)	1128.498[a] (874.78, 1382.22)	NC	NC	NC
$t_{½}$ (h)	1.043[a] (0.33, 1.75)	0.590[a] (0.52, 0.66)	NC	NC	NC
CL (L/h/kg)	5.531[a] (2.21, 8.86)	0.933[a] (0.72, 1.14)	NC	NC	NC
V_z (L/kg)	4.913[a] (4.24, 5.58)	0.815[a] (0.54, 1.09)	NC	NC	NC

[a] N = 2.

Abbreviations: AUC_∞ = area under the concentration-time curve from time zero extrapolated to infinity; AUC_∞/dose = dose-corrected area under the concentration-time curve from time zero extrapolated to infinity; AUC_t = area under the concentration-time curve from time zero to last quantifiable measurement; AUC_t/dose = dose-corrected area under the concentration-time curve from time zero to last quantifiable measurement; CL = apparent clearance; C_{max} = maximum observed concentration; C_{max}/dose = dose-corrected maximum observed concentration; h = hour; NC = not calculated; PK = pharmacokinetic; $t_{½}$ = terminal elimination half-life; t_{max} = time to maximum concentration; V_z = volume of distribution.

Source: LAL-CL06 Week 96 CSR Table 14.2.24.3.3

Study LAL-CL03, study LAL-CL08 : Noncompartmental PK parameters for sebelipase alfa were not generated as concentration data were restricted due to limited PK sampling as a result of the limits on the total blood volume that could be collected in the infants.

Population PK analysis results are detailed below.

2.2.4. PD results from individual studies

2.2.4.1. Serum alanine aminotransferase concentrations

Study LAL-CL01 : Following initiation of treatment with sebelipase alfa, serum ALT concentrations decreased rapidly in 7 of the 9 patients (Figure 2). This reduction in ALT level was apparent within 2 weeks of initiation of treatment, and the ALT level continued to decrease in most patients through Day 28, approximately 1 week after the last infusion. For all 9 patients, the mean (SD) decrease in serum ALT concentration from Baseline to Day 28 was 38.7 (25.6) U/L, representing a 43.1% decrease (LAL-CL01 Final CSR Table 14.2.2.1). By Day 52, ALT levels were at or approaching baseline levels in all patients (Figure 2). There was no evidence of a dose-related effect in the time to onset of in the magnitude of the reduction of serum ALT concentration, or in the reversal of the effect after discontinuation of treatment (Figure 2, LAL-CL01 Final CSR Table 14.2.5.1).

Study LAL-CL04 : Following initiation of sebelipase alfa treatment on a qw dosing regimen, serum ALT concentrations decreased rapidly and these initial improvements were maintained after the patients changed to a qow dosing regimen at Week 6 (Figure 7). At Week 4 (the last assessment on a qw regimen), mean (SD) serum ALT concentration was 46.1 (13.62) U/L, representing a mean (SD) change from baseline of -28.4 (21.9) U/L (LAL-CL04 Final CSR Table 14.4.2.1.1.2). At Week 8 (the first assessment on a qow regimen), mean (SD) serum ALT concentration was 36.8 (15.17) U/L, representing a mean (SD) change from baseline of -37.8 (21.27) U/L. After Week 8, mean ALT levels were generally stable through the end of the study. At the End-of-Study Visit (which occurred between Week 224 and

Week 260), mean (SD) ALT was 50.0 (18.08) U/L, representing a mean (SD) change from baseline of -26.6 (31.10) U/L. The effect of sebelipase alfa on serum ALT levels was similar in both dose cohorts (LAL-CL04 Final CSR Figure 14.3.4.13.1.2).

Study LAL-CL02 : Figure 9 presents mean (SE) serum ALT concentration over time from the start of treatment with sebelipase alfa; ie, prior to the Double-blind Period for the SA/SA Group and prior to the first dose of sebelipase alfa in the Open-label Period for the PBO/SA Group.

For the SA/SA Group, the reduction in serum ALT levels achieved during the Double-blind Period was sustained throughout the Open-label Period, demonstrating durability of clinical response. The mean change from baseline at Week 22, the start of the Open-label Period, was -55.5 U/L (n = 32) and the mean change from baseline to the last Open-label Period assessment was -60.7 U/L (n = 36) (LAL-CL02 Final CSR Table 14.2.4.2.3).

For the PBO/SA Group, a marked reduction in serum ALT concentration was observed following initiation of treatment with sebelipase alfa in the Open-label Period, with a time course similar to that previously observed for the SA/SA Group in the Double-blind Period. A reduction in ALT level was apparent by the first postbaseline assessment at Week 24; ie, after 2 weeks of sebelipase alfa treatment (mean change from baseline: -19.6 U/L, n = 29) with further decreases through Week 42; ie, after 20 weeks of sebelipase alfa treatment (mean change from baseline: -49.3 U/L, n = 30) and continued decreases through Week 88 (mean change from baseline: -53.9 U/L, n = 25). Thereafter, mean serum ALT concentrations were fairly stable over time. After Week 208, data were available for only 5 to 6 patients, and mean levels were less informative. The mean change from baseline to the last assessment in the Open-label Period was -39.1 U/L (n = 30) (LAL-CL02 Final CSR Table 14.2.4.2.3).

Study LAL-CL06 : Following initiation of treatment with sebelipase alfa, serum ALT concentration decreased rapidly (Figure 14). By the first postdose assessment at Week 4 (n = 30), mean serum ALT concentration was 50.4 U/L, representing a mean change from baseline of -25.8 U/L and a mean percent change from baseline of -25.9% (LAL-CL06 Week 144 CSR Table 14.2.1.1.1.2). Mean ALT levels continued to decrease through approximately Week 36, and thereafter were essentially stable with the exception of a transient spike at Week 72, which was primarily driven by increases in 2 patients (LAL-CL06 Week 144 CSR Section 11.4.1.1). At Week 96, mean serum ALT concentration was 38.8 U/L (n = 27), representing a mean change from baseline of -32.4 U/L and a mean percent change of -29.1%. At Week 144 (n = 19), mean serum ALT concentration was 38.2 U/L, representing a mean change from baseline of -40.3 and percent change of -32.0% (LAL-CL06 Week 144 CSR Table 14.2.1.1.1.2).

Study LAL-CL03: Following initiation of treatment with sebelipase alfa, serum ALT concentrations decreased rapidly (Figure 16). Reductions in serum ALT levels were already evident at Week 1, when all patients were receiving sebelipase alfa at a dose of $\leq$ 0.35 mg/kg, with a median reduction from baseline of -23.0 U/L (n = 7) (LAL-CL03 Final CSR Table 14.2.8.4). By Week 4, 2 weeks after most patients escalated to 1 mg/kg qw, the median reduction in ALT levels was -33.0 U/L (n = 5). Median percentage changes from baseline at Week 1 and Week 4 were -31.3%, and -66.00%, respectively. Median ALT levels were fairly stable from Week 4 through Week 240, the last assessment for which data were available for more than 2 patients, although a few patients had fluctuations in serum ALT levels over time.

Study LAL-CL08: A consistent treatment effect on serum ALT concentration was not observed in this study, with both median (and mean) increases and decreases in ALT levels observed over time (Figure 18).

2.2.4.2. Low-density Lipoprotein Cholesterol Concentrations

Study LAL-CL01 : Serum LDL-C concentration increased for the majority of the patients across all dose cohorts by Day 28, which was approximately 1 week after the last infusion of sebelipase alfa (Figure 3). The increase in LDL-C level was more pronounced for the highest dose group (Cohort 3; 3 mg/kg) than for the lower 2 dose groups. By Day 52 serum LDL-C concentrations were within the normal range, and below baseline level for all patients with data available.

Study LAL-CL04 : Following initiation of sebelipase alfa treatment on a qw dosing regimen, a transient increase in serum LDL-C concentration (Figure 8) was observed at Week 4 (the first postdose assessment), at which time mean (SD) serum LDL-C level was 287.6 (143.88) mg/dL, representing a mean (SD) change from baseline of 138.1 (123.57) mg/dL. Serum LDL-C concentration decreased with continued sebelipase alfa treatment, which was administered on a qow dosing regimen beginning at Week 6. By the next assessment at Week 8, mean (SD) serum LDL-C concentration was below baseline levels, with a mean (SD) observed LDL-C concentration of 122.6 (97.47) mg/dL, representing a mean (SD) change from baseline of -26.8 (43.31) mg/dL. Thereafter, mean LDL-C levels were generally stable over time. At the End-of-Study Visit, which occurred between Week 224 and Week 260, mean (SD) serum LDL-C concentration was 93.3 (48.53) mg/dL, representing a mean (SD) change from baseline of -35.0 (42.27) mg/dL. The effect of sebelipase alfa on mean LDL-C levels was similar in both dose cohorts.

Study LAL-CL02 : Figure 10 presents mean (SE) percent change from baseline in serum LDL-C concentrations over time from the start of treatment with sebelipase alfa; ie, prior to the Double-blind Period for the SA/SA Group and prior to the first dose of sebelipase alfa in the Open-label Period for the PBO/SA Group. For the SA/SA Group, the mean percent reduction in LDL-C levels achieved during the Double-blind Period was sustained throughout the Open-label Period. The mean change and mean percent change from baseline at Week 22, the start of the Open-label Period, were -58.8 mg/dL and -33.0%, respectively (n = 33) and the mean change and mean percent change from baseline to the last assessment in the Open-label Period were -45.4 mg/dL and -19.7%, respectively (n = 36).

For the PBO/SA Group, initiation of sebelipase alfa treatment in the Open-label Period was associated with a transient increase in serum LDL-C concentration at Week 24, ie, after 2 weeks of treatment, at which time the mean change and mean percent change from baseline were 26.7 mg/dL and 13.7%, respectively (n = 29). This transient increase in LDL-C level was similar to that observed for the SA/SA Group following initiation of treatment in the Double-blind Period. Levels of LDL-C were decreasing again by the next assessment at Week 26, ie, after 4 weeks of treatment with sebelipase alfa (mean change and mean percent change from baseline of 2.2 mg/dL and 1.0%, respectively, n = 30). A reduction relative to baseline was apparent by Week 28, ie, after 6 weeks of treatment with sebelipase alfa (mean change and mean percent change from baseline of -14.3 mg/dL and -7.7%, respectively, n = 27). Further reductions in LDL-C were apparent through approximately Week 50; ie, after 28 weeks of treatment with sebelipase alfa, at which time the mean change and mean percent change from baseline were -56.3 mg/dL and -27.9%, respectively (n = 28). These improvements in LDL-C were sustained during long-term treatment with sebelipase alfa. At the last open-label assessment, the mean change and mean percent change from baseline were -42.7 mg/dL and -18.1%, respectively (n = 30).

Study LAL-CL06 : Following initiation of treatment with sebelipase alfa, a transient increase in serum LDL-C concentration was observed at the first postdose assessment at Week 4 (Figure 15), at which time mean serum LDL-C concentration was 168.1 mg/dL (n = 28) (LAL-CL06 Week 144 CSR Table 14.2.2.1.1.2). The mean serum LDL-C concentration decreased with continued sebelipase alfa treatment and was 151.0 mg/dL at Week 8 (n = 27) (mean change from baseline -6.0 mg/dL, mean percent change -4.7%). Mean serum LDL-C concentration continued to decrease through Week 36, and thereafter remained essentially stable through Week 144. Mean serum LDL-C concentration was 131.7 mg/dL at

Week 96 (n = 25) (mean change from baseline -40.2 mg/dL, mean percent change -20.5%) and 116.5 mg/dL at Week 144 (n = 19) (mean change from baseline -54.2 mg/dL, mean percent change -31.2%).

Study LAL-CL03: Figure 17 presents individual serum LDL-C concentrations over time. Four patients had both baseline and post-baseline LDL-C data. Each of these 4 patients (01-002, 02-001, 02-003, 05-001) had an increase in serum LDL-C concentration at Week 1 of treatment, with the magnitude of this increase ranging from 5.8 to 76.1 mg/dL. Three of these 4 patients (02-001, 02-003, 05-001) also had LDL-C data at Week 2, at which time serum LDL-C levels were decreasing and continued to decrease at subsequent timepoints. The other patient (01-002) had a further increase in serum LDL-C concentration at the next available assessment at Week 32 after which serum LDL-C concentration began to decrease. After resolution of the transient increase in LDL-C, all 4 patients had serum LDL-C levels that were generally normal or below normal throughout treatment, with the exception of an isolated high value in Patient 02-003 at Week 120 and in Patient 01-002 at 2 unscheduled assessments (peak = 133.0 mg/dL at Day 631 [~Week 90]). Two patients had post-baseline LDL-C data only. The 1 patient (01-003) who had a high serum LDL-C concentration at the first available assessment at Week 1 (154.7 mg/dL) achieved a normal LDL-C level on further treatment. The other patient (02-002) had serum LDL-C concentrations that were normal at the first assessment at Week 3 and normal or below normal throughout treatment.

Study LAL-CL08: Baseline LDL-C data were available for only 3 patients. All 3 patients had an initial transient increase in serum LDL-C concentration following initiation of treatment with sebelipase alfa, with peak levels observed at Week 1, Week 2, or Week 4 and ranging from 140.00 to 212.69 mg/dL. Thereafter, serum LDL-C levels decreased with continued treatment.

2.2.5. Immunogenicity

Study LAL-CL01 : All 9 patients tested negative for ADAs at each of the 4 scheduled timepoints when this testing was performed.

Study LAL-CL04 : One patient (Patient 02-001) tested positive for ADA at a single timepoint (Week 4), with a titer of 80. This single result is unlikely to represent a true seroconversion given that all subsequent ADA results for this patient were negative. The patient tested negative for NAbs in both enzyme activity and cell uptake assays.

Study LAL-CL02 : Six patients had at least 1 confirmed positive titer for ADA during treatment with sebelipase alfa in Study LAL-CL02: 5 patients who received sebelipase alfa during the Double-blind Period and 1 patient who received sebelipase alfa only during the Open-label Period. In general, ADA titers were low and not sustained. Two patients had a positive ADA titer at only a single timepoint (Week 8 and Week 88). The other 4 patients were intermittently ADA positive. Two of the 4 patients were ADA positive by Week 4, the first postbaseline timepoint assessed, with titers of 448 and 816. Thereafter, titers decreased over time in these patients, with 1 patient testing ADA negative at all assessments after Week 12 and the other patient continuing to intermittently test ADA positive with lower titers than those observed at Week 4. Two other patients initially tested ADA positive at Week 12 or Week 42 (after 14 weeks of sebelipase alfa as the latter patient received placebo during the double-blind period); peak titers were observed at the initial ADA positive visit (titer: 35 or 310) and the patients were ADA negative at the majority of the assessments thereafter. Of the 6 patients who had ADA-positive findings, 2 patients developed NAbs: 1 patient who received sebelipase alfa during the Double-blind Period tested positive for antibodies that inhibited cellular uptake (titer: < 5 to 5) and/or enzyme activity on several occasions, and the patient who received placebo during the Double-blind Period tested positive for antibodies that inhibited cellular uptake on 1 occasion during treatment with sebelipase alfa in the Open-label Period

(titer: 5). All patients with any ADA-positive result continued to receive treatment with sebelipase alfa. At the last open-label assessment, 5 of the 6 patients tested ADA negative.

Study LAL-CL06 : Two (6.5%) of 31 patients developed ADAs to sebelipase alfa at a single post-dose timepoint (Week 4 or Week 12). The findings were transient, had low titers (< 20), and were not associated with the formation of NAbs. There was no apparent impact of ADA on sebelipase alfa PK.

Study LAL-CL03: Post-treatment immunogenicity data were available for 7 of the 9 patients; 4 of the 7 patients with post-treatment immunogenicity data had positive ADA titers on at least 1 occasion (initial ADA-positive result at Week 5 (1 patient). Week 8 (2 patients), and Week 59 (1 patient), with persistence of ADA positivity (ie, more than 1 ADA-positive result) observed for all 4 patients. Three of the 4 patients with ADA-positive titers tested positive for NAbs that inhibited LAL enzyme activity, which were concurrent with the first positive ADA titer, and/or that inhibited cellular uptake of LAL, 2 of which were concurrent with the first positive ADA titer.

Study LAL-CL08: Six (60%) of the 10 patients in the study developed ADAs to sebelipase alfa, with the initial ADA-positive result as early as Week 5. Four patients who developed ADAs on or prior to Week 12, all had high titers, with peak titers ranging from 46,774 to 302,963. One patient who first developed ADAs at Week 20 had a moderate titer that peaked at 2,958 at the Week 84 Visit. One patient who had a more delayed onset of ADAs at Week 60 continued to have low titers throughout treatment, with a peak titer of 292 at the follow-up visit. All 6 patients developed NAbs. Further details on the time course for development of ADAs/NAbs, and relationship to dose, are provided in LAL-CL08 CSR.

Integrated analysis:

Across all 6 clinical studies, 19 of 125 (15%) patients had at least 1 postbaseline ADA positive result: 9 children or adults and 10 infants. For children and adult patients with LAL-D, ADA positivity was transient with generally low titers of ADAs reported. On the other hand, persistence of ADA positivity (ie, observation of more than 1 ADA-positive result) was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants.

Eleven of the 19 patients who developed ADAs also developed NAbs during treatment with sebelipase alfa: 2 children or adults and 9 infants.

A quantitative assessment of effect of immunogenicity on exposure was performed using a covariate analysis methodology on the Pop-PK model (N = 75). The effect of time-varying ADA on CL was not significant and the covariate was not retained in the model. The effect of NAb was not formally tested in the Pop-PK model due to the low number of samples with both a measurable concentration and a positive NAb (ie, a total of 1 positive NAb in 1 patient).

Rapporteur's comments

Concerning immunogenicity, the MAH has investigated the overall impact of ADA on exposure using a covariate analysis methodology on the final Pop-PK model. But the total number of patients with samples with measurable concentrations of sebelipase alfa and an ADA status used in this analysis is limited in comparison to the totality of data provided (3 ADA+ on 19 ADA+ in total; 72 ADA- on 106 ADA- in total). The effect of NAb was not formally tested in the population PK model due to the low number of samples with both a measurable concentration and a positive NAb (ie, a total of 1 positive NAb in 1 patient). Thus no conclusion can be currently drawn in relation to PK due to the limited information available. The SmPC should be updated in that sense, unless otherwise justified.

2.2.6. Population PK Model results

Parameter estimates of sebelipase alfa derived with the final population model (run219) as well as between-subjects and residual error parameters are presented in Table 5.

Table 5: Final Population PK Model (run219): Sebelipase Alfa Parameter and Covariate Estimates

Parameter	Estimates	BSV[a]	RSE[c]	Shrinkage	IOV
CL (L/h) Body weight	34.4 $\times (WT/70)^{0.460}$	0.185 (45.0%)	11.1%	17.5%	26.6%
Q (L/h)	1.57	0.298 (59.0)[b]	23.2%	NA	NA
Vc (L) Body weight	4.45 $\times (WT/70)^{0.264}$	0.598 (90.5%)	14.9%	21.6%	NA
Vp (L)	5.98	NA	66.5%	NA	NA
Error model					
Proportional error (%)	0.535	NA	3.2	10.2%	NA
Additive error (ng/mL)	0.0447, Fixed	NA	NA	NA	NA

Note: Parameters are for a typical 70-kg patient, with a body weight of 70 kg. Additional model parameters are presented in Appendix 2 (Section 10.3.1).

[a] BSV is presented as the variance of the random effect (η_i), with the % coefficient of variation ($100 \times (\exp(\omega^2)-1)^{0.5}$) in parentheses.

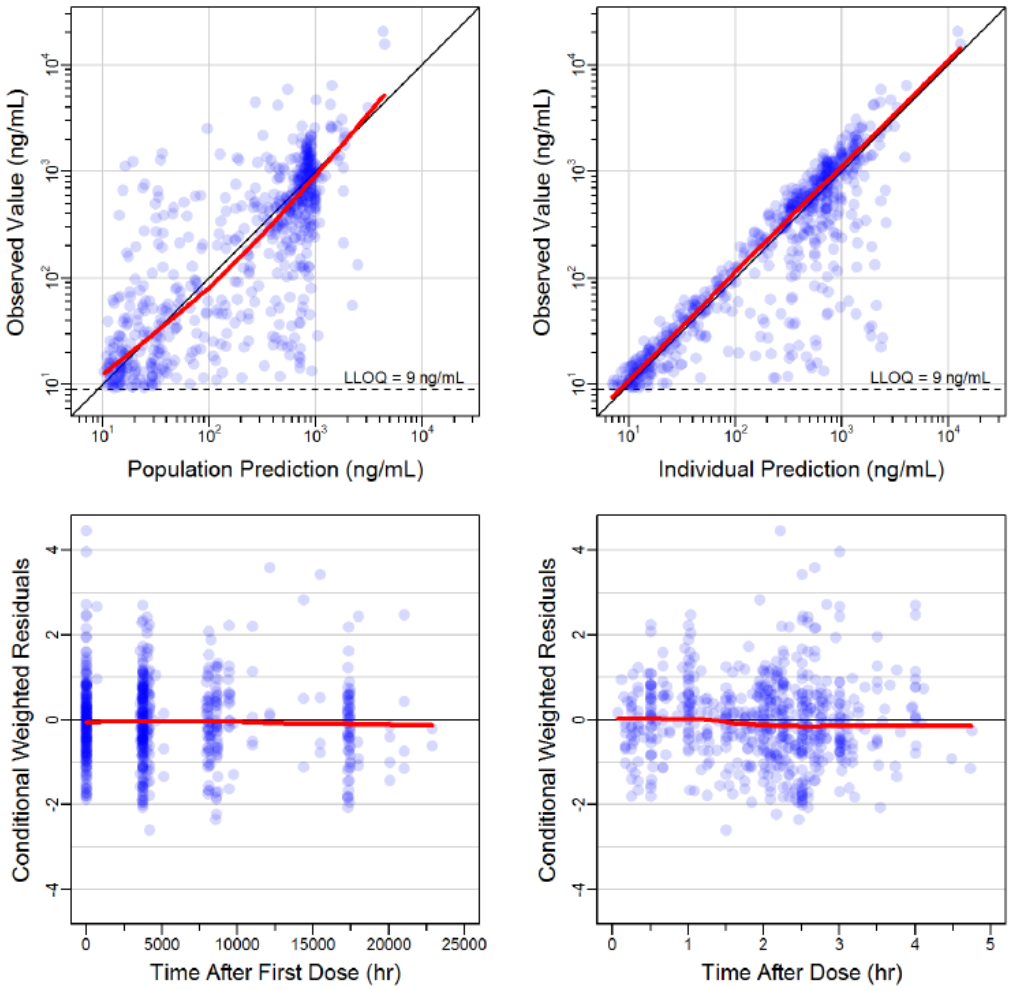
[b] The variance of Q was derived based on a shared ETA of CL which was scaled using a factor of 1.27 (i.e., $0.185 \times (1.27)^2 = 0.298$) and the % coefficient of variation as described above.

[c] The RSE is the relative standard error of the population PK estimate.

Abbreviations: BSV = between-subject variability; CI = confidence interval; CL = clearance; IOV = inter-occasion variability; NA = not applicable; Q intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment; WT = body weight (kg) for each instance of dosing (time-varying).

Goodness-of-fit derived with the final population PK model is presented in Figure 4.

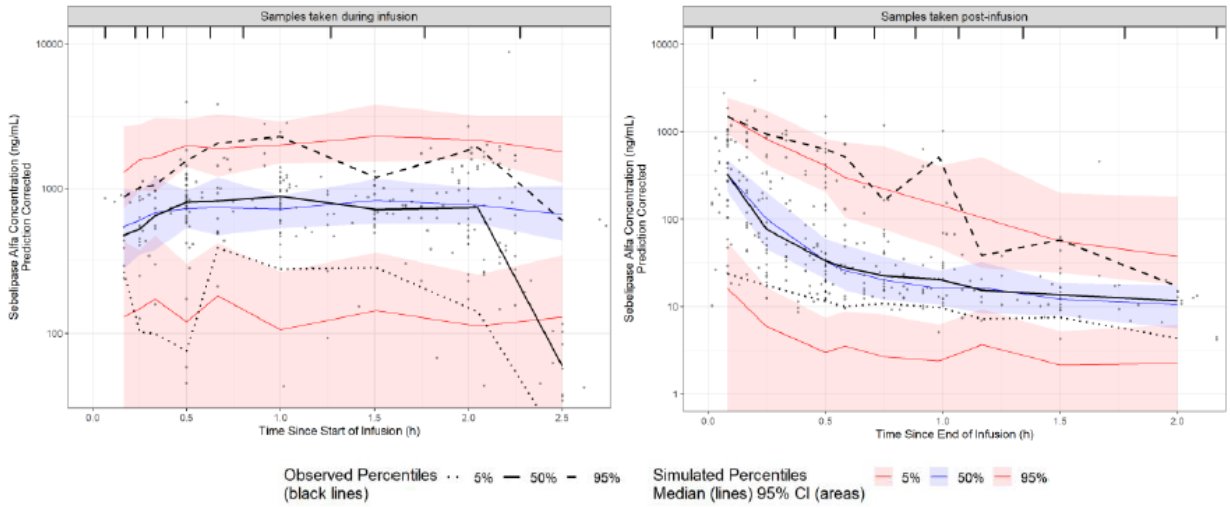
Figure 4: Final Population PK Model of Sebelipase Alfa (run219): Goodness-of-Fit



Abbreviations: LOESS = locally weighted scatter-plot smoothing; PK = pharmacokinetics.

The final model was evaluated by performing a prediction-corrected VPC with 500 simulation replicates. Results of the prediction-corrected VPC (time after dose) on a semi-log scale from the start of infusion is presented in Figure 5.

Figure 5: Final Population PK Model of Sebelipase Alfa (run219): Prediction-corrected Visual Predictive



Notes: The prediction-corrected visual predictive check (pcVPC) retains the visual interpretation of the traditional visual predictive check (VPC) while removing the variability that arises from binning across independent variables by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin.

Abbreviations: CI = confidence interval; pcVPC = prediction-corrected visual predictive check; PK = pharmacokinetics; VPC = visual predictive check.

Rapporteur's comments

The reliability of the model to support the claimed conclusion by the applicant is questioned in particular for children of lowest age groups (<2 years old and from 2-4 y.o).

The assessment of bodyweight effect on clearance and volume of distribution with an estimated exponent is not supported in view of the limited data in the lower age subgroup: data from only 9 patients of < 4 years old were available. Bodyweight should be inputed in the model using allometric scaling with fix exponents of 0.75 and 1 for CL and V parameters, respectively. Additional effect of age/maturation should be tested on this model already including body weight effects.

Nonlinear clearance should also be tested using individual predicted concentrations as exposure marker.

It is noted that Vp parameters was poorly estimated with RSE of 66%, this should be discussed, particularly in light of data exclusion.

Model misspecifications are observed on the IPRED vs OBS and in the pcVPC graphics: this should be further discussed.

Model fitting performances (GOF nad pcVPC) should also be provided by age subgroups.

NPDEs distribution should also be provided as well as NPDE vs PRED and vs time plots.

The applicant is asked to perform additional simulations using the final updated model and identify alternative dosing weight bands leading to comparable PK exposure in adults and in different subgroups of children.

2.2.7. Population PK/PD Modeling results

PK/PD Analysis of ALT

The PK/PD analysis of ALT was performed based on data collected in LAL-CL02 (patients ≥ 4 years) and LAL-CL03 (patient less than 8 weeks) up to 52 weeks. PK/PD modeling of ALT was performed based on data collected up to 52 weeks in study LAL-CL02 and LAL-CL03. Median (5th to 95th percentile) profiles of ALT following repeated administration of sebelipase alfa are presented in Figure 6. A rapid decline in ALT was observed after initiation of sebelipase alfa treatment in study LALCL02 and LAL-CL03. The suppression of ALT concentrations was sustained following prolonged administration. An indirect PD response model with a zero-order production of ALT response and an inhibitory effect of sebelipase alfa on the zero-order production of ALT was used. Parameter derived with the PK/PD model for ALT are presented in Appendix 3 (Sections 11.1). Due to the very rapid decrease in ALT, the IC50 could not be robustly estimated (i.e., values close to zero). As a result, the IC50 in the effect compartment was fixed to 1 ng/mL. The population estimates of baseline (E0), Imax and Kout were 97.3 U/L, 0.601, and 0.00398 h-1, respectively. These above E0, Imax and Kout values were robustly estimated with RSE values less than 20%. A study effect (LAL-CL03) on baseline (E0) was observed suggesting that infants presented a baseline ALT approximately 14% lower than that observed in study LAL-CL03. Based on the estimated Imax, the rate of production of ALT (Kin) in study LAL-CL02 and LALCL03 were similar (i.e., a maximum of 59.9% and 64.8%, respectively). The goodness-of-fit derived with the PK/PD model of ALT and individual observed and predicted concentration-time profiles of ALT are presented below.

11.2. PK/PD Modeling of ALT – Goodness-of-Fit

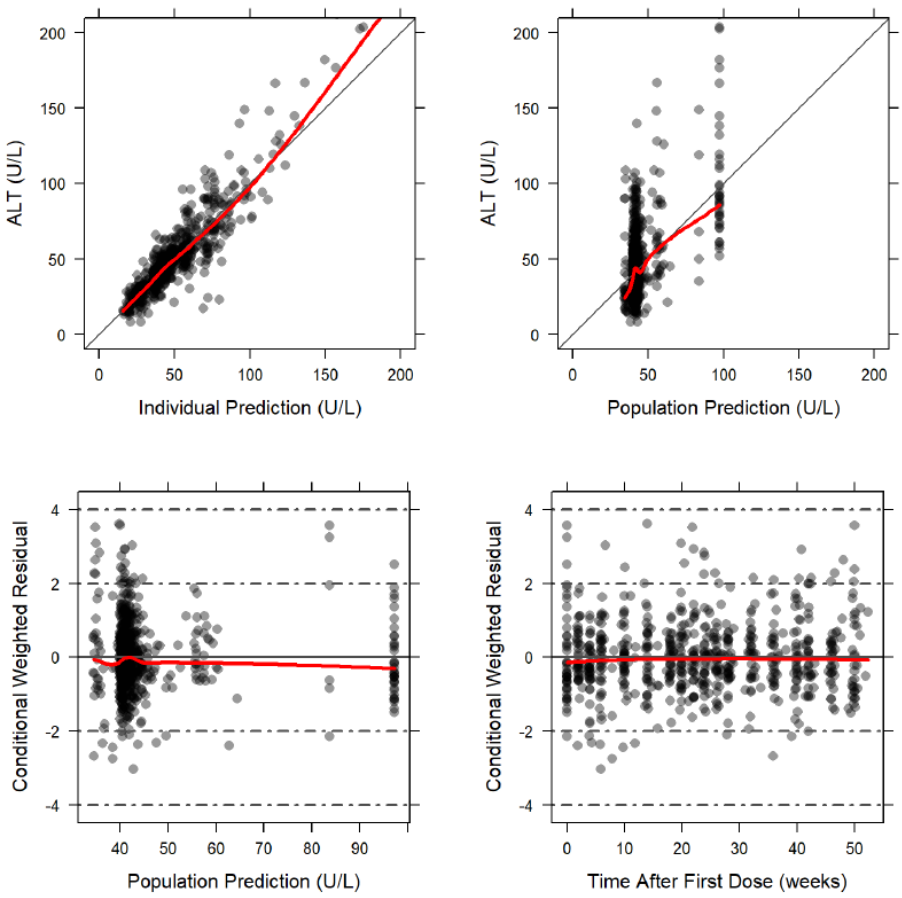
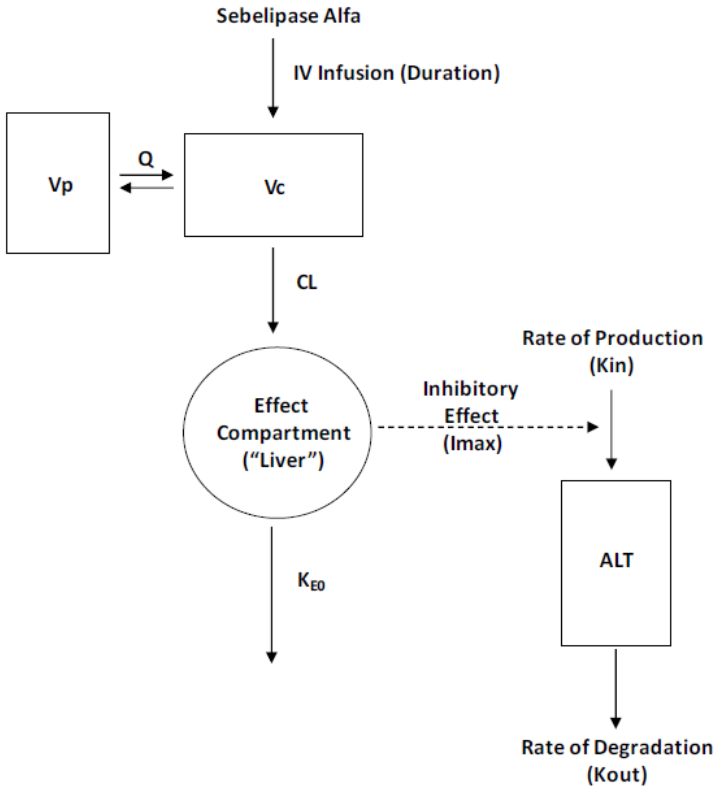


Figure 1: Schematic Representation of the PK/PD Model for the Effect of Sebelipase Alfa on ALT



Abbreviations: ALT = alanine aminotransferase.; CL = clearance; Vc = central volume of distribution; Q = peripheral clearance; Vp = peripheral volume of distribution; K_{E0} = first-order rate of elimination from the effect compartment, K_{in} = zero-order rate of synthesis of ALT, K_{out} = first-order rate of degradation of ALT; I_{max} = maximum inhibition.

PK/PD Analysis of LDL Cholesterol

The PK/PD analysis of LDL cholesterol was performed based on data collected in LAL-CL02 (patients ≥ 4 years) and LAL-CL03 (patient less than 8 weeks) up to 52 weeks. Final model parameters as well as goodness of fit plots and simulated levels using the models are displayed below.

11.4. PK/PD Modeling of LDL Cholesterol – Parameter Estimates

Parameter	Point estimate	RSE%	95% CI
Typical Values			
E_0 (U/L)	4.98	12.2	3.79 – 6.17
E_{max} (fraction)	0.759	23.5	0.409 – 1.11
EC_{50} (ng/mL)	1.00 Fixed	NA	NA
K_{out} (h^{-1})	0.000310	46.0	0.0000308 – 0.000589
K_{e0} (h^{-1})	0.00400 Fixed	NA	NA
K_{pool} (h^{-1})	0.0203	81.8	-0.0122 – 0.0528
Pool initial amount (U/L)	0.360	137	-0.609 – 1.33
Covariate Effect			
Study LAL-CL03 on E_0	0.639	25.9	0.385 – 1.06
Between Subject Variability			
On E_0	0.369	15.3	0.258 – 0.480
On I_{max}	0.588	16.5	0.398 – 0.778
Residual Error			
Proportional Error (%)	0.179	6.21	0.157 – 0.201

Abbreviations: CI = confidence interval; E_0 = baseline; EC_{50} = concentration in the effect compartment associated with 50% of the maximum effect; E_{max} = maximum effect; K_{e0} = rate of elimination of concentration from the effect compartment; K_{out} = rate of degradation; K_{pool} = rate of degradation of LDL from liver to plasma; NA = not applicable; Pool initial amount = accumulated amount in the liver compartment; RSE = relative standard error.

11.5. PK/PD Modeling of LDL Cholesterol – Goodness-of-Fit

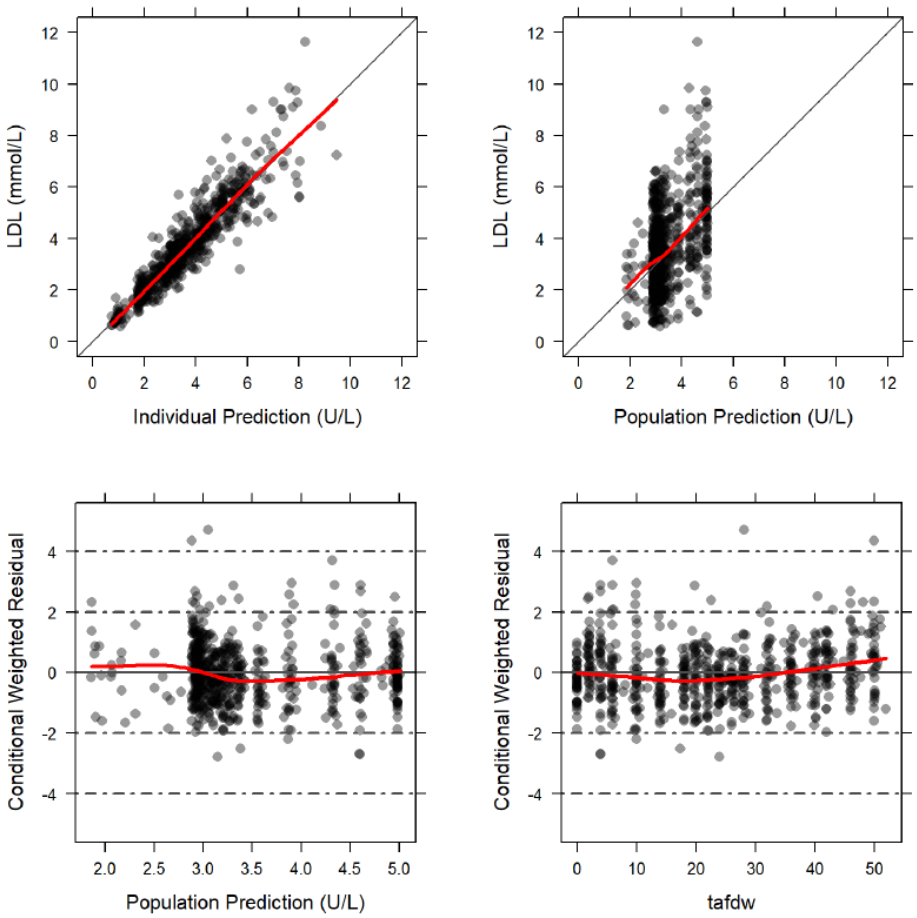
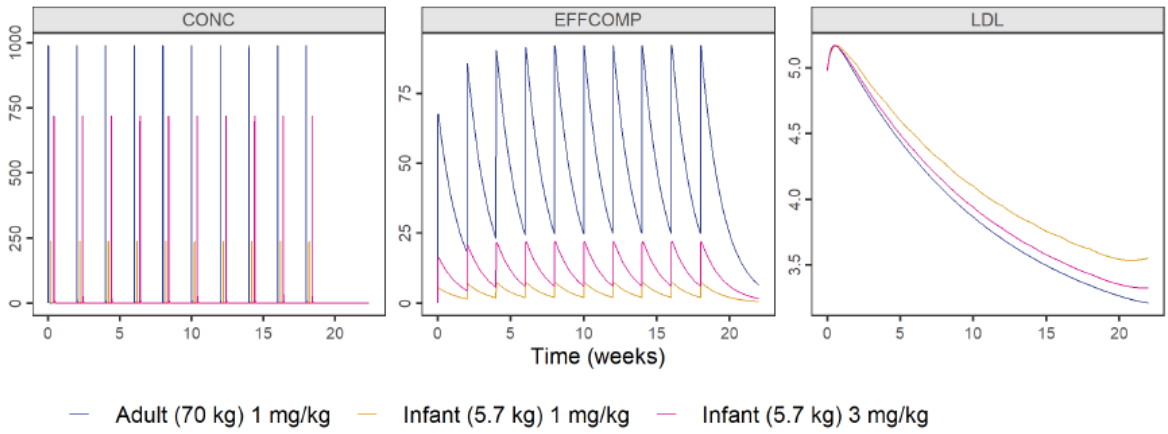


Figure 9: Model Predicted Concentration-Time Profiles of Sebelipase Alfa and LDL in Typical Adult and Infant Patients



Rapporteur's comments

The choice of the 2 PD markers for the modelling exercise need to be better substantiated, as well as acceptance criteria and target levels to be reached for the selected dosing regimens.

Following issues were identified in the 2 PK/PD models:

The exclusion of placebo arm data from the PK/PD analysis is not acceptable given that these data could be informative for adequate description of the time course of the 2 biomarkers.

The selection of the structural model in particular absence of testing alternative structural model with drug clearance from the central compartment and outside the effect compartment need to be justified for both ALT and LDL-cholesterol.

Key parameters (e.g. IC50 and EC50) were fixed without justifications of the source and the plausibility of the values used.

PcVPC should be provided and were not.

Model fitting performances (GOF nad pcVPC) should also be provided by age subgroups.

NPDEs distribution should also be provided as well as NPDE vs PRED and vs time plots.

Based on all the above, it is not acceptable that the PK/PD models are used to justify the adequacy of the proposed dosing regimens and the proposed changes in the SmpC.

2.3. Discussion

As a result of updated clinical pharmacology data mainly related to the final POPPK model results and PK/PD model results presented in this variation, sections 4.2 and 5.2 of the SmPC are being updated:

"4.2 Posology and method of administration

KANUMA treatment should be supervised by a healthcare professional experienced in the management of patients with LAL deficiency, other metabolic disorders, or chronic liver diseases. KANUMA should be administered by a trained healthcare professional who can manage medical emergencies.

Posology

It is important to initiate treatment as early as possible after diagnosis of LAL deficiency.

For instructions on the preventive measures and monitoring of hypersensitivity reactions, see section 4.4. Following the occurrence of a hypersensitivity reaction, appropriate pre-treatment should be considered according to the standard of care (see section 4.4).

Infants (< 6 months of age)
The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation up to 5 mg/kg once weekly should be considered based on clinical response.

Children and adults
The recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to 6 months of age is 1 mg/kg administered as an intravenous infusion once every other week. Dose escalation to 3 mg/kg once every other week should be considered based on clinical response.

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.

Paediatric population
Administration of KANUMA to infants with confirmed multiple-organ failure should be at the discretion of the treating physician.

Overweight patients
The safety and efficacy of KANUMA in overweight patients have not been thoroughly evaluated and therefore no alternative dose regimens can be recommended for these patients at this time.

Elderly population (≥ 65 years old)
The safety and efficacy of KANUMA in patients older than 65 years have not been evaluated and no alternative dose regimens can be recommended for these patients. See section 5.1.

5.2 Pharmaco-kinetic properties

Children and adults
The pharmacokinetics of sebelipase alfa in children and adults were determined using a population pharmacokinetic analysis of 75 patients with LAL deficiency who received intravenous infusions of KANUMA across 4 clinical studies LAL-CL02, LAL-CL03, LAL-CL04 and LAL-CL06 (Table 4). Based on a non-compartmental analysis of data, the pharmacokinetics of sebelipase alfa are nonlinear with a greater than dose-proportional increase in exposure observed between the 1 and 3 mg/kg dosages. No

accumulation is seen at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly.

Table 4: Summary of Pharmacokinetic Parameters for Repeated Administrations of 1 mg/kg Sebelipase Alfa in Patients With LAL Deficiency by Age Group

Parameter	Infants Age < 2 years (N = 4) Mean (CV%)	Children Age 2 to < 18 years (N = 44) Mean (CV%)	Adults ≥ 18 years (N = 24) Mean (CV%)
CL (L/h)	16.1 (45.5)	26.2 (50.7)	37.7 (39.4)
Q (L/h)	2.02 (36.2)	1.57 (40.1)	1.68 (38.8)
V_c (L)	3.25 (62.6)	3.91 (53.6)	6.45 (95.1)
V_{ss} (L)	9.23 (22.0)	9.89 (21.2)	12.4 (49.3)
$t_{½\beta}$ (h)	2.58 (36.9)	3.51 (61.1)	3.05 (46.7)

Note: Data for infants are from Study LAL-CL03, data for children are from Studies LAL-CL02 and LAL-CL06, and data for adults are from Studies LAL-CL02, LAL-CL04, and LAL-CL06.
CL = clearance; PK = pharmacokinetic(s); Q = peripheral clearance; $t_{½\beta}$ = terminal elimination half-life; V_c = central volume of distribution; V_{ss} volume of distribution at steady-state.

Predicted exposure parameters of sebelipase alfa from clinical trials are presented by age group in Table 5.

Table 5: Summary of Exposure Parameters of Sebelipase Alfa by Age Group in Patients With LAL Deficiency Based on Simulations

Parameter Statistic	Infants (Age < 2 years)		Children (Age 2 < 18 years)	Adults (Age ≥ 18 years)	Overall
	1 mg/kg (N = 4)	3 mg/kg (N = 4)	1 mg/kg (N = 44)	1 mg/kg (N = 24)	1 mg/kg (N = 4)
AUC_{ss} (ng × h/mL) Mean (CV%)	487 (44.7)	1460 (44.7)	1560 (57.0)	2070 (41.4)	1670 (55.4)
$C_{max,ss}$ (ng/mL) Mean (CV%)	226 (44.0)	677 (44.0)	746 (56.7)	993 (39.5)	799 (54.8)

Note: Data for infants are from Study LAL-CL03, data for children are from Studies LAL-CL02 and LAL-CL06, and data for adults are from Studies LAL-CL02, LAL-CL04, and LAL-CL06.
AUC_{ss} = area under the curve under steady state; $C_{max,ss}$ = maximum concentration under steady state; CV = coefficient of variation; LAL = lysosomal acid lipase.

Linearity/non-linearity

Based on these data, the pharmacokinetics of sebelipase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure observed at doses greater than 1 mg/kg dose.

Special populations

During the covariate analysis of the population pharmacokinetics model for sebelipase alfa, age, sex and enzyme maturation were found to not have a significant influence on CL (drug clearance) and V_c (central volume of distribution) of sebelipase alfa. Body weight and body surface area are significant covariates on CL. Sebelipase alfa has not been investigated in patients aged 65 years or older.

There is limited information on sebelipase alfa pharmacokinetics in non-Caucasian ethnic groups.

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

As with all therapeutic proteins, there is the potential for the development of immunogenicity. Nineteen of 125 (15%) patients with LAL Deficiency had at least 1◦postbaseline antidrug antibody (ADA) positive result, 9 of which were children and adult patients. For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported. No apparent correlation of antibody development to altered sebelipase alfa pharmacokinetics was observed.

However, concerns are raised about the validity of the entire set of PK data reported as a result of the disqualification of a substantial number of PK study sample results due to data integrity issues during

study sample analysis. Overall, the conclusions drawn on the pharmacokinetics of sebelipase alpha are questioned and an inspection may be warranted depending on the guarantee provided by the MAH at the next round .

In addition to non-reportable samples due to data integrity issue, a number of samples were also considered as non-reportable because they were analysed beyond the validated long-term stability range. Therefore, the summarized non-compartmental PK parameters observed in individual studies LAL-CL04 and LAL-CL06 were based on a limited number of patients for several subgroups. As a consequence, the comparison of the non-compartmental PK parameters between the different categories of age and different doses is compromised. According to the MAH, all the new reportable PK data would be included in the updated population PK analysis. But before the information provided in the SmPC can be considered acceptable, clarifications should be given on the PK samples considered for inclusion in the POPPK analysis (n = 880) in comparison to the PK samples considered as having reportable results from a bioanalytical point of view (n = 1122). The studies with data integrity issues and errors in dosing records should be excluded (i.e. studies LAL-CL01 and LAL-CL08).

Moreover, due to the limited data in the lower age subgroup (only 9 patients of < 4 years old), a major objection has been raised regarding the strategy used to investigate the effect of bodyweight on the clearance and volume of distribution in the POPPK model. Moreover, additional effect of age/maturation should be tested on this model. In view of the identified issues with data integrity/out-of-stability and related data exclusion, the applicant is also asked to provide the distribution of the data used for POPPK modelling by age group and to discuss whether there were enough data in the different age subgroups (<2, 2-4, 4-6, 6-12, and 12-18 y.o) to allow adequate PK characterization in the different age groups. Additional limitations and uncertainties have been identified in the population PK modelling that need to be satisfactorily addressed before conclusions from PK modelling can be used to update the section 5.2 of the SmPC.

Furthermore, a number issues have been identified preventing the use of POPPK and PK/PD models to justify the adequacy of the proposed dosing regimens and the proposed changes in the SmpC.

Regarding the bioanalytical method used for the determination of sebelipase alpha, a number of bioanalytical issues are still pending regarding the specificity, selectivity in lipeamic serum, the higher variability than commonly accepted and missing parallelism data for patients aged < 1 year old. But given (i) the acceptable results for the overall ISR analysis for reportable PK samples and the acceptable results for the additional parallelism experiments provided in addition to the original MAA dossier; and (ii) the orphan status of the disease and the unmet medical need of the disease, it is considered that they would not have an impact on the positive benefit/risk balance for children of > 4 years old.

Concerning immunogenicity, the MAH has investigated the impact of ADA on exposure using a covariate analysis methodology on the final Pop-PK model. But the total number of patients with samples with measurable concentrations of sebelipase alfa and an ADA status used in this analysis is limited in comparison to the totality of data provided (3 ADA+ on 19 ADA+ in total; 72 ADA- on 106 ADA- in total). The effect of NAb was not formally tested in the population PK model due to the low number of samples with both a measurable concentration and a positive NAb (ie, a total of 1 positive NAb in 1 patient). Thus no conclusion can be currently drawn in relation to PK due to the limited information available. The SmPC should be updated in that sense, unless otherwise justified. In addition, the adequacy of the pre-study cut points for the target population should be discussed.

Regarding the modifications in the section 5.2, some updates are already proposed :

- it should be clarified in the title of the table 5 that the parameters were simulated after multiple dose.

- the table 5 is not in line with the table 8 of the PK/PD simulation report. As an example, the total number N for overall subjects is discrepant (N=72 vs N=4). This should be addressed.
- The conclusions on the linearity of sebelipase alpha PK and accumulation over time are drawn based on the non-compartmental analysis in study LAL-CL04 and in study LAL-CL04 and LAL-CL06, respectively. But the number of patients in each category of age was limited and should be reflected in the SmPC. In study LAL-CL04, no accumulation was seen at 1 mg/kg once every other week (qow) or 3 mg/kg qow based on the absence of any increase in pre-infusion concentrations of sebelipase alfa in Study LAL-CL04 (pre-dose < 9.375 ng/ml = LLOQ in all subjects apart from the 1 instance, but considered as biologically implausible and excluded from PK analysis) and the overall lack of increase in the median values for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} over time. In study LAL-CL06, there was no evidence of accumulation following 1 mg/kg dose administration qow. These results are in line with the information reported in the SmPC based on non-compartmental results. But the lack of sign of accumulation for the 3 mg/kg qow dosing is not reported in the SmPC. Instead, lack of accumulation at 3 mg/kg once weekly is mentioned. It should be clarified if the source of this information is the study LAL-CL01 while all the PK samples from this study were disqualified because they were outside the validated stability range. These issues should be addressed and the SmPC updated accordingly.

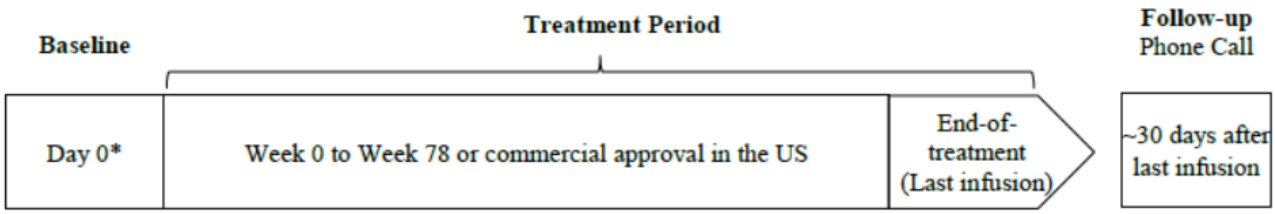
3. Clinical Efficacy aspects

3.1. Efficacy analysis of the completed study LAL-EA01

LAL-EA01 was and open-label expanded access study which meant to allow access to treatment for patients, not eligible for participation in any of the clinical trails, in the US until commercialization of the drug.

After a baseline assessment patients started treatment with sebelipase alfa for up to 78 weeks or until commercial product became available, and all started with an initial dosing od 1mg/kg qow, with permitted dose increases up to 3mg/kg qw based on responses to treatment.

Assessments were done throughout, and a AE-focused follow-up call was done at most 30 days after the last dosing, and those transitioning to commercial product also had to come in for a clinic visit. Figure 1 provides an overview of the study flow and Table 1 an overview of the scheduled assesments:



*Baseline assessments performed on the same date as the first infusion of study drug are reported as occurring on relative Day 1.

Figure 2: *Study Flow Diagram*

Table 13: *Study Design and Schedule of Assessments*

Assessment[a]	Day 0 (Baseline[b])	Every Week[c]	Every 2 Weeks	Every 4 Weeks	Every 12 Weeks	Every 24 Weeks	EOT or ET[d]	Follow-up[e]
Informed Consent/Assent	X							
Inclusion / Exclusion Criteria	X							
Medical History	X							
Confirmation of LAL deficiency	X							
Physical Examination	X				X		X	
Height (patients ≤ 2 years)	X		X				X	
Weight (patients ≤ 2 years)	X		X				X	
Height (patients > 2 years)	X						X	
Weight (patients > 2 years)	X		X				X	
Clinical Laboratory Tests[f]	X				X		X	
Pregnancy Test[g]	X			X			X	
Anti-drug Antibody	X						X	
Vital Signs[h]	X	X[c]	X				X	
Sebelipase Alfa IV Infusion[i]		X[c]	X					
Concomitant Medications[j]	X----------						----------X	
Adverse Events	X----------							----------X

[a] All assessments (including unscheduled assessments performed per site's standard of care) were recorded on the eCRF.
[b] Baseline assessments performed on the same date as the first infusion of study drug are reported as occurring on relative Day 1.
[c] The "every week" assessments were to be completed only for subjects who switched to a qw regimen. No subject in this study switched to qw regimen.
[d] End-of-treatment is defined as Week 78 or when commercial approval of sebelipase alfa was granted in the United States (whichever came first). In the event of commercial approval, patients were required to return to the study center within 28 days of commercial approval to undergo EOT assessments.
[e] All patients received a follow-up phone call at least 30 days after receiving the last dose of non-commercial study drug, to assess adverse events.
[f] Refer to Section 5.8 of the protocol (Appendix 16.1.1) for a list of clinical laboratory tests. Clinical laboratory tests were not repeated at the EOT or ET visit if obtained within the preceding 4 weeks.
[g] Only for female patients of childbearing potential.
[h] On dosing days, vital signs were recorded at the commencement of the infusion and at the end of the infusion
[j] Concomitant medications collection started on Day 1; however, patients were also queried regarding medications that were stopped just prior to dosing (e.g., lipid-lowering therapy)
Abbreviations: ADA = anti-drug antibody; eCRF = electronic case report form; EOT = End-of-treatment; ET = Early termination; IV = intravenous; LAL = lysosomal acid lipase; qw = once weekly

Methods & Results – analysis of data submitted

3.1.1. Variables analysed

As the study was designed to primarily evaluate the safety of IV infusions of sebelipase alfa the following outcome variables were selected:

- Incidence of TEAEs, SAEs, and IARs
- Changes from baseline in clinical laboratory tests (hematology, coagulation, serum chemistry, lipid panel, and ADA titers)
- Changes in vital signs after the infusion relative to pre-infusion values
- Physical examination findings
- Use of concomitant medications, therapies, or procedures

Additionally the following efficacy outcomes were also to be collected:

- Decrease in ALT
- Decrease in AST•Decrease in LDL-C
- Increase in HDL-C
- Decrease in non-HDL-C
- Decrease in triglycerides

- Total and conjugated bilirubin
- Gamma-glutamyltransferase (GGT)
- Markers of macrophage activation, including absolute reductions in serum ferritin, serum chitotriosidase and high-sensitivity C-reactive protein (hs-CRP)
- Hemoglobin level
- Platelet count

Additionally, in paediatric patients the following additional efficacy parameters were also collected:

- For patients ≤ 24 months of age, z-scores and percentile scores based on World Health Organization (WHO) growth charts (WHO Multicentre Growth Reference Study Group, 2006 and 2007) will be determined for the following parameters:
    - Weight-for-age (WFA)oWeight-for-length
    - Length-for-age
    - Body mass index-for-age (BMIA)
    - Head circumference-for-age
- For patients > 24 months of age to 18 years, z-scores and percentile scores based on Center for Disease Control and Prevention (CDC) growth charts will be determined for the following parameters:
    - WFA
    - Weight-for-stature (weight-for-height)
    - Stature-for-age (SFA)
    - BMIA
- For all patients < 18 years, the proportion of patients who meet criteria for under nutrition (underweight, wasting, and stunting) based on WFA, weight-for-length/weight-for-stature, and length-for-age/SFA, respectively (UNICEF, 2009), and combinations of these indicators, will be determined.

3.1.2. In- and Exclusion criteria

Inclusion Criteria

1. Patient will be ≥ 8 months of age at commencement of treatment with sebelipase alfa.
2. Patient has a confirmed diagnosis of LAL Deficiency.
3. Patient or patient's parent or legal guardian (if applicable) consents to participation in the study. If the patient is of minor age, he/she is willing to provide assent where required per local regulations, and if deemed able to do so.
4. Male and female patients of childbearing potential must use a highly reliable method of birth control (expected failure rate less than 5% per year) from the time they commence treatment through 4 weeks after the last dose of sebelipase alfa.
5. Women of childbearing potential must have a negative serum pregnancy test at commencement of treatment with sebelipase alfa.

Exclusion Criteria

1. Women who are nursing or pregnant.
2. Patients who received an investigational product within 30 days (for a small molecule) or 60 days (for a biologic) of commencing treatment, and which in the opinion of the investigator or Sponsor, may negatively impact patient safety.
3. Patients who have received sebelipase alfa as part of a clinical trial that is currently active.
4. Patients with known hypersensitivity to eggs

3.1.3. Disposition, demographics and baseline characteristics

A total of six patients were enrolled, and all (100%) received treatment until completion. At the time of reporting all subjects transitioned to commercial product. The FAS was compromised of all 6 subjects.

All subjects where white males, with one adult in his forties and 5 paediatric subjects (between 10.3 and 17.4 years of age) of which 4 were siblings at time of study entry.

The most frequently reported LAL deficiency clinical manifestations on medical history included dyslipidemia, hepatic steatosis, hepatomegaly, and splenomegaly. The 1 adult subject in the study was also noted to have portal hypertension and esophageal varices, both of which had an onset approximately 39 years after the subject was diagnosed with LAL deficiency and approximately 1 year prior the subject's initiation of treatment with sebelipase alfa under this protocol.

Baseline growth impairment was noted in 4 of the 5 pediatric subjects, having weight-for-age (WFA) percentiles ranging from 7.8% to 48.57% and length-for-age (LFA) percentiles ranging from 0.45% to 30.52% at baseline. The one other pediatric subject in the study had a WFA of 84.04% and LFA of 49.47% at baseline. The adult subjects was obese and of normal height.

Anthropometric data for the 5 pediatric subjects in the study indicated maintenance of growth status during treatment with sebelipase alfa. While modest increases in WFA percentile were observed following initiation of sebelipase alfa therapy in the 4 pediatric subjects with baseline WFA percentiles below the 50th centile at baseline, this improvement in WFA was sustained through EOT in only 2 of the 4 subjects.

No subject had a WFA percentile that crossed (either improving or worsening) a major centile line during the study.

3.1.4. Efficacy analysis

All 6 subjects showed decreases in ALT and AST (figures and respectively), with 5 and subjects respectively achieving normalisation at EOT. Similarly, GGT and ALP levels also improved. All 6 patients had decreases in total cholesterol and LDL-c, with 5 of 6 patients continuing to improve through EOT. The other patient initially improved but was diagnosed with an increase in LDL-c levels at EOT.

Table 14: *Liver Biochemical Parameters Shift Table for Change From Baseline by Visit (FAS)*

			Post-Baseline			
Parameter	Visit	Baseline	Below LLN	Within NR	Above ULN	Missing
Alkaline Phosphatase (IU/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	2 (33.3)	0	0
		Above ULN	0	1 (16.7)	0	0
		Missing	0	3 (50.0)	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	1 (16.7)	1 (16.7)	0
		Above ULN	0	1 (16.7)	0	0
		Missing	0	3 (50.0)	0	0
Alanine Aminotransferase (IU/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	0	6 (100.0)	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	2 (33.3)	4 (66.7)	0
		Missing	0	0	0	0
Aspartate Aminotransferase (IU/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	3 (50.0)	3 (50.0)	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	5 (83.3)	1 (16.7)	0
		Missing	0	0	0	0
Bilirubin (umol/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	3 (50.0)	0	0
		Above ULN	0	1 (16.7)	2 (33.3)	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	3 (50.0)	0	0
		Above ULN	0	0	3 (50.0)	0
		Missing	0	0	0	0
Gamma Glutamyl Transferase (IU/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	1 (16.7)	0	0
		Above ULN	0	3 (50.0)	2 (33.3)	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	1 (16.7)	0	0
		Above ULN	0	4 (66.7)	1 (16.7)	0
		Missing	0	0	0	0

Table 15: *Serum Lipids Shift Table for Change From Baseline by Visit (FAS)*

			Post-Baseline			
Parameter	Visit	Baseline	Below LLN	Within NR	Above ULN	Missing
Cholesterol (mmol/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	1 (16.7)	5 (83.3)	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	2 (33.3)	4 (66.7)	0
		Missing	0	0	0	0
HDL Cholesterol (mmol/L)	Week 12	Below LLN	4 (66.7)	2 (33.3)	0	0
		Within NR	0	0	0	0
		Above ULN	0	0	0	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	3 (50.0)	3 (50.0)	0	0
		Within NR	0	0	0	0
HDL Cholesterol (mmol/L)	End Of Treatment	Above ULN	0	0	0	0
		Missing	0	0	0	0
LDL Cholesterol (mmol/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	0	6 (100.0)	0
		Missing	0	0	0	0
	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	0	0	0
		Above ULN	0	1 (16.7)	5 (83.3)	0
		Missing	0	0	0	0
Triglycerides (mmol/L)	Week 12	Below LLN	0	0	0	0
		Within NR	0	5 (83.3)	0	0
		Above ULN	0	1 (16.7)	0	0
		Missing	0	0	0	0
Triglycerides (mmol/L)	End Of Treatment	Below LLN	0	0	0	0
		Within NR	0	5 (83.3)	0	0
		Above ULN	0	1 (16.7)	0	0
		Missing	0	0	0	0

Serum ferritin and hs-CRP levels were essentially unchanged during treatment with sebelipase alfa, with levels remaining within normal range (5 subjects) or above normal (1 subject) at baseline and throughout the study.

A total of 4 subjects presented with evidence of coagulopathy at baseline, of which 2 subjects had improvements by the EOT visit.

3.1.5. Conclusion and discussion

Efficacy analysis was not an objective of the EA study. However, clinical laboratory and physical examination assessments done as part of the safety analysis also provided information regarding clinical benefit of treatment.

Sebelipase alfa treatment resulted in rapid and marked improvements in LAL deficiency-related liver dysfunction and dyslipidemia in all 6 subjects in this study. Serum transaminases, which were elevated at baseline in all 6 subjects, decreased markedly by the first post-baseline assessment at Week 12, and AST and ALT normalized by EOT in 5 subjects and 2 subjects, respectively. Improvements in other markers of potential liver cell injury were also observed and physical examination findings provide additional supportive data for improvement in liver dysfunction, with a reduction in liver size observed for both subjects who had a palpable liver at baseline. One subject however did develop a palpable liver when he had none at baseline.

Reductions in total cholesterol and LDL-c were typically apparent by the first post-baseline assessment at Week 12, and continued to improve through EOT in 5 of the 6 subjects. These improvements in dyslipidemia occurred in the absence of initiation of treatment with a lipid-lowering medication in 5 of these subjects.

3.2. Integrated efficacy analysis of studies LAL-CL01, LAL-CL04, LAL-CL02, LAL-CL06, LAL-CL03 and LAL-CL08

Assessor's note:

The stand alone report for LAL-CL02 and the responses to LAL-C08 assessment by the Committee were submitted to the EMA separately of this grouped variation and are assessed within this procedure as part of the dataset. Specific reference to these analyses is only made if particular issues would be noted.

Methods & Results – analysis of data submitted

3.2.1. Patient dispositions in the individual studies

3.2.1.1. Overall Background

Sebelipase alfa is currently indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D). The current type II procedure seeks to provide an overview of the cumulative efficacy data from all clinical studies in the sebelipase alfa clinical program and includes data from 125 patients, including 106 children and adults and 19 infants. It serves as an update to the sebelipase alfa Summary of Clinical Efficacy submitted with the original regulatory application, following completion of clinical registration studies.

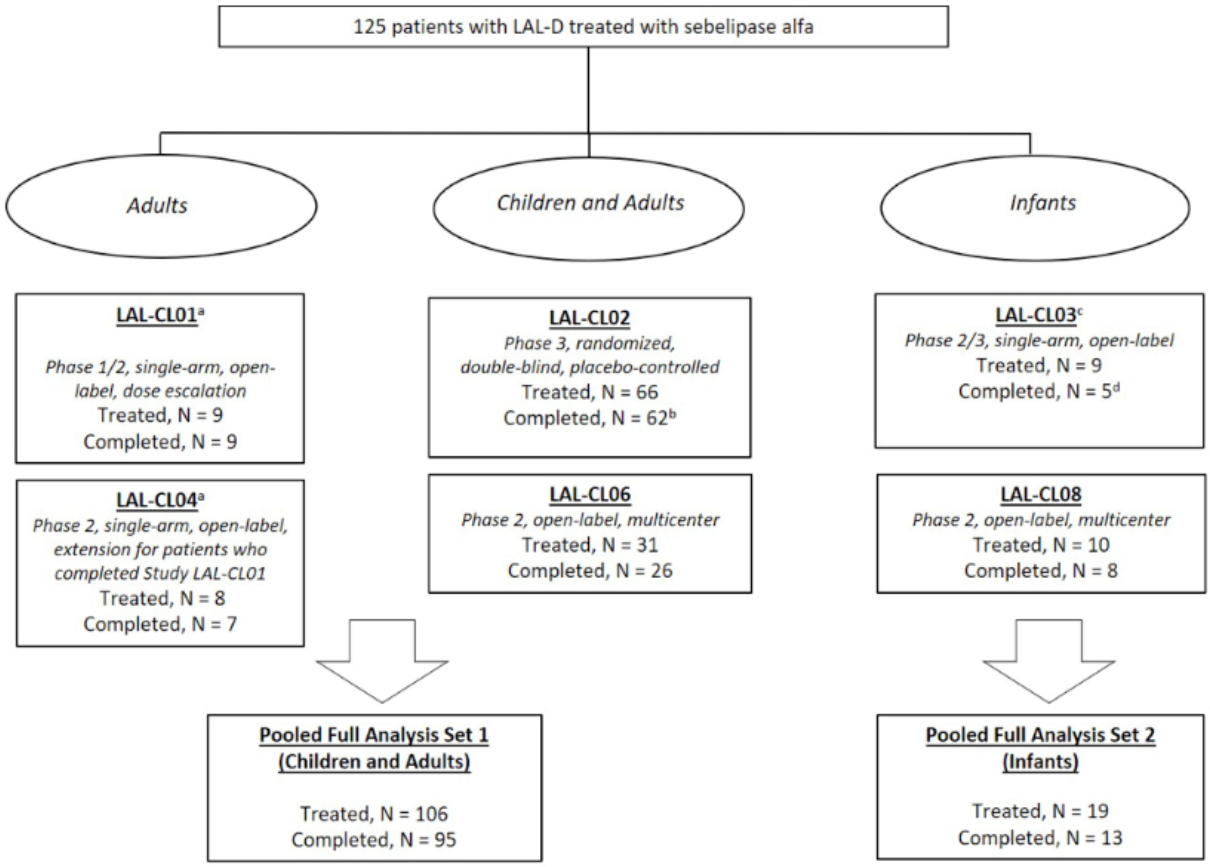
LAL-D is a serious and life-threatening multisystem storage disorder caused by a marked decrease in or absence of lysosomal acid lipase (LAL) enzyme activity caused by mutations affecting the Lipase A, lysosomal acid type (*LIPA*) gene located on chromosome 10q23.2-q23.3.

LAL-D presenting in infants is very rare, with an estimated prevalence of less than 2 lives per million, and growth failure is a key clinical feature and contributor to the early mortality of LAL-D presenting in infants. LAL-D presenting in children and adults is the most common presentation of the disease, yet it is still very rare. While the age of clinical symptom onset is variable, with some patients going undiagnosed until complications manifest in adulthood, the majority of cases described to date were diagnosed before the age of 20.

Overall LAL-D is associated with significant burden of disease and a shortened life expectancy.

Sebelipase alfa is a recombinant human LAL enzyme, which, once bound to the receptors, is internalized and localized to the lysosomal compartment, where it hydrolyzes accumulated substrate in LAL-deficient cells, thus reducing the pathological effects in affected tissues.

Figure 3 and **Table 16** presents a summarized overview of the clinical development program and the included studies respectively for Kanuma:



[a] All but 1 patient in Study LAL-CL01 were enrolled in extension Study LAL-CL04.
[b] Patients were considered to have completed Study LAL-CL02 if they completed Open-label Extension or Expanded Period or moved to commercially available drug: 2 patients were lost-to-follow-up and 2 patients withdrew consent.
[c] Study LAL-CL05 (an open-label extension study of sebelipase alfa in children with LAL-D) was terminated. Data from the 1 enrolled patient were subsequently merged with Study LAL-CL03 and are included in the integrated analyses. Therefore, data from Study LAL-CL05 will not be presented separately from Study LAL-CL03.
[d] Four patients were considered early terminated due to death.

Figure 3: *Sebelipase Alfa Development Program*

Table 16: *Summary of studies in sebelipase afa clinical development plan*

Descriptor	Natural History Studies		Clinical Studies Supporting the Efficacy of Sebelipase Alfa					
	LAL-1-NH01 (Infants)	**LAL-2-NH01 (Children and Adults)**	**LAL-CL03 (Infants)**	**LAL-CL08 (Infants)**	**LAL-CL01 (Adults)**	**LAL-CL04 (Adults)**	**LAL-CL02 (Children and Adults)**	**LAL-CL06 (Children and Adults)**
Pivotal publication	Jones S, et al. *Genet Med.* 2016;18(5): 452-458.	Burton BK, et al. *J Pediatr Gastroenterol Nutr.* 2015;61(6): 619-625.	Jones SA, et al. *Orphanet J Rare Dis.* 2017;12(1):25.	NA	Balwani M, et al. *Hepatology.* 2013;58(3):950-957. Valayannopoulos V, et al. *J Hepatol.* 2014;61(5):1135-1142		Burton BK, et al. *N Engl J Med.* 2015;373(11): 1010-1020.	NA
Study design	Multicenter, retrospective chart review	Multicenter, retrospective chart review	Phase 2/3, multicenter, open-label, dose escalation	Phase 2, Multicenter, open-label, supportive study	Phase 1/2, multicenter, open-label, dose escalation	Phase 2, multicenter, open-label, extension study	Phase 3, multicenter, randomized, double-blind, placebo-controlled with open-label extension period	Phase 2, Multicenter, open-label supportive study
Patients enrolled	35	49	9	10	9	8	66	38
Age (inclusion criteria)	≤ 2 years	≥ 5 years	≤ 24 months	≤ 8 months	≥ 18 and ≤ 65 years	≥ 18 and ≤ 65 years	≥ 4 years	> 8 months
Age at enrollment	NA	56% of the patients were < 20 years and 17% were < 10 years	Median (min, max) age: 3.0 (1.1, 5.8) months	Median (min, max) age: 3.70 (0.5, 9.9) months	Median (min, max) age: 29 (19, 45) years	Median (min, max) age: 29 (19, 45) years	*Age in SA treatment group*: Median (min, max):14.0 (4.7, 55.0) years *Age in placebo treatment group*: Median (min, max): 13.2 (4.9, 58.8) years	Median (min, max): 11.6 (3, 55) years
Primary efficacy endpoint	Time to death	Clinical history summary	Proportion of patients with growth failure surviving to 12 months of age. Only patients ≤ 8 months of age at first infusion were eligible for the primary efficacy analysis.	There was no primary efficacy endpoint. Secondary efficacy endpoints included proportions of patients surviving to 12, 18, 24, and 36 months of age, median age at death, and anthropometric parameters.	Efficacy was not assessed in this study	There was no primary efficacy endpoint. Efficacy endpoints included changes from baseline in liver and spleen volumes and liver and spleen fat content, and histologic assessments in patients who consented to liver biopsy.	Proportion of patients who achieved ALT normalization	There was no primary efficacy endpoint. Secondary efficacy endpoints included changes from baseline in ALT, AST, and serum lipids.
Additional information	NA	NA	Sebelipase alfa initiated at 0.35 mg/kg qw in 8/9 patients and escalated to 1 mg/kg qw in 7 patients and then to 3 mg/kg qw in 6 patients; 2 patients escalated to 5 mg/kg qw. Primary Efficacy Set only included infants < 8 months of age at the first infusion (n = 9).	All 10 patients initiated SA 1 mg/kg qw. 9/10 patients escalated to 3 mg/kg qw, 7 of these patients had a subsequent escalation to 5 mg/kg qw, and 1 patient had a further escalation to 7.5 mg/kg qw.	Patients received SA infusions of 0.35, 1, or 3 mg/kg qow on Days 0, 7, 14, and 21.	Patients received 4 weeks of qw SA infusions at same dose as in Study LAL-CL01 (0.35 mg/kg, 1.0 mg/kg or 3.0 mg/kg) followed by infusions of 1.0 mg/kg or 3.0 mg/kg qow.	Patients received 1 mg/kg SA or placebo qow for 20 weeks (11 infusions), followed by an open-label period at 1 mg/kg qow. Twelve patients had dose escalation to 3 mg/kg qow after 34 to 144 weeks of treatment with SA.	All initiated SA 1 mg/kg qow. 11/31 patients had a dose escalation to 3 mg/kg qow and 4 patients escalated to 3 mg/kg qw. Study included a treatment period of 52 to 96 weeks and an expanded treatment period of ≤ 48 weeks (total of ≤ 144 weeks of treatment).

Primary efficacy endpoint results	Patients with GF (n = 26): median age at death was 3.5 months; probability of survival past age 12 months was 0.038 (95%CI: 0.000, 0.112). Patients undergoing HSCT and/or liver transplant (n = 10) survived longer than nontransplant patients (n = 25) (median age at death, 8.6 months vs. 3.0 months).	Mean (min, max) age at first disease-related abnormality was 9 (0, 42) years; mean (min, max) age at diagnosis was 15.2 years (1, 46). Laboratory findings in majority of patients: elevated ALT, AST, LDL-C, TC and reduced HDL-C; evidence of steatosis and/or fibrosis and cirrhosis.	67% (6/9; [95% CI: 29.93%, 92.51%]) of SA–treated infants survived to 12 months of age compared with 0% for a historical control group (Study LAL-1-NH01).	No primary efficacy endpoint. Percentage (95% CI) of patients surviving were 90% (55.5%, 99.7%) at 12 months, 80% (44.4%, 97.5%) at 18 months, 80% (44.4%, 97.5%) at 24 months, and 75% (34.9%, 96.8%) at 36 months of age.	Not applicable.	No primary efficacy endpoint. Reduction (improvement) in liver volume was apparent during treatment with sebelipase alfa; spleen volumes were variable and did not clearly decrease. Improvements in lipid profile were observed and sustained over time.	Mean (SD) ALT at baseline was 105.1 (45.31) U/L in SA group and 99.0 (42.23) U/L in placebo group. At 20 weeks, ALT had normalized in 31% of patients in the SA group versus 7% in the placebo group (p=0.0271).	No primary efficacy endpoint. Improvements in serum transaminases and an improved serum lipid profile were noted.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; GF = growth failure; HDL-C = high density lipoprotein cholesterol; HSCT = hematopoietic stem cell transplant; LDL-C = low density lipoprotein cholesterol; max = maximum; min = minimum; NA = not applicable; qow = once every other week; qw = once weekly; SA = sebelipase alfa; SD = standard deviation; TC = total cholesterol.

As can be seen. the dosing regimens varied among the protocols, and individual dose adjustments were allowed in each protocol. The first clinical study (Study LAL-CL01) was designed primarily to evaluate the safety and tolerability of sebelipase alfa, following administration as once weekly (qw) intravenous infusions in adult patients. Given the requirement for chronic administration in patients with LAL-D, a once every other week (qow) dosing regimen was considered preferable to a qw dosing regimen for patients whose clinical condition permitted (in infants with rapidly progressing disease, a qw regimen was still considered necessary).

In the qow dose regimen, sebelipase alfa was administered at an initial dose of 1 mg/kg, with the potential for dose escalation to 3 mg/kg qow and 3 mg/kg qw based on evidence of disease progression. The starting dose of 1 mg/kg qow was the sole dose evaluated in the pivotal study in children and adults (Study LAL-CL02). When sebelipase alfa received marketing approval,

1 mg/kg qow was the recommended dose for children and adults presenting with LAL-D.

Sebelipase alfa was initiated at 0.35 mg/kg qw in the pivotal first study in infants (Study LAL-CL03) and at 1 mg/kg qw in the second study in infants (Study LAL-CL08). Patients had dose escalations as required by the protocols and by their individual clinical responses. The maximum dose in an infant study was 7.5 mg/kg qw (in 1 patient). When sebelipase alfa received marketing approval, the recommended starting dose for infants was 1 mg/kg qw, with an escalation to 3 mg/kg qw for patients who did not achieve an optimal clinical response.

Endpoints were chosen based on the fact that elevation of serum transaminases, elevated LDL-C, elevated non-high density lipoprotein cholesterol (non-HDL-C), decreased HDL-C, and elevated triglycerides are important markers of the diseases and thus a successful therapy for LAL-D should produce clinically meaningful corrections of these abnormalities.

Therapeutic efficacy was further evaluated by improvement in survival and improvement in growth parameters in infants, children, and adults. Reductions in liver fat content and liver volume and improvement in liver histology are also considered evidence of the therapeutic efficacy of the treatment. Patient reported health outcomes (ie, Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue, Pediatric Quality of Life Inventory [PedsQL], and Chronic Liver Disease Questionnaire [CLDQ]) and

development assessments (ie, Denver II development scale) were additionally used to provide additional insights into the potential impact of therapy in patients with LAL-D.

Not that not all studies in the development programme studied the same efficacy variables and thus the comparison of results across studies will be done on those that were shared between trials (ie, survival, liver and spleen assessments [organ volumes, organ fat content, and liver histopathology], serum transaminases, other liver biochemical markers, serum lipids, and patient health outcomes).

Rapporteur's comments

As noted by the Applicant, due to various degrees of non-congruency between individual trails, the integrated analysis will inherently suffer from certain paucities in possible analyses. Note however that the individual studies making up the body of data for this integral analysis have been analysed separately prior in individual procedures and generally no egregious efficacy or safety analysis were noticed during these individual assessments.

3.2.1.2. Individual study disposition: LAL-CL-01

The study had nine patients enrolled (3 patients per treatment group), all of which completed the study.

All patients were white and 6 were male. Mean (SD) age at the time of enrollment was 32 (11) years. The 3 treatment groups were similar with respect to the numbers of male and female patients and patient age. All patients except one were non-obese.

On screening physical examination, hepatomegaly was present in 8 patients and 6 patients had ALT > upper limit of normal (ULN), 6 patients had AST > ULN, and 2 patients had AST or ALT $\geq 1.5 \times$ ULN (but $< 3 \times$ ULN). Eight of the 9 patients had lipid abnormalities and 7 patients were receiving lipid-modifying medications. The activity of LAL (acid esterase) in peripheral blood mononuclear cells (PBMCs) ranged from 10.4 to 57 µmol/g/h at Screening (normal range 350 to 2000 µmol/g/h). Beta-galactosidase was assayed concurrently as a control lysosomal enzyme, and its levels were between 109 to 233 µmol/g/h (normal range 100 to 400 µmol/g/h).

3.2.1.3. Individual study disposition: LAL-CL-02

Of the 66 enrolled patients, 36 were randomized to sebelipase alfa and 30 to placebo, and all received at least 1 infusion of the study drug. Sixty-five patients completed the double-blind period, while one patient withdrew after experiencing a serious atypical infusion-associated reaction; this patient was later successfully rechallenged in the Open-label Period and then continued to receive sebelipase alfa.

In the Open-label Extension Period, all 66 patients received sebelipase alfa. Seven patients discontinued open-label treatment (during either the Open-label Extension Period or Expanded Treatment Period), including 2 patients who were lost to follow-up, 2 patients who withdrew consent, and 3 patients who received between 200 and 208 weeks of treatment in the study prior to being discontinued by the Sponsor when the study was terminated following approval of sebelipase alfa in all study regions.

Table 17: *Patient Disposition in Study LAL-CL02 (Full Analysis Set)*

Category	SA/SA (N = 36) n (%)	PBO/SA (N = 30) n (%)	Total (N = 66) n (%)
Patients entering Double-blind Period	36 (100)	30 (100)	66 (100)
Patients completing Double-blind Period	35 (97)	30 (100)	65 (98)
Patients discontinued during Double-blind Period	1 (3)	0	1 (2)
Reasons for discontinuation			
Did not tolerate treatment	1 (3)	0	1 (2)
Patients entering Open-label Extension Period	36 (100)	30 (100)	66 (100)
Patients completing Open-label Extension Period	34 (94)	29 (97)	63 (95)
Patients discontinued during Open-label Extension Period	2 (6)	1 (3)	3 (5)
Reasons for discontinuation			
Lost to follow-up	1 (3)	0	1 (2)
Withdrawal by patient	1 (3)	1 (3)	2 (3)
Patients entering Open-label Expanded Treatment Period	26 (72)	21 (70)	47 (71)
Patients completing Open-label Expanded Treatment Period	24 (67)	19 (63)	43 (65)
Patients discontinued during Open-label Expanded Treatment Period	2 (6)	2 (7)	4 (6)
Reasons for discontinuation:			
Lost to follow-up[a]	1 (3)	0	1 (2)
Sponsor study termination[b]	1 (3)	2 (7)	3 (5)

a One patient completed 256 weeks of treatment prior to being lost to follow-up.
b Three patients completed between 200 and 208 weeks of treatment in Study LAL-CL02 prior to being discontinued by the Sponsor when the study was terminated following approval of sebelipase alfa in all study regions.
Note: Percentages were based on the number of patients in the FAS.
Patient 2106-044 discontinued from the study during the Double-blind Period then re-entered the study during the Open-label Extension Period.
Patients who transitioned to commercial product were counted as having completed the study period.
Abbreviations: FAS = Full Analysis Set; N = number of patients in specified treatment group; n = number of patients with data available; PBO/SA = placebo during the Double-Blind Period followed by sebelipase alfa; SA/SA = sebelipase alfa during the Double-Blind Period followed by sebelipase alfa.

Mean age at randomization was 16.62 years and median age was 13.35 years (range: 4.7 to 58.8 years). Of the 66 patients, 24 (36%) were < 12 years of age, 23 (35%) were between 12 and < 18 years of age, and 19 (29%) were ≥ 18 years of age at randomization. Most patients (83%) were white. Thirty-three patients (50%) were male. At baseline, 24 patients (36%) were receiving a lipid-lowering medication (LLM).

All 66 patients had a confirmed diagnosis of LAL-D. Genetic testing showed that 56 (85%) of the 66 patients had at least one copy of the c.849G>A common exon 8 splice junction mutation (21 homozygotes, 35 compound heterozygotes); the remaining 10 patients had other mutations.

The most frequently presenting abnormality at symptom onset was elevated serum transaminases (31 patients, 47%), followed by hypercholesterolemia (8 patients, 12%).

As required by the entrance criteria, all patients had an ALT > 1.5 × ULN at baseline; 17 patients (26%) had ALT ≥ 3 × ULN. Mean (SD) ALT was 100.47 (44.058) U/L and median ALT was 87.00 U/L (range: (35.7 to 212.3 U/L. All but 1 patient had elevated AST at baseline. Baseline gamma glutamyltransferase (GGT) was elevated in 27 patients (41%).

Baseline assessments of lipids demonstrated marked dyslipidemia. Overall, 35 patients (53%) had LDL-C values in the very high range ≥ 190 mg/dL). Triglyceride levels were ≥ 200 mg/dL in 13 patients

(20%). Low baseline HDL-C levels were noted for 38 patients (58%). High baseline total cholesterol levels were noted for 49 patients (74%).

Mean (SD) baseline liver fat content, as assessed by MRI, was 8.48% (3.667%) for the 60 patients with available data. Mean (SD) liver volume for the 63 patients with available data was 1.44 (0.366) MN.

3.2.1.4. Individual study disposition: LAL-CL-03

Nine patients were enrolled and treated, of which five (56%) patients completed the study and 4 (44%) patients were considered early terminated due to death. One other patient in France initially received emergency therapy with sebelipase alfa under a Temporary Use Authorization, ATU, and later transitioned onto Study LAL-CL05 at Week 40 before eventually enrolling in Study LAL-CL03 at Week 85.

The study population included 5 male patients and 4 female patients, of which 4 patients were white, 1 was black, and 1 patient was Asian. The median (range) age of patients at the time of initiation of dosing was 3.0 (1.1 to 5.8) months.

Eight patients had confirmed growth failure within the first 6 months of life, with 7 having a decrease in weight percentile across at least 2 major centiles since birth. One other patient had other evidence of rapidly progressive disease requiring urgent medical intervention, including marked abdominal distension since 8 weeks of age; a medical history of ascites, vomiting, and diarrhea; and massive hepatosplenomegaly, anemia, hypoalbuminemia, and elevated AST and lactate dehydrogenase at Screening. Median WFA percentile decreased from 81.33% at birth to 3.08% at the baseline assessment approximately 1 to 6 months later in the 8 patients with available data.

All patients had marked abnormalities in liver biochemical parameters at baseline. Hepatomegaly and/or splenomegaly were evident on baseline physical examination in all 8 patients with available data.

3.2.1.5. Individual study disposition: LAL-CL-04

This study enrolled 8 the 9 patients who completed Study LAL-CL01 were treated in Study LAL-CL04, 7 of which continued to receive treatment in Study LAL-CL04 until they transitioned to commercial therapy; these 7 patients received between 224 and 260 weeks of sebelipase alfa in Study LAL-CL04 and were considered to have completed treatment in the study. One other patient was lost to follow-up.

All patients were white and 6 patients (67%) were male. The mean age of the patients at the time of enrollment in Study LAL-CL01 was 30.3 years. Patients initiated treatment in Study LAL-CL04 approximately 9 to 28 weeks after completing their last dose in Study LAL-CL01.

All patients had previously received 4 doses of sebelipase alfa in Study LAL-CL01. The time between diagnosis of LAL-D and enrollment in Study LAL-CL04 ranged from 3.0 to 36.6 years.

During the 9 to 28 weeks between the last infusion in Study LAL-CL01 and the baseline clinical laboratory assessments in Study LAL-CL04, the improvements in serum transaminases and serum lipids that had occurred in Study LAL-CL01 were reversed for all patients. At baseline, median ALT was 81.5 U/L, above normal range (ULN = 67 U/L), and median AST was 50.0 U/L, at upper end of the normal range (ULN = 50 U/L). Six of the 8 patients had baseline ALT or AST levels > ULN, although most of these abnormalities were mild. No patient had a baseline AST > 1.5 × ULN and only 1 (13%) patient had a baseline ALT > 1.5 × ULN.

3.2.1.6. Individual study disposition: LAL-CL-06

Thirty-one patients started sebelipase alfa, all at 1 mg/kg qow. Twenty-eight patients completed the 96-week treatment period. Of the 3 patients who did not complete the treatment period, one patient transitioned to commercial product and was considered to have completed the study.

Twenty-five of the 28 patients who completed the 96-week treatment period continued to receive sebelipase alfa during the extended treatment period and 19 patients completed the 144-week extended treatment period.

2The study population was 61% male and predominantly white (87%). There were no Japanese or other Asian patients. The FAS included 9 adults and 22 children, of whom 6 were in the 2 to < 4 year age group and 16 were in the 4 to 18 year age group.

Baseline hepatic dysfunction was evidenced by elevated serum transaminases, increased liver and spleen volumes and fat content by MRI, and abnormal liver histopathology. Baseline ALT and AST levels were > 1.5 × ULN for 18 (58%) and 15 (48%) patients, respectively. Mean baseline ALT was 74.6 U/L and mean baseline AST was 77.5 U/L. Serum transaminases were higher in children than in adults. Mean baseline ALT levels were 121.8 U/L in the 2 to < 4 year age group, 72.1 U/L in the 4 to 18 year age group, and 47.5 U/L in the > 18 year age group. Individual ALT levels were > 1.5 × ULN for all 6 (100%) patients in the 2 to < 4 year age group (all of whom had levels > 2 × ULN), for 9 (56%) of 16 patients in the 4 to 18 year age group, and for 3 (33%) of 9 patients in the > 18 year age group. Mean baseline AST levels were 120.8 U/L, 79.7 U/L, and 44.9 U/L, respectively, and were > 1.5 × ULN in 3 (50%) patients, 10 (63%) patients, and 2 (22%) patients in the respective age groups.

Other biochemical markers of potential liver injury measured at baseline included GGT, total bilirubin, and alkaline phosphatase. While some patients were noted to have baseline levels of GGT, total bilirubin, and/or alkaline phosphatase that were above the age- and gender- appropriate ULN (as defined by the central laboratory), these biochemical markers were not routinely elevated at baseline.

Mean triglycerides were 176.3 mg/dL at baseline, and 18 (58%) of 31 patients had a baseline triglycerides level above the ULN. Mean LDL-C was 159.7 mg/dL at baseline, and 19 (63%) of 30 patients had a baseline LDL-C above the ULN. Mean HDL-C was 30.7 mg/dL at baseline, and levels were below the lower limit of normal (LLN) in 22 (71%) of 31 patients.

Stunting at baseline was noted in 1 of 6 patients (17%) aged 2 to < 4 years and in 5 of 16 patients (31%) aged 4 to 18 years. Median weight-for-age (WFA) and stature-for-age (SFA) percentile scores were lower in patients 4 to 18 years (18.4% and 18.5%, respectively) than in patients 2 to < 4 years (27.8% and 27.9%, respectively). At baseline, the mean BMI in adult patients was 23.67 kg/m2 (median 23.53 kg/m^2).

3.2.1.7. Individual study disposition: LAL-CL-08

A total of 10 patients enrolled and were treated. Six patients completed the study, all of whom continued to receive sebelipase alfa after study completion. Two patients were considered early terminated due to death. The other 2 patients remained in the study until it was terminated following approval of sebelipase alfa in all study regions; they then transitioned to commercial therapy.

The study population included 5 male and 5 female patients, with 6 Asian patients (all non-Japanese; 4 male and 2 female) and 1 patient each who reported as the following: white, American Indian or Alaskan native, Egyptian, and Turkish/Kurdish. The median (range) birth weight of patients was 3.330 (2.90 to 5.04) kg. The median (range) age of the patients on the date of their first infusion of sebelipase alfa was 2.83 (0.5 to 4.1) months.

The mean (range) duration between a patient's diagnosis with LAL-D and their first infusion of sebelipase alfa in Study LAL-CL08 was 13.6 (4 to 37) days. All 10 patients had LAL activity in dried blood spots and/or PBMCs that was below the normal range (or classified as "affected" or "carrier" for results presented in nmol/punch/h).

LIPA genetic mutation analysis was performed by the central laboratory for 5 of the 10 patients. Four of the 5 patients had documented causative mutations of the LIPA gene that were classified as pathogenic (including 1 patient with the c.894G> A mutation). One of the 5 patients with genotyping data did not have a documented causative mutation. Three patients, who were from a homogenous population in the UK, had a homozygous deletion affecting both alleles of the genes LIPA and Cholesterol 25-Hydroxylase (hereafter referred to as dual WGD) (data on file at Alexion).

Median (range) AST was 99.5 (56 to 441) U/L in the 8 patients with available data and was elevated in 6 of these patients. Median (range) ALT was 37 (28 to 248) U/L in the 9 patients with available data and was elevated in 3 of these patients. Elevations in GGT, total bilirubin, and alkaline phosphatase were reported in 6 patients, 3 patients, and 2 patients, respectively, of the 9 patients who had baseline data for each of these parameters. On baseline physical examination, all 8 patients had a palpable liver. Among the 7 patients with baseline ultrasound data, the median (range) liver volume was 3.16 (0.1 to 4.4) MN.

Among patients with available data, baseline lipid abnormalities included elevated triglycerides (3 of 5 patients), elevated LDL-C (2 of 3 patients), elevated total cholesterol (1 of 6 patients), and low HDL-C (1 of 4 patients).

Coagulation parameter data were available for 6 patients at baseline and included a prolonged activated partial thromboplastin time (aPTT) (3 patients), a shortened aPTT (2 patients), or a shortened prothrombin time (1 patient). Hematology data were available for 7 patients at baseline. Hemoglobin levels were low in 6 of the 7 patients, and platelet counts were low in 4 of the 7 patients.

Baseline assessments showed evidence of impaired growth, liver dysfunction, coagulopathy and hematological abnormalities, and dyslipidemia. Baseline WFA percentile was low in most patients, with a median of 1.059 and a mean of 12.513. A pronounced deceleration in weight between birth and the baseline assessment was observed for all patients. Percentile scores for other anthropometric parameters (ACFA, HCFA, BMIFA, WFL/WFH, and LFA/HFA) were also low at baseline.

3.2.2. Cross-Study Result Analysis

For the cross-study analysis the various patient groups for the individual studies were separated in two broad analysis pools (used for both cross-study efficacy and safety analyses), with Pool 1 representing studies in children and adults diagnosed with LAL-D, whereas Pool 2 representing studies of infants who developed growth failure or other evidence of a rapidly progressive course of LAL-D.

A summary of the included studies and associated dosing regimens represented in each pool is presented in Table 2 below.

***Table 18**: Pooled Groups for Efficacy Analysis*

Population	Pooled Studies	Summarized Treatment Groups	Description
Pooled Group 1	LAL-CL01/LAL-CL04 (extension study) LAL-CL02 LAL-CL06	0.35 mg/kg qw 0.35 mg/kg qow 0.68 mg/kg qow 1 mg/kg qw 1 mg/kg qow 3 mg/kg qow 3 mg/kg qw	Studies of children and adults diagnosed with LAL-D
Pooled Group 2	LAL-CL03 LAL-CL08	0.2 mg/kg qw[a] 0.35 mg/kg qw 0.5 mg/kg qw[a] 0.75 mg/kg qw[a] 1 mg/kg qw 1 mg/kg qow 3 mg/kg qw 3 mg/kg qow 5 mg/kg qw 5 mg/kg qow 7.5 mg/kg qw	Studies of infants who developed growth failure or other evidence of a rapidly progressive course of LAL-D

Note: For the dose subgroup analysis, treatment groups with associated data are presented.
[a] This dosage regimen was not planned per protocol.
Abbreviations: LAL-D = lysosomal acid lipase deficiency; qow = every other week; qw = once weekly.

The Pooled FAS for each pooled group includes all patients included in the individual study full FAS as described in each individual protocol and SAP, and thus encompasses patients who were enrolled in a study and received at least 1 dose of sebelipase alfa. Therefore three different FAS groups were defined:

- Pooled FAS 1: for Pooled Group 1.
- Pooled FAS 2: for Pooled Group 2.
- FAS 3: includes both Pooled FAS 1 and Pooled FAS 2.

The Pooled Safety Set included all patients who received at least 1 dose (partial or complete) of sebelipase alfa, and the following stratifications were taken into account:

- Pooled Safety Set 1 includes data from subjects in Pooled Group 1.
- Pooled Safety Set 2 includes data from in Pooled Group 2.

In addition select subgroup analyses were performed on the pooled safety set, as shown in Table 3.

***Table 19**:Subgroup Analyses Performed for the Pooled Safety Set*

	Pooled Safety Set		Subgroups Within Pooled Analyses						
Safety Data	**Pooled Safety Set 1[a]**	**Pooled Safety Set 2[b]**	**Age[c]**	**Gender**	**Race**	**Baseline LLM[d]**	**ADA Positive Status[e]**	**Liver Cirrhosis**	**Dose**
Disposition	X	X	NA	NA	NA	NA	NA	NA	NA
Demographics	X	X	NA	NA	NA	NA	NA	X	NA
Exposure	X	X	X	X	X	X	X	NA	NA
Baseline disease characteristics	X	X	NA	NA	NA	NA	NA	X	NA
Concomitant medications	X	X	X	X	X	X	X	NA	X
TEAEs	X	X	X	X	X	X	X	NA	X
Laboratory evaluations	X	X	X	X	X	X	X	X	X
Immunogenicity	X	X	X	X	X	X	NA	NA	X
Vital signs	X	X	X	X	X	X	X	NA	X

[a] Includes patients in Studies LAL-CL01/LAL-CL04, LAL-CL02, and LAL-CL06.
[b] Includes patients in Studies LAL-CL03 and LAL-CL08.
[c] Age categories were only analyzed for Pooled Safety Set 1.
[d] A patient was considered to have taken a LLM if it was administered during the period between the informed consent date and the date of the first infusion of study drug.
[e] Antidrug antibody positivity was defined as the period after an ADA positive result until an ADA negative result and ADA negativity was defined as the period before an ADA positive result or the period between an ADA negative result and an ADA positive result. ADA positivity was confirmed if both screening and confirmatory assays were positive.

Abbreviations: ADA = antidrug antibody; LLM = lipid-lowering medication; NA = not applicable; TEAE = treatment-emergent adverse event.

Rapporteur's comments

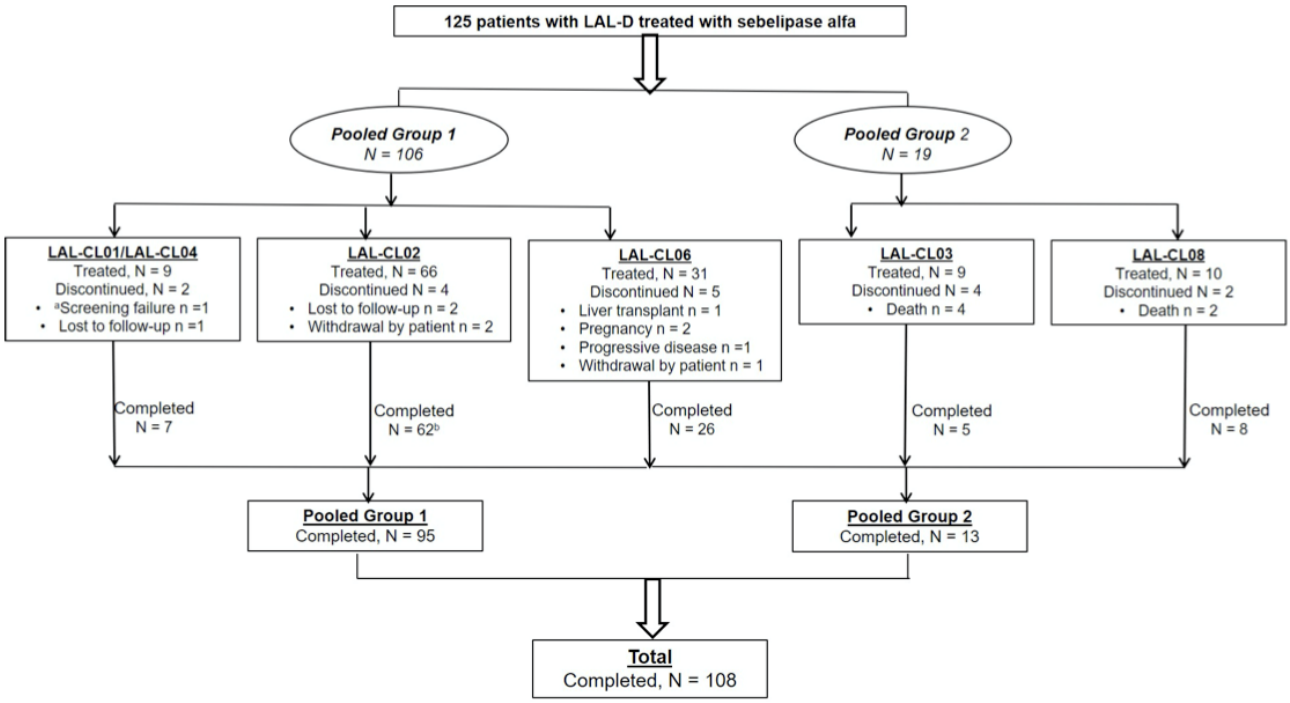
Note that for all intents and purposes the Pooled FAS 1 & 2 and the Pooled SS 1 & 2 are identical.

3.2.2.1. Cross-Study Efficacy analysis

A schematic overview of patient disposition for the total of 125 patients compromising the two analysis pools is presented in **Figure 4**.

In Pooled FAS 1 the median age at first dose of sebelipase alfa was 13.49 years with the majority of patients in the age category < 18 years (69 patients; 65%). There were 58 male patients (55%) and 48 female patients (45%). The majority of patients were white (91 patients; 86%) and 16 patients (15%) were Hispanic or Latino. Forty-six patients (43%) were using LLMs at baseline.

In Pooled FAS 2 the median age at first dose was 3.02 months. There were 10 male patients (53%) and 9 female patients (47%). Most of the patients enrolled were Asian in origin (7 patients; 44%), followed by white (5 patients; 31%) and no patients were Hispanic or Latino. Four patients (21%) were using LLMs at baseline.



[a] Screening failure for Study LAL-CL04.
[b] "Completed" for Study LAL-CL02 refers to patients who completed the open-label extension or expanded period, or moved to commercially available drug.
Abbreviations: LAL-D = lysosomal acid lipase deficiency; N = number of patients in a specified subgroup.

Figure 4:*Schematic Patient Disposition*

Rapporteur's comments

Overall, and taking into account the limitations inherent in the pooled cross-study nature of the data, the Pooled groups are internally more or less balanced in key demographics, save for group 1 where a majority of patients were of Caucasian descent. However, during the prior clinical evaluation, both pre- and post-approval, race was never found to be a differentiating factor in neither efficacy nor safety parameters. Therefore this imbalance is not regarded as a problematic issue.

Survival analysis

Survival analyses was done on the Pooled FAS 2 based on up to 5 year yearly data. It was based on the proportion of patients surviving to a certain age, with 12 months being a timepoint considered a clinically meaningful treatment response given the natural pathologic mortality of 6 months.

The percentages of patients surviving to 12, 24, 36, 48, and 60 months of age were 79%, 68%, 65%, 56%, and 43%, respectively. More patients survived in up to 36 months in the LAL-CL08 study versus the CL03 one, though follow-up in the former did not allow for analysis up to 60 months.

Table 20 gives an overall overview of the proportions of patients surviving through the defined survival analysis points.

Table 20: *Proportions of Patients Surviving to 12, 24, 36, 48, and 60 Months: Pooled FAS 2*

Parameter	LAL-CL03 (N = 9)	LAL-CL08 (N = 10)	Pooled FAS 2 (N = 19)
Survival through 12 months of age, n (%)			
No[a]	3 (33)	1 (10)	4 (21)
Yes	6 (67)	9 (90)	15 (79)
NA[b]	0	0	0
Percent surviving, (95% CI)[c]	67 (29.93, 92.51)	90 (55.50, 99.75)	79 (54.43, 93.95)
Kaplan-Meier estimate of survival to 12 months of age, (%)	67	90	79
Survival through 24 months of age, n (%)			
No[a]	4 (44)	2 (20)	6 (32)
Yes	5 (56)	8 (80)	13 (68)
NA[b]	0	0	0
Percent surviving, (95% CI)[c]	56 (21.20, 86.30)	80 (44.39, 97.48)	68 (43.45, 87.42)
Kaplan-Meier estimate of survival to 24 months of age, (%)	56	80	68
Survival through 36 months of age, n (%)			
No[a]	4 (44)	2 (20)	6 (32)
Yes	5 (56)	6 (60)	11 (58)
NA[b]	0	2 (20)	2 (11)
Percent surviving, (95% CI)[c]	56 (21.20, 86.30)	75 (34.91, 96.81)	65 (38.33, 85.79)
Kaplan-Meier estimate of survival to 36 months of age, (%)	56	80	68
Survival through 48 months of age, n (%)			
No[a]	4 (44)	0	4 (21)
Yes	5 (56)	0	5 (26)
NA[b]	0	10 (100)	10 (53)
Percent surviving, (95% CI)[c]	56 (21.20, 86.30)	NA	56 (21.20, 86.30)
Kaplan-Meier estimate of survival to 48 months of age, (%)	56	NA	68
Survival through 60 months of age, n (%)			
No[a]	4 (44)	0	4 (21)
Yes	3 (33)	0	3 (16)
NA[b]	2 (22)	10 (100)	12 (63)
Percent surviving, (95% CI)[c]	43 (9.90, 81.59)	NA	43 (9.90, 81.59)
Kaplan-Meier estimate of survival to 60 months of age, (%)	56	NA	68

Note: In Study LAL-CL08, patients were enrolled at an early age (< 8 months) and duration of treatment was 18 months to 3 years. The study was therefore not designed to capture survival to 60 months.

[a] Includes patients, if any, who were permanently lost to follow-up prior to the age specified in the analysis.

[b] Patients alive and discontinued study prior to reaching the age specified in the analysis. These patients were excluded from the Percent Surviving analyses and censored in Kaplan-Meier analyses.

[c] Exact confidence interval calculated using Clopper-Pearson method. Patients with unknown survival status at the age specified in the analysis were excluded.

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; NA = not applicable.

Rapporteur's comments

Survival analysis being done only on Pooled FAS 2 is a logical and acceptable approach. Infants with LAL-D usually present with the most aggressive and lethal form of the syndrome, whereas those that present with the pathology during later stages of life have a markedly lower mortality risk.

Overall the integrated analysis confirm what the data from the individual studies showed, and integrated analysis does not change this perception for the worse.

Growth analysis – Adults and Children

In the Pooled FAS 1, mean (SD) changes from baseline in weight, height, and BMI of patients at the EOS were 11.974 (12.0149) kg, 15.837 (9.8465) cm, and 2.20 (2.864) kg/m^2, respectively (analyses of height include patients under 18 years of age only).

Note that Studies LAL-CL02 and LAL-CL06 also included children and therefore increases in weight and BMI were smallest in Studies LAL-CL01/LAL-CL04, and postbaseline changes in height were not assessed in those latter studies.

Mean changes from baseline for patients < 18 years of age and patients ≥ 18 years of age are shown in **Table 21**, showing that younger patients had an expected higher increase in weight and BMI parameters.

Table 21: *Summary of Subgroup Analysis by Age Category – Pooled FAS 1 - Growth*

Parameter	Tables Displaying Analysis	Summary		
Height, Weight, and BMI	ISE Table 14.2.2.1.2.1	Patients < 18 years of age showed progressive increases from baseline in height and weight; patients ≥ 18 years of age did not. Patients < 18 years of age showed greater increases in BMI than patients ≥ 18 years of age. These differences are expected. Mean (SD) changes from baseline to EOS by age group were:		
		Parameter	**< 18 years of age**	**≥ 18 years of age**
		Weight	16.656 (10.7733) kg	1.495 (7.0596) kg
		Height	15.837 (9.8465) cm	No data
		BMI	3.04 (2.708) kg/m^2	0.34 (2.302) kg/m^2

Analyses for weight, height, and body mass index-for-age percentile (WFA, HFA, BMIFA) were not undertaken for adult patients and thus only data of studies LAL-CL02 and CL06 were considered.

In general, proportions of patients in the lowest percentile categories tended to decrease and proportions in the highest categories tended to increase, suggesting improvement, as shown in tables Table 22, Table 23 & Table 24. Changes from baseline in normalized anthropometric data percentiles were generally consistent with observations for other anthropometric parameters

Table 22: *WFA Percentile by Visit: Pooled FAS 1*

Percentile Category	Pooled FAS 1 (N = 69) n (%) at Visit							
Visit	Baseline	Month 3	Month 6	Month 12	Month 24	Month 36	Month 48	End of Study
Patients with data	69	67	59	67	62	12	18	44
0% - 10%	13 (19)	13 (19)	14 (24)	13 (19)	10 (16)	2 (17)	2 (11)	4 (9)
> 10% - 20%	8 (12)	7 (10)	3 (5)	6 (9)	7 (11)	1 (8)	2 (11)	4 (9)
> 20% - 30%	8 (12)	5 (7)	7 (12)	6 (9)	6 (10)	2 (17)	0	3 (7)
> 30% - 40%	5 (7)	7 (10)	9 (15)	11 (16)	7 (11)	2 (17)	3 (17)	8 (18)
> 40% - 50%	11 (16)	8 (12)	2 (3)	2 (3)	3 (5)	1 (8)	1 (6)	1 (2)
> 50% - 60%	5 (7)	10 (15)	6 (10)	2 (3)	3 (5)	0	1 (6)	2 (5)
> 60% - 70%	6 (9)	2 (3)	5 (8)	11 (16)	5 (8)	0	2 (11)	3 (7)
> 70% - 80%	4 (6)	7 (10)	2 (3)	3 (4)	7 (11)	2 (17)	3 (17)	5 (11)
> 80% - 90%	3 (4)	2 (3)	4 (7)	6 (9)	7 (11)	0	2 (11)	5 (11)
> 90% - 100%	6 (9)	6 (9)	7 (12)	7 (10)	7 (11)	2 (17)	2 (11)	9 (20)

Note: Only patients who were less than 18 years old were included in the analyses. Thus, Studies LAL-CL01/LAL-CL04 were not included in this table. Age at the time of the measurement was used to calculate percentiles.
Study LAL-CL06: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Study LAL-CL02: Baseline is the average of the last, up to 3, non-missing assessments (including unscheduled) prior to the first infusion of sebelipase alfa. For PBO/SA treatment sequence, the last, up to 3, non-missing assessments must be within 45 days.
Abbreviations: FAS = Full Analysis Set; PBO = placebo; SA = sebelipase alfa.

***Table 23**: HFA Percentile by Visit: Pooled FAS 1*

Percentile Category	Pooled FAS 1 (N = 69) n (%) at Visit							
Visit	**Baseline**	**Month 3**	**Month 6**	**Month 12**	**Month 24**	**Month 36**	**Month 48**	**End of Study**
Patients with data	69	64	59	61	54	7	9	43
0% - 10%	17 (25)	16 (25)	18 (31)	14 (23)	12 (22)	1 (14)	0	6 (14)
> 10% - 20%	9 (13)	8 (13)	6 (10)	6 (10)	5 (9)	2 (29)	2 (22)	6 (14)
> 20% - 30%	10 (14)	8 (13)	6 (10)	10 (16)	9 (17)	1 (14)	1 (11)	5 (12)
> 30% - 40%	9 (13)	6 (9)	8 (14)	9 (15)	3 (6)	0	0	2 (5)
> 40% - 50%	1 (1)	6 (9)	3 (5)	4 (7)	5 (9)	0	0	7 (16)
> 50% - 60%	4 (6)	2 (3)	2 (3)	4 (7)	7 (13)	0	0	2 (5)
> 60% - 70%	3 (4)	2 (3)	0	2 (3)	4 (7)	0	0	3 (7)
> 70% - 80%	7 (10)	3 (5)	4 (7)	3 (5)	1 (2)	1 (14)	2 (22)	3 (7)
> 80% - 90%	4 (6)	8 (13)	6 (10)	5 (8)	6 (11)	2 (29)	3 (33)	5 (12)
> 90% - 100%	5 (7)	5 (8)	6 (10)	4 (7)	2 (4)	0	1 (11)	4 (9)

Note: Only patients who were less than 18 years old were included in the analyses. Thus, Studies LAL-CL01/LAL-CL04 were not included in this table. Age at the time of the measurement was used to calculate percentiles.
Study LAL-CL06: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Study LAL-CL02: Baseline is the average of the last, up to 3, non-missing assessments (including unscheduled) prior to the first infusion of sebelipase alfa. For PBO/SA treatment sequence, the last, up to 3, non-missing assessments must be within 45 days.
Abbreviations: FAS = Full Analysis Set; PBO = placebo; SA = sebelipase alfa.

***Table 24:** BMIFA Percentile by Visit: Pooled FAS 1*

Percentile Category	Pooled FAS 1 (N = 69) n (%) at Visit							
Visit	**Baseline**	**Month 3**	**Month 6**	**Month 12**	**Month 24**	**Month 36**	**Month 48**	**End of Study**
Patients with data	69	64	59	61	54	7	9	43
0% - 10%	3 (4)	5 (8)	5 (8)	5 (8)	6 (11)	0	1 (11)	2 (5)
> 10% - 20%	6 (9)	5 (8)	8 (14)	6 (10)	4 (7)	1 (14)	0	4 (9)
> 20% - 30%	11 (16)	8 (13)	8 (14)	9 (15)	4 (7)	0	0	1 (2)
> 30% - 40%	6 (9)	6 (9)	2 (3)	5 (8)	10 (19)	0	0	6 (14)
> 40% - 50%	6 (9)	7 (11)	8 (14)	4 (7)	8 (15)	2 (29)	0	3 (7)
> 50% - 60%	12 (17)	10 (16)	6 (10)	10 (16)	5 (9)	1 (14)	2 (22)	7 (16)
> 60% - 70%	10 (14)	8 (13)	6 (10)	4 (7)	2 (4)	1 (14)	1 (11)	3 (7)
> 70% - 80%	5 (7)	5 (8)	4 (7)	7 (11)	4 (7)	1 (14)	2 (22)	4 (9)
> 80% - 90%	5 (7)	4 (6)	7 (12)	5 (8)	6 (11)	0	1 (11)	4 (9)
> 90% - 100%	5 (7)	6 (9)	5 (8)	6 (10)	5 (9)	1 (14)	2 (22)	9 (21)

Note: Only patients who were < 18 years old were included in the analyses. Thus, Studies LAL-CL01/LAL-CL04 were not included in this table. Age at the time of the measurement was used to calculate percentiles.
Study LAL-CL06: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Study LAL-CL02: Baseline is the average of the last, up to 3, non-missing assessments (including unscheduled) prior to the first infusion of sebelipase alfa. For PBO/SA treatment sequence, the last, up to 3, non-missing assessments must be within 45 days.
Abbreviations: FAS = Full Analysis Set; PBO = placebo; SA = sebelipase alfa.

At baseline in Pooled FAS 1, 8 of 69 patients (12%) met the definition of underweight, defined as a WFA at least 2 SDs below the median WFA of a reference population, and 12 of 69 patients (17%) met the definition of stunting, defined as a HFA at least 2 SDs below the median HFA of a reference population. None of the patients met the definition of wasting, defined as a WFH at least 2 SDs below the median WFH of a reference population. At Month 24, there was no notable change in the proportion of patients who were underweight or had stunting. One patient (Patient 0101-035) in Study LAL-CL06 was observed with wasting and this condition continued until the last assessment. Another patient in Study LAL-CL06 experienced transient wasting at Month 6.

Rapporteur's comments

Overall, the integrated analysis shows a similar picture as seen in the individual studies in the past, confirming that a positive effect on growth can be achieved in children.

Growth analysis – Infants

Mean (SD) changes from baseline in weight, height and BMI of patients in Pooled FAS 2 at Week 144 were 9.984 (1.4817) kg, 36.410 (4.9449) cm, and 2.94 (2.726) kg/m^2, respectively. Height and weight increased gradually. Body mass index was higher at postbaseline visits than at baseline. Increases in height, weight, and BMI were generally greater in Study LAL-CL08 than in Study LAL-CL03.

Weight-for-age percentile was a key measure of growth in the LAL-CL03 and CL08 studies. In Pooled FAS 2 at baseline, 14 patients (78%) were in the age-normalized weight percentile category of 0% to 10% and none were in the categories of 80% to 90% or 90% to 100%. Treatment with sebelipase alfa was associated with an improvement in WFA percentile with some patients reaching the 80th percentile or higher. Results were similar for HFA and BMIFA percentiles, see tables **Table 25**, **Table 26** & **Table 27**.

Table 25: *WFA Percentile by Visit: Pooled FAS 2*

Percentile Category	Pooled FAS 2 (N = 19) n (%) at Visit								
Visit	**Baseline**	**Week 12**	**Week 24**	**Week 48**	**Week 96**	**Week 144**	**Week 192**	**Week 240**	**End of Study**
Patients with data	18	15	15	13	13	10	5	5	5
0% - 10%	14 (78)	9 (60)	5 (33)	2 (15)	1 (8)	0	1 (20)	1 (20)	2 (40)
> 10% - 20%	1 (6)	0	2 (13)	2 (15)	2 (15)	2 (20)	1 (20)	1 (20)	0
> 20% - 30%	1 (6)	0	0	4 (31)	2 (15)	1 (10)	1 (20)	1 (20)	1 (20)
> 30% - 40%	0	4 (27)	3 (20)	0	2 (15)	1 (10)	0	0	0
> 40% - 50%	0	0	0	1 (8)	1 (8)	0	0	0	0
> 50% - 60%	0	1 (7)	0	0	1 (8)	0	0	0	0
> 60% - 70%	0	1 (7)	3 (20)	0	1 (8)	2 (20)	0	0	0
> 70% - 80%	2 (11)	0	1 (7)	2 (15)	1 (8)	2 (20)	0	0	1 (20)
> 80% - 90%	0	0	1 (7)	1 (8)	2 (15)	1 (10)	2 (40)	1 (20)	0
> 90% - 100%	0	0	0	1 (8)	0	1 (10)	0	1 (20)	1 (20)

Note: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Abbreviation: FAS = Full Analysis Set.

Table 26: *HFA Percentile by Visit: Pooled FAS 2*

Percentile Category	Pooled FAS 2 (N = 19) n (%) at Visit								
Visit	**Baseline**	**Week 12**	**Week 24**	**Week 48**	**Week 96**	**Week 144**	**Week 192**	**Week 240**	**End of Study**
Patients with data	17	14	14	13	13	10	5	5	5
0% - 10%	10 (59)	4 (29)	5 (36)	3 (23)	4 (31)	1 (10)	2 (40)	2 (40)	2 (40)
> 10% - 20%	1 (6)	2 (14)	2 (14)	1 (8)	0	3 (30)	0	0	0
> 20% - 30%	1 (6)	1 (7)	1 (7)	1 (8)	0	0	0	0	0
> 30% - 40%	0	1 (7)	0	1 (8)	1 (8)	1 (10)	0	1 (20)	0
> 40% - 50%	1 (6)	2 (14)	1 (7)	1 (8)	1 (8)	1 (10)	2 (40)	0	2 (40)
> 50% - 60%	2 (12)	3 (21)	1 (7)	0	3 (23)	2 (20)	0	1 (20)	0
> 60% - 70%	1 (6)	0	1 (7)	1 (8)	0	1 (10)	1 (20)	0	0
> 70% - 80%	0	0	1 (7)	2 (15)	2 (15)	0	0	0	0
> 80% - 90%	1 (6)	0	1 (7)	3 (23)	2 (15)	1 (10)	0	0	0
> 90% - 100%	0	1 (7)	1 (7)	0	0	0	0	1 (20)	1 (20)

Note: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Abbreviation: FAS = Full Analysis Set.

Table 27: *BMIFA Percentile by Visit: Pooled FAS 2*

Percentile Category	Pooled FAS 2 (N = 19) n (%) at Visit								
Visit	**Baseline**	**Week 12**	**Week 24**	**Week 48**	**Week 96**	**Week 144**	**Week 192**	**Week 240**	**End of Study**
Patients with data	17	14	14	13	13	10	5	5	5
0% - 10%	9 (53)	6 (43)	3 (21)	3 (23)	1 (8)	0	0	0	0
> 10% - 20%	3 (18)	2 (14)	1 (7)	0	0	0	2 (40)	1 (20)	1 (20)
> 20% - 30%	0	3 (21)	2 (14)	3 (23)	2 (15)	0	0	1 (20)	0
> 30% - 40%	1 (6)	1 (7)	4 (29)	0	1 (8)	2 (20)	0	0	1 (20)
> 40% - 50%	1 (6)	0	1 (7)	1 (8)	1 (8)	1 (10)	0	0	1 (20)
> 50% - 60%	0	1 (7)	1 (7)	1 (8)	1 (8)	0	0	0	0
> 60% - 70%	1 (6)	0	0	1 (8)	4 (31)	2 (20)	0	1 (20)	0
> 70% - 80%	1 (6)	1 (7)	1 (7)	3 (23)	3 (23)	2 (20)	0	0	0
> 80% - 90%	0	0	0	1 (8)	0	0	1 (20)	0	1 (20)
> 90% - 100%	1 (6)	0	1 (7)	0	0	3 (30)	2 (40)	2 (40)	1 (20)

Note: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Abbreviation: BMI = body mass index; FAS = Full Analysis Set.

Baseline percentile scores for normalized anthropometric data percentiles WFH (weight for height), ACFA (upper arm circumference for age), and HCFA (head circumference for age) were generally low on baseline and improved to various degrees on post-baseline and final assessments.

At Week 48, about 50% of patients showed improvement in the WFH percentile category, 4 patients remained in the same percentile category, and 2 patients had a decrease in percentile category. At Week

144, except for 1 patient who was in the percentile category of > 80% to 100% at baseline, all patients (9 patients) either remained in the same WFH percentile category or had a shift to a higher percentile category.

Likewise, median changes from baseline in Z-scores for WFH, ACFA and HCFA showed improvement under treatment.

The results on stunting wasting and underweight are presented in **Table 28**.

Table 28: *Patients Underweight or With Stunting or Wasting: Pooled FAS 2*

Category	Visit	Number and Percentage of Patients, n/N (%)		
		LAL-CL03 n/N (%)	LAL-CL08 n/N (%)	Pooled FAS 2 n/N (%)
Underweight[a]	Baseline	2/8 (25)	6/10 (60)	8/18 (44)
	Week 12	3/6 (50)	3/9 (33)	6/15 (40)
	Week 24	3/6 (50)	1/9 (11)	4/15 (27)
Stunting[b]	Baseline	4/8 (50)	4/9 (44)	8/17 (47)
	Week 12	1/6 (17)	1/8 (13)	2/14 (14)
	Week 24	2/6 (33)	2/8 (25)	4/14 (29)
Wasting[c]	Baseline	2/8 (25)	5/9 (56)	7/17 (41)
	Week 12	1/6 (17)	2/8 (25)	3/14 (21)
	Week 24	1/6 (17)	1/7 (14)	2/13 (15)

Note: For underweight, N is the number of patients with weight measurements; For stunting, N is the number of patients with height measurements; For wasting, N is the number of patients with both height and weight measurements. For each measure of growth deficiency, n represents the number of patients who met the definition for each measure at the specific visit.

Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.

[a] Underweight was defined as a WFA at least 2 SDs below the median WFA of a reference population.

[b] Stunting was defined as an LFA/HFA at least 2 SDs below the median LFA/HFA of a reference population.

[c] Wasting was defined as a WFL/WFH at least 2 SDs below the median WFL/WFH of a reference population.

Abbreviations: FAS = Full Analysis Set; HFA = height-for-age; LFA = length-for-age; SD = standard deviation; WFA = weight-for-age; WFL = weight-for-length; WFH = weight-for-height.

Rapporteur's comments

Overall, the integrated analysis mirrors the experience in the individual past studies , confirming that a positive effect on growth and weight can be achieved in infants, though one should be cognisant of the fact that there is a strong paucity in the number of infant subject, which makes the results seen hopeful though lacking a measure of statistically confirmative rigour.

Liver and Spleen Assessment & Biopsy – Children and Adults

At baseline, mean (SD) liver volume in Pooled FAS 1 was 1.41 (0.384), mainly due to the influence os studies LAL-CL02 and CL06, as baseline parameters were near normal in LAL-CL01/CL04. Regardlessly, liver volumes decreased as early as Month 3 (in the 8 patients who had a Month 3 assessment) and continued through EOS with a mean change of -0.39 (0.267).

Spleens were markedly enlarged at baseline, with a mean (SD) volume of 3.62 (3.047) MN and spleen volumes generally decreased during treatment with sebelipase alfa, with a mean change of -1.04 (1.295) at EOS. Spleen volumes showed more consistent and marked decreases in Studies LAL-CL02 and LAL-CL06, where baseline spleen volumes were higher, than in Studies LAL-CL01/LAL-CL04.

Liver fat content averaged approximately 8% at baseline and decreased during sebelipase alfa treatment, while spleen fat content averaged approximately 1% to 2% at baseline and fluctuated over time with no

clear treatment effect. Patients whose liver fat content was at least 5% at baseline showed decreases in liver fat content and saw decreases that were almost double at EOS compared to those observed in Pooled FAS 1 as a whole. Changes in spleen fat content for patients with high fat content could not be analysed due to the low number of patients.

Liver biopsy data was gleamed from studies LAL-CL02 and CL06, whereas LAL-CL08 had biopsy data but lacked baseline data. Measured values were Ishak Stage, portal inflammation, lobular inflammation, macrovesicular steatosis, and microvesicular steatosis, as well as computer-assisted morphometric quantified steatosis, collagen, fibrogenic cell, and macrophage percentages.

In study LAL-CL02 biopsies were taken at baseline and at the end of the double-blind period. Optional biopsies were possible in the open label and open label extension phases. Biopsies were to be taken in adults, but could be optionally performed in children. If no baseline biopsy data was available a historical biopsy no older than 26 Weeks could be used instead if adequate for histological examination. A total of 29 subjects had baseline data available and 26 of them had at least one post-baseline liver biopsy.

The protocol for Study LAL-CL06 foresaw liver biopsies to be obtained at Screening and Week 48 ± 2 weeks (or earlier for patients who had at least 20 weeks of treatment but discontinued the study prior to Week 48). A historical biopsy obtained within 26 weeks prior to Screening and adequate for histological examination could be used in lieu of a Screening biopsy. Optional liver biopsies could be done at Week 96.

Baseline liver biopsies were obtained for all 31 patients enrolled and treated with sebelipase alfa, and postbaseline liver biopsies were obtained for 30 of these patients

Ishtak stage scoring was determined based on histopathological assessment of the liver biopsies and ranged between a value of 0-6, whereby each successive score reflects more scarring than the preceding stage.

At baseline, 3 of 59 patients (5%) had Ishak scores of 0 (no fibrosis); 15 patients (25%) had Ishak scores of 6 (probable or definite cirrhosis). Ishak scores improved by Month 12, when 9 patients (24%) had Ishak scores of 0 and 7 patients (18%) had Ishak scores of 6. A total of 47% of subjects had a ≥ 1 point reduction (improvement) in Ishak scores from baseline to Month 12, 39% had no change, and 14% had a ≥ 1 point increase (worsening). As shown in **Table 29**, shift analysis indicated that there was relatively more improvement than worsening in the pooled FAS 1.

Table 29: *Shifts in Ishak Scores: Pooled FAS 1*

Postbaseline	Ishak Stage at Baseline							
	Stage 0 n (%)	Stage 1 n (%)	Stage 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)	Stage 6 n (%)	Total n (%)
Ishak Stage at Month 12 (N = 36)								
Stage 0	1 (3)	2 (6)	1 (3)	3 (8)	0	1 (3)	0	8 (22)
Stage 1	0	2 (6)	1 (3)	3 (8)	0	0	0	6 (17)
Stage 2	0	1 (3)	1 (3)	2 (6)	0	0	0	4 (11)
Stage 3	0	0	1 (3)	3 (8)	1 (3)	0	1 (3)	6 (17)
Stage 4	0	0	0	0	1 (3)	0	1 (3)	2 (6)
Stage 5	0	0	0	2 (6)	0	0	1 (3)	3 (8)
Stage 6	0	0	0	1 (3)	0	0	6 (17)	7 (19)
Total	1 (3)	5 (14)	4 (11)	14 (39)	2 (6)	1 (3)	9 (25)	36 (100)

Abbreviation: FAS = Full Analysis Set.

Measurements of lobular inflammation, macrovesicular steatosis, microvaesicular steatosis and portal inflammation are shown in tables 30-33.

Table 30: *Liver Biopsy Assessments: Lobular Inflammation: Pooled FAS 1*

Parameter	LAL-CL02 (N = 66) n (%)	LAL-CL06 (N = 31) n (%)	Pooled FAS 1 (N = 106) n (%)
Lobular Inflammation at Baseline	**29**	**30**	**59**
None	0	1 (3)	1 (2)
One focus or less per 10× objective	17 (59)	11 (37)	28 (47)
Two to four foci per 10× objective	11 (38)	14 (47)	25(42)
Five to ten foci per 10× objective	1 (3)	2 (7)	3 (5)
More than 10 foci per 10× objective	0	2 (7)	2 (3)
Lobular Inflammation at Month 12	**13**	**25**	**38**
None	2 (15)	0	2 (5)
One focus or less per 10× objective	8 (62)	6 (24)	14 (37)
Two to four foci per 10× objective	3 (23)	9 (36)	12 (32)
Five to ten foci per 10× objective	0	7 (28)	7 (18)
More than 10 foci per 10× objective	0	3 (12)	3 (8)

Abbreviation: FAS = Full Analysis Set.

Table 31: *Liver Biopsy Assessments: Macrovesicular Steatosis: Pooled FAS 1*

Parameter	LAL-CL02 (N = 66) n (%)	LAL-CL06 (N = 31) n (%)	Pooled FAS 1 (N = 106) n (%)
Macrovesicular Steatosis at Baseline	**29**	**30**	**59**
None	25 (86)	25 (83)	50 (85)
Fat vacuoles replacing < 5% of hepatocyte area	2 (7)	3 (10)	5 (8)
Fat vacuoles replacing 5 - 33% of hepatocyte area	2 (7)	2 (7)	4 (7)
Fat vacuoles replacing 33 - 66% of hepatocyte area	0	0	0
Fat vacuoles replacing > 66% of hepatocyte area	0	0	0
Macrovesicular Steatosis at Month 12	**13**	**25**	**38**
None	9 (69)	22 (88)	31 (82)
Fat vacuoles replacing < 5% of hepatocyte area	3 (23)	2 (8)	5 (13)
Fat vacuoles replacing 5 - 33% of hepatocyte area	1 (8)	1 (4)	2 (5)
Fat vacuoles replacing 33 - 66% of hepatocyte area	0	0	0
Fat vacuoles replacing > 66% of hepatocyte area	0	0	0

Abbreviation: FAS = Full Analysis Set.

Table 32: *Liver Biopsy Assessments: Microvesicular Steatosis: Pooled FAS 1*

Parameter	LAL-CL02 (N = 66) n (%)	LAL-CL06 (N = 31) n (%)	Pooled FAS 1 (N = 106) n (%)
Microvesicular Steatosis at Baseline	**29**	**30**	**59**
None	0	2 (7)	2 (3)
Fat vacuoles replacing < 5% of hepatocyte area	1 (3)	0	1 (2)
Fat vacuoles replacing 5 - 33% of hepatocyte area	2 (7)	3 (10)	5 (8)
Fat vacuoles replacing 33 - 66% of hepatocyte area	2 (7)	4 (13)	6 (10)
Fat vacuoles replacing > 66% of hepatocyte area	24 (83)	21 (70)	45 (76)
Microvesicular Steatosis at Month 12	**13**	**25**	**38**
None	0	2 (8)	2 (5)
Fat vacuoles replacing < 5% of hepatocyte area	2 (15)	5 (20)	7 (18)
Fat vacuoles replacing 5 - 33% of hepatocyte area	2 (15)	6 (24)	8 (21)
Fat vacuoles replacing 33 - 66% of hepatocyte area	2 (15)	2 (8)	4 (11)
Fat vacuoles replacing > 66% of hepatocyte area	7 (54)	10 (40)	17 (45)

Abbreviation: FAS = Full Analysis Set.

Table 33:*Liver Biopsy Assessments: Portal Inflammation: Pooled FAS 1*

Parameter	LAL-CL02 (N = 66) n (%)	LAL-CL06 (N = 31) n (%)	Pooled FAS 1 (N = 106) n (%)
Portal Inflammation at Baseline	**29**	**30**	**59**
None	0	1 (3)	1 (2)
Mild, some or all portal areas	17 (59)	6 (20)	23 (39)
Moderate, some or all portal areas	10 (34)	15 (50)	25 (42)
Moderate/marked, all portal areas	2 (7)	7 (23)	9 (15)
Marked, all portal areas	0	1 (3)	1 (2)
Portal Inflammation at Month 12	**13**	**25**	**38**
None	1 (8)	0	1 (3)
Mild, some or all portal areas	4 (31)	8 (32)	12 (32)
Moderate, some or all portal areas	8 (62)	12 (48)	20 (53)
Moderate/marked, all portal areas	0	5 (20)	5 (13)
Marked, all portal areas	0	0	0

Abbreviation: FAS = Full Analysis Set.

CD68 immunostaining revealed a tendency for the macrophages ratio to improve with a mean change of -3.386 (SD: 5.3915) from baseline to month 12, whereas histological steatosis assessment also indicated a mean decrease of -5.714 (SD: 13.2958).

In general, the overall trend, as seen in both studies LAL-CL02 and CL06, is supportive of improvement of progression of liver damage in patients treated with sebelipase alfa for 12 months compared to baseline.

Rapporteur's comments

Overall, integrated analysis of liver and spleen parameters showed a fairly nebulous picture with no immediate picture of a clear improvement. Shift tables did however show that there was generally more improvement, but in actual clinical practice these improvements seem to be limited. Given that no clear line can be seen in either the individual study results, nor in the integrated pooled analysis, it is difficult to attach any meaningful clinical benefit assessments these findings.

Liver and Spleen Assessment – Infants

Measurements of change of liver and spleen volume using MRI imaging were only scantly available for infants and of insufficient quantity to allow statistical inference. Ultrasound volume estimations were more readily available, with mean baseline liver and spleen volumes being 3 and 6 MN respectively. Liver volumes had a mean change of -1.24 (.888) MN versus baseline at EOS, while spleen volumes were reduced by a mean of -3.30 (3.756) MN.

Rapporteur's comments

Liver and spleen parameters were more limited and more crude in infants, though the overall results do seem to indicate a trend towards improvement for both.

Biological parameters – Children and Adults

Generally treatment induced a progressive decrease in ALT and AST in the Pooled FAS 1 group, with a proportion of patients seeing a normalization of the transaminase levels (**Table 34**). Shifts from abnormal levels to worse abnormal levels were quite rare.

Table 34: *Normalization of Serum Transaminase Levels: Pooled FAS 1*

Visit	Patients With ALT in "Normal" Category, n/N (%)		Patients With AST in "Normal" Category, n/N (%)	
	Normal at Baseline	Normal at Indicated Postbaseline Visit	Normal at Baseline	Normal at Indicated Postbaseline Visit
Month 3	10/97 (10%)	43/97 (44%)	12/92 (13%)	45/92 (49%)
Month 6	10/101 (10%)	49/101 (49%)	13/99 (13%)	49/99 (49%)
Month 12	9/65 (14)	38/65 (58%)	11/64 (17%)	38/64 (59%)
Month 24	8/89 (9%)	49/89 (55%)	12/86 (14%)	59/86 (69%)
Month 36	2/26 (8%)	18/26 (69%)	2/25 (8%)	16/25 (64%)
Month 48	1/28 (4%)	14/28 (50%)	2/27 (7%)	18/27 (67%)

Note: "Normal" is based on investigator's assessment or laboratory normal range if investigator's assessment is missing (laboratory normal ranges are shown in ISE Listing 16.3.13.3).
Studies LAL-CL01/LAL-CL04 and LAL-CL06: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Study LAL-CL02: Baseline is the average of the last, up to 3, non-missing assessments (including unscheduled) prior to the first infusion of sebelipase alfa.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FAS = Full Analysis Set; N = number of patients with values at both baseline and the indicated postbaseline visit; n = number of patients in the specified category at the indicated postbaseline visit.

GGT levels decreased from an overall mean of 50.15 (48.6) U/L with a mean amount of 18.49 U/L, which was maintained throughout the assessment period, and overall level normalizations increased.

Table 35: *Normalization of Serum GGT Levels: Pooled FAS 1*

Visit	Patients With GGT in "Normal" Category, n/N (%)	
	Normal at Baseline	Normal at Indicated Postbaseline Visit
Month 3	61/98 (62%)	74/98 (76%)
Month 6	63/101 (62%)	82/101 (81%)
Month 12	43/65 (66%)	55/65 (85%)
Month 24	54/89 (61%)	80/89 (90%)
Month 36	15/26 (58%)	23/26 (88%)
Month 48	15/28 (54%)	24/28 (86%)

Note: "Normal" is based on investigator's assessment or laboratory normal range if investigator's assessment is missing (laboratory normal ranges are shown in ISE Listing 16.3.13.3).
Studies LAL-CL01/LAL-CL04 and LAL-CL06: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Study LAL-CL02: Baseline is the average of the last, up to 3, non-missing assessments (including unscheduled) prior to the first infusion of sebelipase alfa.
Abbreviations: FAS = Full Analysis Set; GGT = gamma glutamyltransferase; N = number of patients with values at both baseline and the indicated postbaseline visit; n = number of patients in the specified category at the indicated postbaseline visit.

The results for total bilirubin were more variable and decreases tended to vary according to study. The majority of patients did however not experience much improvement in bilirubin levels with treatment.

Likewise, alkaline phosphatase level results were also quite heterogeneous between individual studies, though an overall normalization trend was observed.

No significant changes in albumin levels were apparent, given that most patients had normal levels at baseline and maintained those during the assessment period.

Rapporteur's comments

The integrated analysis results mostly echoed the results already seen in the individual studies with clear improvements in ALT, AST and GGT; and less clear results in other parameters.

Biological parameters – Infants

Similar to the changes in Pooled FAS 1, an initial decrease in serum transaminase levels and subsequent maintenance of decreased levels was seen in Pooled FAS 2. There was a general increase of proportions of infants with normalized levels and improvement shifts generally occurred more than worsening.

In infants there was a general trend towards improvements in GGT, bilirubin, alkaline phosphatase and albumin levels. Proportional shifts to normalization could generally not be interpreted due to the too small sample sizes.

Rapporteur's comment

Results in infants mostly echoed those in adults, though with a trend of somewhat positive improvements in non-ALT, -AST and -GGT parameters.

Serum Lipids – Children and Adults

High density lipoprotein cholesterol showed evident increases were evident at Month 3 which continued through EOS, with a mean overall increase of 9.63 mg/dL (SD: 8.846). Low density lipoprotein cholesterol tended to increase at the Month 1 timepoint but then decreased from Month 3 until EOS onward. Non-HDL-C and LDL-C mirrored these patterns.

At baseline less than half of the overall patients had normal ranges of tryglicerides, HDL-C and LDL-C; generally these proportions increased during treatment.

Table 36: *Normalization of HDL and LDL Cholesterol Levels: Pooled FAS 1*

Visit	Patients With HDL Cholesterol in "Normal" Category, n/N (%)		Patients With LDL Cholesterol in "Normal" Category, n/N (%)	
	Normal at Baseline	Normal at Indicated Postbaseline Visit	Normal at Baseline	Normal at Indicated Postbaseline Visit
Month 3	42/98 (43%)	58/98 (59%)	29/97 (30%)	38/97 (39%)
Month 6	41/100 (41%)	61/100 (61%)	28/97 (29%)	48/97 (49%)
Month 12	25/62 (40%)	42/62 (68%)	18/59 (31%)	30/59 (51%)
Month 24	33/87 (38%)	63/87 (72%)	24/84 (29%)	40/84 (48%)
Month 36	11/24 (46%)	18/24 (75%)	10/24 (42%)	17/24 (71%)
Month 48	12/28 (43%)	25/28 (89%)	11/28 (39%)	17/28 (61%)

Note: "Normal" is based on investigator's assessment or laboratory normal range if investigator's assessment is missing (laboratory normal ranges are shown in ISE Listing 16.3.13.3).
Studies LAL-CL01/LAL-CL04 and LAL-CL06: Baseline is the last non-missing assessment (including unscheduled) prior to the first infusion of sebelipase alfa.
Study LAL-CL02: Baseline is the average of the last, up to 3, non-missing assessments (including unscheduled) prior to the first infusion of sebelipase alfa.
Abbreviations: FAS = Full Analysis Set; HDL = high density lipoprotein; LDL = low density lipoprotein; N = number of patients with values at both baseline and the indicated postbaseline visit; n = number of patients in the specified category at the indicated postbaseline visit.

Rapporteur's comments

The integrated cross-study analysis did generally echo the same observations already made in the individual studies, namely that HDL-C and LDL-C levels generally improved under treatment, with a sizeable number of patients achieving normalisation.

Serum Lipids – Infants

Levels of HDL-C generally increased with sebelipase alfa treatment, and triglycerides generally decreased. Levels of LDL-C generally appeared to decrease, but sample sizes were too small to allow conclusions to be drawn. Conclusions on overall normalization were uncertain because of small sample sizes.

Rapporteur's comment

The trend in Pooled FAS 2 echoes the observations in the Pooled FAS 1, but as noted by the Applicant already, the numbers were too few to make any conclusive deduction.

QOL assessments - All

Overall, there was too little data to have any meaningful analysis of QOL responses on the FACIT, CLDQ, PedsQL and Denver II questionnaires.

Dietary change assessments - All

Overall, interpretation of data was not possible to due high variability and small sample sizes.

Dose and Dose Changes – Children and Adults

Across the sebelipase alfa clinical program, patients could be considered for dose escalation if they exhibited a suboptimal clinical response to treatment based on specific protocol-defined criteria.

In regards to the current cross-study comparison exercise, the MAH conducted a medical review of efficacy data to identify the key clinical findings that were most often observed in patients who received a dose increase from the protocol-defined starting dose to evaluate whether this dose escalation was associated with a change in the clinical course for these patients. The efficacy parameters included in this review represent the primary disease manifestations contributing to the significant burden of disease and reduced life expectancy across the disease spectrum.

Dose changes were rarely used in the LAL-CL01/04 study, and as such analysis was only done on changes in studies LAL-CL02 and CL06, both of which had a starting dose of 1 mg/kg qow. In LAL-CL02 dose escalation to 3 mg/kg qow was permitted for patients who met protocol-defined criteria, and dose reduction to 0.35 mg/kg qow was permitted in the event of poor tolerability. These dose adaptations were only permitted in the open-label period. In LAL-CL06 dose escalation to 3 mg/kg qow, and subsequent escalation to 3 mg/kg qw, were permitted for patients who met protocol-defined criteria. Dose reduction, to a minimum dose of 0.35 mg/kg qow, was permitted in the event of poor tolerability.

Overall, the starting dose of 1 mg/kg qow demonstrated a positive effect on clinically relevant parameters: serum transaminases, lipids, and in some children, WFA. Most dose escalations to 3 mg/kg qow were implemented after 1.5 years of treatment or longer and were initiated in response to an increase in serum transaminase levels, an increase in serum lipids, or a decrease in WFA in children.

Following the dose escalation, most patients had improvement in serum transaminases and lipids that were sustained until the end of the study. However, most children remained below the age-related median WFA despite showing improvements in other clinical parameters. Four patients underwent subsequent dose escalations to 3 mg/kg qw in an effort to optimize disease management.

Table 37 provides an overview on the doses administered and the number of patients that received said doses:

Table 37*: Sebelipase Alfa Doses: Pooled Safety Set 1*

Dose	Number of Patients Who Received This Dose During Study			
	LAL-CL01/ LAL-CL04 (N = 9)	LAL-CL02 (N = 66)	LAL-CL06 (N = 31)	Pooled Safety Set 1 (N =106)
0.35 mg/kg qow	1	1	1	3
0.35 mg/kg qw	3	0	0	3
0.68 mg/kg qow	0	1	0	1
1 mg/kg qow	5	66	31	102
1 mg/kg qw	3	0	2	5
3 mg/kg qow	3	12	11	26
3 mg/kg qw	3	0	4	7

Note: A patient may be included in more than 1 dose category. A patient is included if they had 1 or more infusions at the dose and regimen specified.
Abbreviations: qow = once every other week; qw = once weekly.

Subgroup analyses did not did not reveal any impact of liver cirrhosis status at baseline, race, or race group on dose modifications.

Rapporteur's comments

The findings in the integrated analysis support the notion already noticed in the individual trails that the majority of patients is adequately managed with a 1 mg/kg qow dose. Upregulation of doses up to 3mg/kg qow have been relatively frequently used and show that there is a certain dose proportionality in reponse. Even higher doses have been administer in the clinical programme, but these events were relatively rare and the vast majority of patients could be adequately managed with either 1 mg/kg and 3 mg/kg qow.

Based on these findings, in combination with the safety findings, the MAH proposes to adapt the posology to allow up-regulation to 3 mg/kg qow based on clinical response. From a clinical efficacy point of view this could be acceptable given the improved response in patients that failed to be adequately managed under a lower dose.

Dose and Dose Changes – Infants

Across the sebelipase alfa clinical program, patients could be considered for dose escalation if they exhibited a suboptimal clinical response to treatment based on specific protocol-defined criteria.

In regards to the current cross-study comparison exercise, the MAH conducted a medical review of efficacy data to identify the key clinical findings that were most often observed in patients who received a dose increase from the protocol-defined starting dose to evaluate whether this dose escalation was associated with a change in the clinical course for these patients. The efficacy parameters included in this review represent the primary disease manifestations contributing to the significant burden of disease and reduced life expectancy across the disease spectrum.

In LAL-CL03 initial dose escalation was undertaken until the baseline dose of 1mg/kg w was reached (these initial escalations are not included in the cross-study analysis) after which a dose escalation to 3 mg/kg qw, and subsequent escalation to 5 mg/kg qw, were permitted for patients who met protocol-defined criteria. Reduction in dosing frequency from qw to qow were permitted for patients who met protocol-defined criteria. In a similar vein, patients in study LAL-CL08 patients initiated treatment at a dose of 1 mg/kg qw and dose linear escalations to 3 mg/kg qw, 5 mg/kg qw and 7.5 mg/kg qw were permitted for patients who met protocol-defined criteria. Furthermore, reductions in dosing frequency from qw to qow were permitted for patients who met protocol-defined criteria.

Table 38 shows the number of patients that received individual dose levels at least once during their study participation.

Table 38: *Sebelipase Alfa Doses: Pooled Safety Set 2*

Dose	Number of Patients Who Received This Dose During Study		
	LAL-CL03 (N = 9)	LAL-CL08 (N = 10)	Pooled Safety Set 2 (N =19)
0.2 mg/kg qw	1	0	1
0.35 mg/kg qw	8	0	8
0.5 mg/kg qw	1	0	1
0.75 mg/kg qw	1	0	1
1 mg/kg qow	1	0	1
1 mg/kg qw	7	10	17
3 mg/kg qow	3	0	3
3 mg/kg qw	6	9	15
5 mg/kg qow	2	0	2
5 mg/kg qw	2	7	9
7.5 mg/kg qw	0	1	1

Note: A patient may be included in more than 1 category. A patient is included if they had 1 or more infusions at the dose and regimen specified.
Abbreviations: qow = once every other week; qw = once weekly.

A medical review was undertaken to key contributors to morbidity and mortality in infants with rapidly progressive LAL-D, such as there are:

- Growth parameters: WFA, LFA, and mid-upper arm circumference
- Liver parameters: ALT, AST
- Serum lipid parameters: Total cholesterol, triglycerides, LDL-C, HDL-C.

Suboptimal clinical response in predefined parameters for weight gain, based on WFA growth charts, was the most frequently observed clinical finding among the patients who went on to receive a dose escalation to 5 mg/kg qw, the latter which was associated with clear improvement in growth, as evidenced by increases in WFA percentile. While other factors such as dietary changes or acute illness may have had some impact on growth, these cannot account for the consistent and sustained improvement observed in most infants receiving a dose escalation to 5 mg/kg qw. Serum transaminases and serum lipids also generally improved after dose escalation to 5 mg/kg qw.

There were 3 patients in LAL-CL08 whom presented with dual WGD (whole-gene deletion), characterized as a homozygous deletion affecting both alleles of the genes *LIPA* and Cholesterol 25-Hydroxylase, whom had clinical courses that were complicated by persistent high antidrug antibody (ADA)/neutralizing antibody titers, and all 3 patients required a dose escalation to 5 mg/kg qw. Two patients had some changes in clinical parameters consistent with improvement in the underlying disease at the dose of 5 mg/kg qw, while 1 patient failed to improve consistently and received a further dose escalation to 7.5 mg/kg qw. Two of the patients with dual WGD received BMT or HSCT. Following the transplant, the

Investigator was able to reduce the dose of sebelipase alfa to 1 or 3 mg/kg qw to maintain an optimal clinical response.

Finally, subgroup analyses did not reveal any impact of race or race group on the dose modifications.

Rapporteur's comments

The findings in the infant population in a way echoed the findings in the Pooled FAS 1 population, with dose increases up to 7.5 mg/kg qw having been deployed. Overall dose escalations were associated with clear improvements in those infants that failed to adequately respond to the standard 1 mg/kg qw dosing.

Proportionally more infants seem to need dose upregulation, which can be considered a logical consequence that early-onset LAL-D is generally a more aggressive and severe form of the syndrome compared to the late-onset form.

Based on these findings, in combination with the safety findings, the MAH proposes to adapt the posology to allow up-regulation to 5 mg/kg qw based on clinical response in infants.

From a clinical efficacy point of view it is difficult to either support or decline this suggestion. Overall the total population of LAL-D infants was very limited, making rigorous analysis and decision making all but impossible. It is agreed that some patients needed dose upregulation past the currently approved 3 mg/kg qw upper limit, and that these dose increases seem to aid said patients in maintaining a satisfactory response.

On the other hand, 3 out of 9 subjects whom received 5+ mg/kg qw doses were the dual WGD subjects whom have shown to have a far worse clinical reponse than single deletion patients. One of these patients even needed to further escalate, whereas two patients required HSCT or BMT despite being on high dose sebelipase alfa. Thus in total only 6 'regular' subjects were subjected to the 5 mg/kg qw dose ans it is not clear how many PY in exposure these 6subjects represent.

ADA findings – All

Overall infants showed a greater proportional development of ADAs compared to adults/children.

The number of ADA positive patients in Pooled FAS 1 and 2 were too small to allow impact analysis on the efficacy endpoints.

As noted, 3 patients in Study LAL-CL08 presented with dual WGD and development of high ADA titers which was associated with decreased WFA and other parameters suggesting failure to thrive. These 3 patients required dose escalations of sebelipase alfa to achieve maximum clinical benefit. They also received treatments including immunomodulatory therapy with rituximab or bortezomib; one of these patients then had an HSCT and one had a BMT. After the HSCT/BMT, ADA titers decreased and sebelipase alfa was resumed at a lower dosage regimen. The third patient continued to receive sebelipase alfa 5 mg/kg qw and continued to have high titers of ADAs. This patient has improved clinically with bortezomib, but is being prepared for an eventual BMT (data on file at Alexion).

Given the observations made and the worry that this particular genetic combination of dual deletion may represent a subpopulation that is at increased risk of immunogenic responses with cnsequences reduced efficacy, the applicant was asked to do a retrospective integrated analysis of immunology, with specific

focus on the disease-underlying genetic mutations, in paediatric patients enrolled in the trails of the clinical development programme.

However, as reported by the Applicant, most studies do lack genetic data and this in combination with the very limited numbers of infant patients make it impossible to do such analysis, and that the relative contribution of either genetic defect to the observed phenotype and the response to sebelipase alfa enzyme replacement therapy, the LIPA gene deletion or the deletion of the neighboring Cholesterol 25-Hydroxylase gene, is unknown at this stage.

Subgroup analyses

In the Pooled FAS 1 analyses it appeared that mostly age and liver cirrhosis status had an influence on efficacy parameters (mainly on chemistry laboratory findings). Neither dose, race or race group showed any clear influence.

In infants generally the numbers were too small to allow any inference for the planned analyses.

Rapporteur's comments

Overall the findings in the subgroup analyses were difficult to interpret given the generally low numbers and often heterogeneous findings. Though age and liver cirrhosis parameters appeared to show a trend of influence in adults it is impossible to adhere any clear clinical inference to these findings.

Dosing and long-term effect

In the overall clinical development and post-approval investigation of sebelipase alfa 19 non-infant patients received a dose escalation to a maximum dose of 3 mg/kg qow and 4 patients received a dose escalation to a maximum dose of 3 mg/kg qw. The dosing regimens used by the largest numbers of patients in Pooled FAS 1 were 1 mg/kg qow and 3 mg/kg qow, and the maximum dosage used in any study on children and adults was 3 mg/kg qw.

The general reason given for these dose escalations was suboptimal clinical response where by dose escalation usually led to improvement in one or more of the key clinical parameters. In children and adults, the overall exposure to dosages of 3 mg/kg qow or higher was 53 PYs compared to 293 PYs of exposure to 1 mg/kg qow.

In view of the number of patients with dose escalation above 1 mg/kg qow in the study most closely resembling the general population in LAL-D, the significant overall exposure to dosages above 1 mg/kg qow, and the clinical improvements observed in most of the patients with dose escalation to 3 mg/kg qow, the MAH proposes to adjust the recommended dose for children and adults from 1 mg/kg qow to 1 to 3 mg/kg qow, given the absence of any safety signals.

Rapporteur's comments

The overall exposure to 3 mg/kg qow in children and adults was about 5.5 times smaller than to the previously approved 1 mg/kg qow dosing. However, given the fact that patient-numbers for an ultra-rare disease will always be low it seems not entirely avoidable that a large discrepancy like this will be noted when the majority of patients can be adequately controlled on one dose. Given the fact that there are indeed patients that continue to have progressive worsening of their condition on the 'normal' dose level, for which the vast

majority achieved control at the 3 mg/kg qow level, and in light of the acceptable safety at this dosage it is considered acceptable to increase the upper limit of treatment in adults and children to 3 mg/kg qow if circumstances do so require.

In infants, investigators were allowed to escalate the dose of sebelipase alfa beyond the 1 mg/kg qw initial dose. As infants represent the most critically ill patients they received higher doses of sebelipase alfa than children and adults, and underwent more frequent protocol-allowed dose modifications. The dosing regimen used by the largest numbers of patients in Pooled FAS 2 was 1 mg/kg qw, followed closely by 3 mg/kg qw, and the maximum dosage used in any study on infants was 7.5 mg/kg qw. The general reason given for dose escalations was suboptimal clinical response whereby dose escalations were mostky followed by improvement in one or more of the key clinical parameters.

In infants, the overall exposure to dosages of 5 mg/kg qw or higher was 14 PYs compared to 26 PYs of exposure to 3 mg/kg qw, without clear safety signals in the patient groups treated with higher dosages. In view of the frequent dose escalations above 3 mg/kg qw based upon maintaining optimal clinical response, and the significant overall exposure to dosages above 3 mg/kg qw, and the clinical improvements observed in most of the patients with dose escalation to 5 mg/kg qw, the MAH suggests adjusting the recommended dose for infants with rapidly progressive LAL-D from 1 to 3 mg/kg qw to 1 to 5 mg/kg qw based upon clinical response.

Rapporteur's comments

As noted before, a third of the patients exposed to 5+ mg/kg qw sebelipase alfa in the Pooled FAS 2 were of the 'non-regular' dual WGD phenotype, which seems to be characterised by a worse clinical profile and worse response to treatment. Thus only 6 'regular' patients have had need of exposure to higher dosings and it is not clear how many PY of exposure these six patients represent.

Therefore an increase of the maximal posology in infant patients is not supported based on the raw data available.

On the other hand, given the aggressive nature of early-onset LAL-D and the fact that in general the safety of the higher sebelipase alfa dosing seems to be fine (though with the caveat that the numbers of patients and thus data are very limited), it may still be prudent to allow admission of a higher dose of product in those patients that do not achieve control on the current maximal dose of 3 mg/kg qw.

In this case the Applicant should also provide a dosing guideline that clearly explains how to escalate and de-escalate the dose as necessary, and also provides guidance on how to proceed with patients that are not well controlled even on the significantly higher dose of 5 kg/mg qow.

Among children and adults in the LAL-D clinical programme, 85% of patients received sebelipase alfa for at least 130 weeks for a total of 348.09 PYs of exposure, with a maximum duration of exposure of 60.48 months. Among infants, 68% of patients received sebelipase alfa for at least 52 weeks and 47% for at least 156 weeks. Infants received a total of 47.73 PYs of exposure, with a maximum duration of exposure of 60.19 months.

In these long-running studies, sustained improvements were observed in multiple efficacy endpoints and here was no evidence of tolerance or of loss of efficacy over time, with the possible exception of 3 patients in Study LAL-CL08 who had dual WGD and required high doses of sebelipase alfa in order to

achieve maximum clinical benefit. Overall, the data support the long-term efficacy of sebelipase alfa for the treatment of LAL-D in infants, children and adults.

4. Clinical Safety aspects

4.1. Safety analysis of the completed study LAL-EA01

Methods & Results– analysis of data submitted

The 6 patients of the FAS had a combined total of 67 sebelipase alfa infusions, with a median of 11 per patient [min,max: 8,15). All infusions were of a dose level of 1mg/kg qow and no rate changes of interruptions occurred. One incomplete infusion was also registered, where infusion interruption happened due to an infusion-associated reaction.

Table 39 provides an overview of the TEAE landscape as noted in this study:

Table 39: *Overview of Treatment-Emergent Adverse Events*

Category	Sebelipase Alfa (N=6)
Number of subjects with at least 1 TEAE, n (%)	6 (100)
Number of subjects with at least 1 severe TEAE, n (%)	0
Number of subjects with at least 1 related TEAE, n (%)	4 (66.7)
Number of subjects with TEAE Leading to Discontinuation from Study, n (%)	0
Number of subjects with at least 1 IAR, n (%)	1 (16.7)
Number of subjects with at least 1 serious TEAE, n (%)	0
Number of Deaths, n (%)	0

Abbreviations: TEAE = treatment-emergent adverse event

As noted no deaths, TESEAs or discontinuations occurred and treatment-related TEAEs were reported for 4 subjects, including 1 subject who experienced treatment-related IARs during 2 study infusions. These IARs either resolved spontaneously or were managed by interruption of the infusion and administration of antihistamines, and the subject continued to receive treatment in the study.

A summary of TEAEs by SOC is provided in table below.

Table 40: *Summary of the Number (Percentage) Subjects Reporting Treatment*

System Organ Class Preferred Term	Sebelipase Alfa (N=6)	
	All TEAEs	Related TEAEs[a]
Any TEAE	6 (100)	4 (66.7)
Gastrointestinal disorders		
Diarrhea	1 (16.7)	1 (16.7)
General disorders and administration site conditions		
Fatigue	2 (33.3)	2 (33.3)
Infusion site rash	1 (16.7)	0
Infections and infestations		
Nasopharyngitis	1 (16.7)	0
Parainfluenzae virus infection	1 (16.7)	0
Injury, poisoning and procedural complications		
Infusion related reaction	1 (16.7)	1 (16.7)
Investigations		
Alanine aminotransferase increased	4 (66.7)	2 (33.3)
Aspartate aminotransferase increased	2 (33.3)	0
Blood cholesterol increased	3 (50.0)	0
Gamma-glutamyltransferase increased	1 (16.7)	0
Low density lipoprotein increased	3 (50.0)	0
Musculoskeletal and connective tissue disorders		
Back pain	1 (16.7)	0
Neck pain	1 (16.7)	0
Nervous system disorders		
Headache	1 (16.7)	1 (16.7)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (16.7)	0
Nasal congestion	1 (16.7)	0
Skin and subcutaneous disorders		
Xanthoma	1 (16.7)	0
Vascular disorders		
Flushing	1 (16.7)	1 (16.7)

[a] Includes events that were assessed by the Investigator as related or possibly related to treatment with sebelipase alfa

Abbreviations: TEAE = treatment-emergent adverse event

As noted, four subjects experienced treatment-related events. Of these, one subject experienced 3 treatment-related TEAEs of infusion-related reaction, one of which was further characterized as an IAR. All other treatment-related TEAEs reported in this study were not considered IARs. Treatment-related TEAEs reported by more than 1 subject included fatigue (2 subjects) and ALT increased (2 subjects).

No severe TEAEs were reported, though 2 of 6 subjects experienced events of mild severity. All other subjects had at most moderate TEAEs.

One subject reported an IAR of rash and an infusion-related reaction, the former which resolved naturally and the latter which was managed by a temporary interruption of infusion and anti-histamine administration. The subject was also found to be ADA-negative at these times.

No subjects did at any time test positive for ADAs during treatment.

There were no clinically meaningful mean changes in any laboratory parameter over time that would suggest a safety concern for treatment with sebelipase alfa, and no haematological abnormalities were reported in the study.

Serum ferritin was essentially unchanged on treatment, with 5 subjects having a serum ferritin level that was within normal range at baseline and remained normal through EOT, and 1 subject having a serum ferritin level that was elevated at baseline and throughout the study.

Four subjects, all enrolled at one clinical site, had abnormalities in liver and/or lipid parameters that were reported by the investigator as TEAEs. These laboratory TEAEs included ALT increased (4 subjects), AST increased (2 subjects), blood cholesterol increased (3 subjects), LDL-c increased (3 subjects) and/or GGT increased (1 subject). A majority of these laboratory abnormalities were assessed as unrelated to treatment. Treatment-related TEAEs were reported for 2 pediatric subjects, both of whom had a treatment-related TEAE of ALT increased.

Two subjects had a palpable liver at baseline, and both subjects had a reduction in liver size during treatment with sebelipase alfa, with the palpable area decreasing from a baseline up to 50%. One other subject in the study had a liver and spleen that were non-palpable at baseline, but were reported as palpable at Day 87 and continued to be palpable to the same extent at the EOT visit.

Finally, There were no trends in vital sign data that would suggest a safety concern for sebelipase alfa.

Discussion

No deaths or serious TEAEs were reported, and no subject discontinued from the study due to a TEAE. All TEAEs were mild or moderate in severity, and most events were considered unrelated to treatment.

Treatment-related TEAEs were reported for 4 subjects in the study. One subject experienced events that were characterized as IARs. This subject experienced IARs at 2 study infusions, including a mild infusion site rash at Day 29 and a moderate infusion-related reaction at Day 80. The rash resolved without medical intervention, and the infusion-related reaction was managed by interruption of the infusion and administration of antihistamine. The subject continued to receive treatment in the study.

None of the 5 subjects with post-baseline immunogenicity data tested positive for ADAs following initiation of treatment with sebelipase alfa.

Clinical laboratory, vital sign, and physical examination results did not indicate any clinically meaningful trends that would present a safety concern for sebelipase alfa.

4.2. Integrated safety analysis of studies LAL-CL01, LAL-CL04, LAL-CL02, LAL-CL06, LAL-CL03 and LAL-CL08

Methods – analysis of data submitted

4.2.1. Overall Background

This integrated safety analysis provides the complete characterization of the safety profile of sebelipase alfa in the treatment of lysosomal acid lipase deficiency (LAL-D), a serious and life-threatening multisystem storage disorder caused by a marked decrease or absence in lysosomal acid lipase (LAL) activity, and discusses the cross-study safety observations as made in the completed clinical study programme (Table 26).

This integrated analysis includes the safety data gleamed from a total of 125 patients (19 infants, 69 children and 37 adults), which were separate in two pooled safety groups for this exercise: Pooled SS1 (including all children and adults) and Pooled SS 2 (including all infants). Note that patients form the US-based expanded access protocol LAL-EA01 were not included for safety analysis.

Table 41: *Integrated Summary of Safety Populations*

Population	Pooled Studies	Summarized Treatment Groups
Pooled Safety Set 1 – studies of noninfants (children and adults) diagnosed with LAL-D	LAL-CL01/LAL-CL04 (extension study) LAL-CL02 LAL-CL06	0.35 mg/kg qw 0.35 mg/kg qow 0.68 mg/kg qow[a] 1 mg/kg qw 1 mg/kg qow 3 mg/kg qow 3 mg/kg qw
Pooled Safety Set 2 – studies of infants who developed growth failure or other evidence of a rapidly progressive course of LAL-D	LAL-CL03 LAL-CL08	0.2 mg/kg qw[a] 0.35 mg/kg qw 0.5 mg/kg qw[a] 0.75 mg/kg qw[a] 1 mg/kg qw 1 mg/kg qow 3 mg/kg qw 3 mg/kg qow 5 mg/kg qw 5 mg/kg qow 7.5 mg/kg qw

Note: For the dose subgroup analysis, treatment groups with associated data were to be presented.
[a] This dosage regimen was not planned per protocol.
Abbreviations: LAL-D = lysosomal acid lipase deficiency; qow = once every other week; qw = once weekly.

Figure 5 provides a schematic overview of the Pooled SS composition flow, while **Table 42** and **Table 43** provide an overview of the analysed safety and subgroup parameters respectively.

Table 42: *Safety Data Evaluated for the Integrated Summary of Safety Analysis*

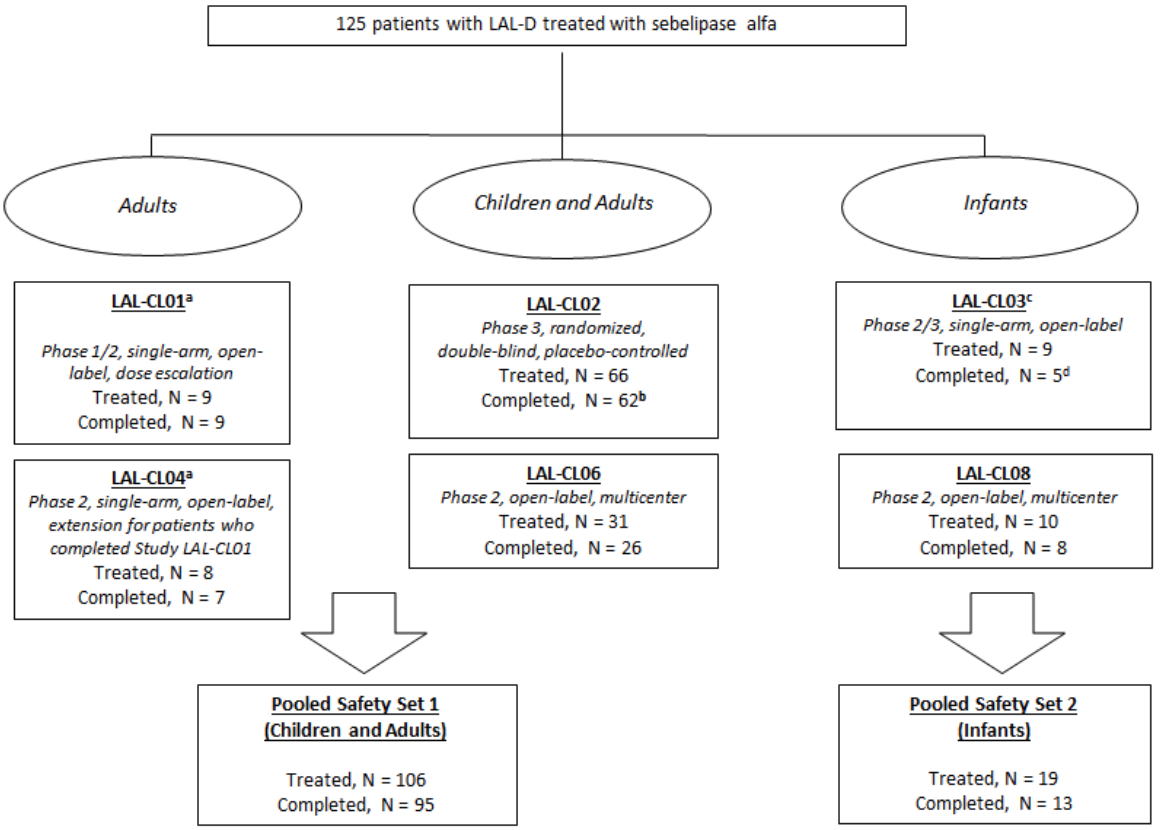
Safety Data	Pooled Data From ISS Analysis	Study Data From Individual CSRs
Disposition	X	X
Duration of exposure	X	X
Demographics	X	X
Baseline disease characteristics	X	X
Other characteristics[a]	X	X
AEs[b], SAEs[b], AESIs	X	X
Laboratory parameters (hematology and coagulation parameters, clinical chemistry, urinalysis)	X	X
Vital signs	X	X
Immunogenicity (ADA and NAb)	X	X

[a] Other characteristics include prior and concomitant medications, and nonpharmacologic therapies and procedures.
[b] All AEs were considered as TEAEs unless specified otherwise.
Abbreviations: ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; CSR = clinical study report; ISS = Integrated Summary of Safety; NAb = neutralizing antibody; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 43: *Subgroup Analyses Performed for the Pooled Safety Set*

	Pooled Safety Set		Subgroups Within Pooled Analyses						
Safety Data	**Pooled Safety Set 1[a]**	**Pooled Safety Set 2[b]**	**Age[c]**	**Gender**	**Race**	**Baseline LLM[d]**	**ADA Positive Status[e]**	**Liver Cirrhosis**	**Dose**
Disposition	X	X	NA	NA	NA	NA	NA	NA	NA
Demographics	X	X	NA	NA	NA	NA	NA	X	NA
Exposure	X	X	X	X	X	X	X	NA	NA
Baseline disease characteristics	X	X	NA	NA	NA	NA	NA	X	NA
Concomitant medications	X	X	X	X	X	X	X	NA	X
TEAEs	X	X	X	X	X	X	X	NA	X
Laboratory evaluations	X	X	X	X	X	X	X	X	X
Immunogenicity	X	X	X	X	X	X	NA	NA	X
Vital signs	X	X	X	X	X	X	X	NA	X

[a] Includes patients in Studies LAL-CL01/LAL-CL04, LAL-CL02, and LAL-CL06.
[b] Includes patients in Studies LAL-CL03 and LAL-CL08.
[c] Age categories were only analyzed for Pooled Safety Set 1.
[d] A patient was considered to have taken a LLM if it was administered during the period between the informed consent date and the date of the first infusion of study drug.
[e] Antidrug antibody positivity was defined as the period after an ADA positive result until an ADA negative result and ADA negativity was defined as the period before an ADA positive result or the period between an ADA negative result and an ADA positive result. ADA positivity was confirmed if both screening and confirmatory assays were positive.



[a] All but 1 patient in Study LAL-CL01 were enrolled in extension Study LAL-CL04.
[b] Patients were considered to have completed Study LAL-CL02 if they completed Open-label Extension or Expanded Period or moved to commercially available drug: 2 patients were lost-to-follow-up and 2 patients withdrew consent.
[c] Study LAL-CL05 (an open-label extension study of sebelipase alfa in children with LAL-D) was terminated. Data from the 1 enrolled patient were subsequently merged with Study LAL-CL03 and are included in the integrated analyses. Therefore, data from Study LAL-CL05 will not be presented separately from Study LAL-CL03.
[d] Four patients were considered early terminated due to death.

Figure 5: *Flow of Patients From Clinical Studies Into the Pooled Safety Sets*

Table 44: *Completed Clinical Studies With Sebelipase Alfa Included in Pooled Safety Sets 1 and 2*

	Protocol Number					
	Pooled Safety Set 1 (Children and Adults)				Pooled Safety Set 2 (Infants)	
Descriptor	**LAL-CL01**	**LAL-CL04**	**LAL-CL02**	**LAL-CL06**	**LAL-CL03[a]**	**LAL-CL08**
Study design	Phase 1/2, open-label, dose escalation; safety, tolerability, and PK, PD of SBC-102 in adult patients with liver dysfunction due to LAL-D	Phase 2, open-label extension for adult patients who successfully completed Study LAL-CL01; long-term safety, tolerability, efficacy, PK, and PD in adult patients with liver dysfunction due to LAL D	Phase 3, randomized, placebo-controlled, double-blind period followed by open-label (extension and expanded treatment) period; efficacy, safety, tolerability, immunogenicity, and PK of SBC-102 versus placebo in patients with LAL-D	Phase 2, open-label study, safety, efficacy, immunogenicity, and PK in patients with LAL-D	Phase 2/3, open-label, repeat dose, intra-patient dose escalation; efficacy, safety, tolerability, and PK of SBC-102 in infants with growth failure due to LAL-D	Phase 2, open-label, repeat-dose; safety, tolerability, efficacy, and PK infants with rapidly progressive LAL-D in infants with rapidly progressive LAL-D
Study population	Adult (≥ 18 years)	Adult (≥ 18 years)	Pediatric / adult (≥ 4 years)	Pediatric / adult (> 8 months)	Infant (≤ 2 years)	Infant (≤ 2 years)
Planned	9	9	50	30	10	10
Treated	9	8	66	31	9	10
Completed	9	7	62[b]	26	5	8
Dosage regimen	Cohort 1: 0.35 mg/kg, qw, IV dose Cohort 2: 1 mg/kg, qw, IV dose Cohort 3: 3 mg/kg, qw, IV dose	0.35, 1, or 3 mg/kg, qw, IV doses for 4 weeks followed by 1 or 3 mg/kg, qow IV	1 mg/kg, qow, IV dose	Starting dose of 1 mg/kg qow, IV; dose escalation to 3 mg/kg qow and subsequently to 3 mg/kg qw	Starting dose of 0.2 or 0.35 mg/kg qw, IV; dose escalations to 1 mg/kg qw, 3 mg/kg qw, or 5 mg/kg qw; IV	Starting dose of 1 mg/kg, qw, IV; dose escalation to 3 mg/kg qw, and further to 5 mg/kg qw or 7.5 mg/kg qw IV[c]
Treatment duration	4 weeks	Up to 5 years	20-week Double-blind Period, followed by an Open-label Period of up to 234 weeks (up to130 weeks of Extension Period, followed by an Expanded Treatment Period of up to 104 weeks)	Up to 144 weeks	Up to 5 years	Up to 3 years
CSR database lock/cutoff date	07 Dec 2015 (final CSR)[d]	15 Sep 2017 (final CSR)	30 May 2014 (Double-blind Period CSR) 21 Feb 2019 (final Open-label Period)	16 Apr 2018 (final CSR)	10 Apr 2018[e] (final CSR)	23 Jan 2019 (final CSR)

[a] Study LAL-CL05, an extension of Study LAL-CL03, was merged with Study LAL-CL03. Only 1 patient was enrolled in Study LAL-CL05 and this patient transitioned into Study LAL-CL03.

[b] Patients were considered to have completed Study LAL-CL02 if they completed Open-label Extension or Expanded Treatment Period or moved to commercially available drug: 2 patients were lost-to-follow-up and 2 patients withdrew consent.

[c] Patients receiving treatment in the UK could be considered for a further dose escalation to 7.5 mg/kg qw if a thorough case review indicated that a patient continued to have evidence of disease progression at a dose of 5 mg/kg qw.

[d] The CSR has been updated to version 2. Text has been revised to reflect that PK data was disqualified as all samples were evaluated outside of validated assay stability.

[e] Approximate date – exact date is unknown.

Abbreviations: CSR = clinical study report; IV = intravenous(ly); NA = not applicable; PD = pharmacodynamic(s); PK = pharmacokinetic(s); qow = once every other week; qw = once weekly; UK = United Kingdom.

4.2.2. Exposure

4.2.2.1. Overall Exposure – Children & Adults

The median duration of exposure for children and adults was 35.515 months cumulating in a total of 348.09 patient years (PY) of exposure. A similar proportion of patients were exposed to sebelipase alfa during discrete time periods through approximately 3 years (156 weeks) after initial exposure. Thereafter, the cumulative exposure decreased as only Studies LAL-CL04 and LAL-CL02 were ongoing after that timepoint.

A summary of exposure by dose, study and overall is provided in Table 45. Note that due to dose flexibility a patient may be included in more than 1 dose category.

Table 45: *Duration of Exposure to Sebelipase Alfa by Dose, by Study and Overall – Pooled Safety Set 1*

Parameter	Statistic	LAL-CL01/ LAL-CL04 (N = 9)	LAL-CL02 (N = 66)	LAL-CL06 (N = 31)	Pooled Safety Set 1 (N = 106)
Duration (months)					
0.35 mg/kg qow	n	1	1	1	3
	Mean (SD)	0.920 (NA)	1.413 (NA)	16.033 (NA)	6.122 (8.5867)
	Median (min, max)	0.920 (0.92, 0.92)	1.413 (1.41, 1.41)	16.033 (16.03, 16.03)	1.413 (0.92, 16.03)
	Q1, Q3	0.92, 0.92	1.41, 1.41	16.03, 16.03	0.92, 16.03
0.35 mg/kg qw	n	3	NA	NA	3
	Mean (SD)	1.906 (0.0657)	NA	NA	1.906 (0.0657)
	Median (min, max)	1.906 (1.84, 1.97)	NA	NA	1.906 (1.84, 1.97)
Parameter	**Statistic**	**LAL-CL01/ LAL-CL04 (N = 9)**	**LAL-CL02 (N = 66)**	**LAL-CL06 (N = 31)**	**Pooled Safety Set 1 (N = 106)**
	Q1, Q3	1.84, 1.97	NA	NA	1.84, 1.97
0.68 mg/kg qow	n	NA	1	NA	1
	Mean (SD)	NA	0.460 (NA)	NA	0.460 (NA)
	Median (min, max)	NA	0.460 (0.46, 0.46)	NA	0.460 (0.46, 0.46)
	Q1, Q3	NA	0.46, 0.46	NA	0.46, 0.46
1 mg/kg qow	n	5	66	31	102
	Mean (SD)	50.983 (10.9694)	38.002 (14.2451)	24.115 (9.9614)	34.418 (14.8120)
	Median (min, max)	55.326 (32.36, 58.61)	40.805 (6.93, 59.14)	27.598 (5.98, 33.35)	33.199 (5.98, 59.14)
	Q1, Q3	50.10, 58.51	29.93, 49.68	16.56, 33.15	24.57, 47.08
1 mg/kg qw	n	3	NA	2	5
	Mean (SD)	1.478 (0.6546)	NA	1.840 (1.5797)	1.623 (0.9367)
	Median (min, max)	1.840 (0.72, 1.87)	NA	1.840 (0.72, 2.96)	1.840 (0.72, 2.96)
	Q1, Q3	0.72, 1.87	NA	0.72, 2.96	0.72, 1.87
3 mg/kg qow	n	3	12	11	26
	Mean (SD)	58.448 (0.0657)	24.285 (9.2375)	11.117 (6.7489)	22.656 (16.4119)
	Median (min, max)	58.448 (58.38, 58.51)	28.172 (5.88, 33.45)	11.992 (2.83, 27.17)	18.628 (2.83, 58.51)
	Q1, Q3	58.38, 58.51	17.87, 30.37	4.63, 13.54	11.07, 30.03
3 mg/kg qw	n	3	NA	4	7
	Mean (SD)	1.862 (0.0190)	NA	9.782 (3.6242)	6.388 (4.9490)
	Median (min, max)	1.873 (1.84, 1.87)	NA	11.302 (4.40, 12.12)	4.402 (1.84, 12.12)
	Q1, Q3	1.84, 1.87	NA	7.64, 11.93	1.87, 11.73
Number of infusions received[a]					
0.35 mg/kg qow	n (% of N)	2 (11)	3 (2)	34 (3)	39 (3)
0.35 mg/kg qw	n (% of N)	24 (33)	0	0	24 (3)
0.68 mg/kg qow	n (% of N)	0	1 (2)	0	1 (1)
1 mg/kg qow	n (% of N)	506 (56)	5275 (100)	1609 (100)	7390 (96)
1 mg/kg qw	n (% of N)	20 (33)	0	5 (6)	25 (5)
3 mg/kg qow	n (% of N)	379 (33)	616 (18)	276 (35)	1271 (25)
3 mg/kg qw	n (% of N)	24 (33)	0	164 (13)	188 (7)
Patient-years[b]					
0.35 mg/kg qow	Total	0.08	0.12	1.34	1.53
0.35 mg/kg qw	Total	0.48	0	0	0.48
0.68 mg/kg qow	Total	0	0.04	0	0.04
1 mg/kg qow	Total	21.24	209.01	62.30	292.55
1 mg/kg qw	Total	0.37	0	0.31	0.68
3 mg/kg qow	Total	14.61	24.28	10.19	49.09
3 mg/kg qw	Total	0.47	0	3.26	3.73

Note: Patients could receive study drug at more than 1 dose level; therefore, within each study, a patient may be included in more than 1 dose category. Percentage (%) was based on N.

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

[b] Patient-years of exposure is per 100 years of exposure.

4.2.2.2. Overall Exposure – Infants

The median duration of exposure for infants was 35.61 months with 47.73 PYs of exposure. All patients were exposed to sebelipase alfa up to the first 4 weeks of treatment. Subsequently, a similar proportion of patients were exposed to sebelipase alfa during discrete time periods through approximately 3 years (156 weeks) after initial exposure. Thereafter, the cumulative exposure decreased primarily due to patients completing Study LAL-CL08.

A summary of sebelipase alfa exposure by dose level in the Pooled Safety Set 2 is provided in table.

Table 46: *Duration of Exposure to Sebelipase Alfa by Dose and Study and Overall - Pooled Safety Set 2*

Parameter	Statistic	LAL-CL03 (N = 9)	LAL-CL08 (N = 10)	Pooled Safety Set 2 (N = 19)
Duration (months)				
0.2 mg/kg qw[a]	n	1	NA	1
	Mean (SD)	0.493 (NA)	NA	0.493 (NA)
	Median (min, max)	0.493 (0.49, 0.49)	NA	0.493 (0.49, 0.49)
	Q1, Q3	0.49, 0.49	NA	0.49, 0.49
0.35 mg/kg qw	n	8	NA	8
	Mean (SD)	0.341 (0.1907)	NA	0.341 (0.1907)
	Median (min, max)	0.427 (0.03, 0.46)	NA	0.427 (0.03, 0.46)
	Q1, Q3	0.23, 0.46	NA	0.23, 0.46
0.5 mg/kg qw[a]	n	1	NA	1
	Mean (SD)	0.230 (NA)	NA	0.230 (NA)
	Median (min, max)	0.230 (0.23, 0.23)	NA	0.230 (0.23, 0.23)
	Q1, Q3	0.23, 0.23	NA	0.23, 0.23
0.75 mg/kg qw[a]	n	1	NA	1
	Mean (SD)	0.197 (NA)	NA	0.197 (NA)
	Median (min, max)	0.197 (0.20, 0.20)	NA	0.197 (0.20, 0.20)
	Q1, Q3	0.20, 0.20	NA	0.20, 0.20
1 mg/kg qow	n	1	NA	1
	Mean (SD)	0.296 (NA)	NA	0.296 (NA)
	Median (min, max)	0.296 (0.30, 0.30)	NA	0.296 (0.30, 0.30)
	Q1, Q3	0.30, 0.30	NA	0.30, 0.30
1 mg/kg qw	n	7	10	17
	Mean (SD)	4.675 (6.8464)	4.021 (4.0589)	4.290 (5.1917)
	Median (min, max)	2.267 (0.23, 19.84)	2.661 (0.49, 13.31)	2.267 (0.23, 19.84)
	Q1, Q3	0.95, 4.83	0.82, 5.75	0.95, 5.06
3 mg/kg qow	n	3	NA	3
	Mean (SD)	4.249 (3.8429)	NA	4.249 (3.8429)
	Median (min, max)	3.680 (0.72, 8.34)	NA	3.680 (0.72, 8.34)
	Q1, Q3	0.72, 8.34	NA	0.72, 8.34
3 mg/kg qw	n	6	9	15
	Mean (SD)	30.089 (19.7624)	14.386 (9.0752)	20.667 (15.8098)
	Median (min, max)	25.922 (6.74, 54.54)	12.189 (0.92, 27.47)	15.409 (0.92, 54.54)
	Q1, Q3	14.98, 52.44	8.57, 23.72	8.57, 27.47
5 mg/kg qow	n	2	NA	2
	Mean (SD)	0.214 (0.0232)	NA	0.214 (0.0232)
	Median (min, max)	0.214 (0.20, 0.23)	NA	0.214 (0.20, 0.23)
	Q1, Q3	0.20, 0.23	NA	0.20, 0.23
5 mg/kg qw	n	2	7	9
	Mean (SD)	33.380 (8.4098)	14.470 (6.9403)	18.672 (10.7003)
	Median (min, max)	33.380 (27.43, 39.33)	14.982 (5.55, 24.11)	15.901 (5.55, 39.33)
	Q1, Q3	27.43, 39.33	7.89, 22.05	10.81, 24.11
7.5 mg/kg qw	n	NA	1	1
	Mean (SD)	NA	4.600 (NA)	4.600 (NA)
	Median (min, max)	NA	4.600 (4.60, 4.60)	4.600 (4.60, 4.60)
	Q1, Q3	NA	4.60, 4.60	4.60, 4.60
Number of infusions received[b]				
0.2 mg/kg qw[a]	n (% of N)	2 (11)	0	2 (5)
0.35 mg/kg qw	n (% of N)	14 (89)	0	14 (42)
0.5 mg/kg qw[a]	n (% of N)	1 (11)	0	1 (5)
0.75 mg/kg qw[a]	n (% of N)	1 (11)	0	1 (5)
1 mg/kg qow	n (% of N)	1 (11)	0	1 (5)
1 mg/kg qw	n (% of N)	132 (78)	177 (100)	309 (89)
3 mg/kg qow	n (% of N)	33 (33)	0	33 (16)
3 mg/kg qw	n (% of N)	773 (67)	554 (90)	1327 (79)
5 mg/kg qow	n (% of N)	2 (22)	0	2 (11)
5 mg/kg qw	n (% of N)	290 (22)	442 (70)	732 (47)
7.5 mg/kg qw	n (% of N)	0	20 (10)	20 (5)
Patient-years[c]				
0.2 mg/kg qw[a]	Total	0.04	0	0.04
0.35 mg/kg qw	Total	0.23	0	0.23
0.5 mg/kg qw[a]	Total	0.02	0	0.02
0.75 mg/kg qw[a]	Total	0.02	0	0.02
1 mg/kg qow	Total	0.02	0	0.02
1 mg/kg qw	Total	2.73	3.35	6.08
3 mg/kg qow	Total	1.06	0	1.06
3 mg/kg qw	Total	15.04	10.79	25.83
5 mg/kg qow	Total	0.04	0	0.04
5 mg/kg qw	Total	5.56	8.44	14.00
7.5 mg/kg qw	Total	0	0.38	0.38

Note: Patients could receive study drug at more than 1 dose level; therefore, within each study, a patient may be included in more than 1 dose category. Percentage (%) was based on N.

[a] Administered to 1 patient in Study LAL-CL03 who started treatment under ATU in France.

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

[c] Patient-years of exposure is per 100 years of exposure.

Abbreviations: ATU = Temporary Authorisation for Use; max = maximum; min = minimum; N = number of patients in specified subgroup; n = number of patients with available data; NA = not applicable; Q1 = 25th percentile; Q3 = 75th percentile; qow = once every other week; qw = once weekly; SD = standard deviation.

4.2.3. Other Characteristics

4.2.3.1. Demographics – Children & Adults

The demographics of Pooled SS 1 are provided in Table 47.

Table 47: *Demographics by Study and Overall - Pooled Safety Set 1*

Parameter	Statistic	LAL-CL01/ LAL-CL04 (N = 9)	LAL-CL02 (N = 66)	LAL-CL06 (N = 31)	Pooled Safety Set 1 (N = 106)
Age (years) at first dose					
	n	9	66	31	106
	Mean (SD)	31.56 (10.737)	16.62 (10.930)	16.92 (14.678)	17.98 (12.712)
	Median (min, max)	29.00 (19.0, 45.0)	13.35 (4.7, 58.8)	11.71 (3.0, 54.8)	13.49 (3.0, 58.8)
	Q1, Q3	21.0, 41.0	11.3, 18.9	6.2, 25.5	10.5, 21.1
Age (years) subgroup at first dose, n (%)					
< 18		0	47 (71)	22 (71)	69 (65)
≥ 18		9 (100)	19 (29)	9 (29)	37 (35)
Gender, n (%)					
	n	9	66	31	106
Male		6 (67)	33 (50)	19 (61)	58 (55)
Female		3 (33)	33 (50)	12 (39)	48 (45)
Ethnicity, n (%)					
	n	9	66	31	106
Hispanic or Latino		0	10 (15)	6 (19)	16 (15)
Not Hispanic or Latino		9 (100)	56 (85)	25 (81)	90 (85)
Race, n (%)					
	n	9	66	31	106
Asian		0	3 (5)	0	3 (3)
Japanese		0	2 (67)	0	2 (67)
Non-Japanese		0	1 (33)	0	1 (33)
Black or African-American		0	1 (2)	0	1 (1)
White		9 (100)	55 (83)	27 (87)	91 (86)
Other		0	7 (11)	4 (13)	11 (10)
Parameter	**Statistic**	**LAL-CL01/ LAL-CL04 (N = 9)**	**LAL-CL02 (N = 66)**	**LAL-CL06 (N = 31)**	**Pooled Safety Set 1 (N = 106)**
Weight (kg)					
	n	8	66	31	105
	Mean (SD)	76.04 (13.228)	48.43 (19.721)	40.30 (28.169)	48.13 (23.707)
	Median (min, max)	75.90 (56.0, 94.6)	45.45 (16.5, 98.9)	31.67 (12.4, 130.2)	43.30 (12.4, 130.2)
	Q1, Q3	66.4, 86.6	30.2, 62.0	18.3, 57.0	29.5, 64.0
BMI (kg/m^2)					
	n	8	66	31	105
	Mean (SD)	25.68 (3.416)	19.89 (3.729)	19.79 (7.241)	20.30 (5.197)
	Median (min, max)	26.05 (19.9, 31.3)	18.96 (14.8, 28.6)	17.78 (14.1, 50.1)	18.94 (14.1, 50.1)
	Q1, Q3	23.6, 27.5	16.8, 22.6	15.5, 22.4	16.4, 23.5
Use of lipid-lowering medications at baseline, n (%)					
	n	9	66	31	106
Yes		5 (56)	25 (38)	16 (52)	46 (43)
No		4 (44)	41 (62)	15 (48)	60 (57)

Note: Percentage (%) was based on N.

Abbreviations: BMI = body mass index; N = number of patients in specified subgroup; n = number of patients with available data; max = maximum; min = minimum; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

4.2.3.2. Demographics – Infants

The demographics of Pooled SS 2 are provided in Table 48.

Table 48: *Demographics by Study and Overall - Pooled Safety Set 2*

Parameter	Statistic	LAL-CL03 (N = 9)	LAL-CL08 (N = 10)	Pooled Safety Set 2 (N = 19)
Age (months) at first dose				
	n	9	10	19
	Mean (SD)	3.41 (1.649)	2.66 (1.214)	3.02 (1.447)
	Median (min, max)	3.02 (1.1, 5.8)	2.83 (0.5, 4.1)	3.02 (0.5, 5.8)
	Q1, Q3	2.7, 4.3	1.7, 3.6	1.7, 3.9
Gender, n (%)				
	n	9	10	19
Male		5 (56)	5 (50)	10 (53)
Female		4 (44)	5 (50)	9 (47)
Ethnicity, n (%)				
	n	6	10	16
Hispanic or Latino		0	0	0
Not Hispanic or Latino		6 (100)	10 (100)	16 (100)
Race, n (%)				
	n	6	10	16
American-Indian or Alaska native		0	1 (10)	1 (6)
Asian		1 (17)	6 (60)	7 (44)
Japanese		0	0	0
Non-Japanese		0	6 (100)	6 (86)
Unknown		1 (100)	0	1 (14)
Black or African-American		1 (17)	0	1 (6)
White		4 (67)	1 (10)	5 (31)
Other		0	2 (20)	2 (13)
Weight (kg)				
	N	9	10	19
	Mean (SD)	4.87 (1.506)	4.31 (0.771)	4.57 (1.177)
	Median (min, max)	4.90 (3.3, 7.9)	4.40 (2.9, 5.6)	4.50 (2.9, 7.9)
	Q1, Q3	3.4, 5.7	4.0, 4.6	3.5, 5.3
BMI (kg/m^2)				
	N	8	9	17
	Mean (SD)	14.86 (1.841)	13.75 (1.856)	14.27 (1.879)
	Median (min, max)	15.45 (11.9, 17.4)	13.71 (10.3, 16.3)	13.75 (10.3, 17.4)
	Q1, Q3	13.3, 16.0	13.2, 15.0	13.2, 15.8
Use of lipid-lowering medications at baseline, n (%)				
	N	9	10	19
Yes		3 (33)	1 (10)	4 (21)
No		6 (67)	9 (90)	15 (79)

Note: Percentage (%) was based on N.
Abbreviations: BMI = body mass index; max = maximum; min = minimum; N = number of patients in specified subgroup; n = number of patients with available data; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

4.2.3.3. Baseline disease and concomitant medications – Children & Adults

The baseline disease parameters in Pooled SS 1 are shown in Table 31. In this pooled grouping the most frequently used types of concomitant medications/therapies were analgesics (79% patients), systemic antibiotics (74% patients), anti-inflammatory/anti-rheumatic products (59% patients), vitamins (48% patients), and systemic antihistamines and LLMs (each in 47% patients).

Table 49: *Baseline Disease Characteristics by Study and Overall - Pooled Safety Set 1*

Parameter	Statistic	LAL-CL01/ LAL-CL04 (N = 9)	LAL-CL02 (N = 66)	LAL-CL06 (N = 31)	Pooled Safety Set 1 (N = 106)
Age (years) at diagnosis					
	n	9	65	31	105
	Mean (SD)	18.46 (17.016)	6.00 (5.189)	10.30 (10.372)	8.34 (9.127)
	Median (min, max)	12.10 (4.1, 42.4)	5.00 (0.0, 20.0)	7.13 (0.1, 41.8)	5.00 (0.0, 42.4)
	Q1, Q3	4.7, 38.6	1.7, 10.0	3.2, 14.0	2.5, 11.0
Time (days) since diagnosis[a]					
	n	9	65	31	105
	Mean (SD)	4969.22 (4383.155)	2079.26 (2486.368)	2406.29 (3794.052)	2423.52 (3173.249)
	Median (min, max)	3246.00 (637.0, 13352.0)	1157.00 (0.0, 14030.0)	477.00 (36.0, 16184.0)	1083.00 (0.0, 16184.0)
	Q1, Q3	1107.0, 8576.0	442.0, 3060.0	230.0, 2883.0	310.0, 3226.0
Method of diagnosis[b]					
	n	0	66	31	97
Enzyme activity[c]	n (%)	0	43 (65)	26 (84)	69 (71)
Genetic sequencing	n (%)	0	5 (8)	9 (29)	14 (14)
Other[d]	n (%)	0	18 (27)	9 (29)	27 (28)
Mutation type[e]					
	n	0	66	29	95
Heterozygous common mutation	n (%)	0	35 (53)	13 (45)	48 (51)
Homozygous common mutation	n (%)	0	21 (32)	7 (24)	28 (29)
Other mutation	n (%)	0	10 (15)	9 (31)	19 (20)
Family members with LAL-D					
	n	0	23	31	54
Yes	n (%)	0	23 (100)	10 (32)	33 (61)
No	n (%)	0	0	21 (68)	21 (39)

Note: Percentage (%) was based on N.

[a] Time since diagnosis was calculated relative to first infusion date.

[b] Patients may have been diagnosed by more than 1 method.

[c] Evaluated via dried blood spot testing.

[d] The percentages in each category do not add up to 100% because for a particular patient, multiple diagnostic methods were used.

[e] Patients may have more than 1 type of mutation.

Abbreviations: LAL = lysosomal acid lipase; LAL-D = lysosomal acid lipase deficiency; max = maximum; min = minimum; N = number of patients in specified subgroup; n = number of patients with available data; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

4.2.3.4. Baseline disease and concomitant medications – Infants

The baseline disease parameters in Pooled SS 1 are shown in Table 32. In this pooled grouping the most frequently used types of concomitant medications/therapies were systemic antibiotics and blood substitutes and perfusion solutions (100% patients), analgesics (95% patients), vitamins (89% patients), drugs for acid-related disorders (84% patients), antithrombotic agents and systemic corticosteroids (each in 79% patients), antihistamines and psycholeptics (each in 74% patients).

Table 50: *Baseline Disease Characteristics by Study and Overall - Pooled Safety Set 2*

Parameter	Statistic	LAL-CL03 (N = 9)	LAL-CL08 (N = 10)	Pooled Safety Set 2 (N = 19)
Age (months) at diagnosis				
	N	9	10	19
	Mean (SD)	2.77 (1.862)	2.25 (1.216)	2.50 (1.534)
	Median (min, max)	2.79 (0.0, 5.8)	2.33 (0.3, 3.9)	2.63 (0.0, 5.8)
	Q1, Q3	2.5, 3.0	1.1, 3.3	1.1, 3.3
Time (days) since diagnosis[a]				
	N	9	10	19
	Mean (SD)	16.11 (14.794)	13.60 (10.189)	14.79 (12.282)
	Median (min, max)	12.00 (1.0, 42.0)	9.50 (4.0, 37.0)	10.00 (1.0, 42.0)
	Q1, Q3	6.0, 28.0	7.0, 20.0	6.0, 22.0
Method of diagnosis[b]				
	N	9	10	19
Enzyme activity[c]	n (%)	6 (67)	10 (100)	16 (84)
Genetic sequencing	n (%)	0	2 (20)	2 (11)
Other	n (%)	3 (33)	0	3 (16)
Mutation type[d]				
	N	7	5	12
Heterozygous common mutation[e]	n (%)	2 (29)	0	2 (17)
Homozygous common mutation	n (%)	0	1 (20)[f]	1 (8)[f]
Other mutation	n (%)	5 (71)	4 (80)	9 (75)
Family members with LAL-D				
	N	9	10	19
Yes	n (%)	3 (33)	4 (40)	7 (37)
No	n (%)	6 (67)	6 (60)	12 (63)

Note: Percentage (%) was based on N.

[a] Time since diagnosis was calculated relative to first infusion date.
[b] Patients may have been diagnosed by more than 1 method; therefore, the percentages in each category do not add up to 100%.
[c] Evaluated via dried blood spot testing.
[d] Patients may have more than 1 type of mutation.
[e] Not reported for any patient with dual WGD.
[f] One patient classified as homozygous for the common mutation actually had c.894+1 G>A, which results in complete loss of gene function.

Abbreviations: LAL-D = lysosomal acid lipase deficiency; max = maximum; min = minimum; N = number of patients in specified subgroup; n = number of patients with available data; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; WGD = whole gene deletion.

4.2.4. Adverse Event Analysis

4.2.4.1. Overall high level summary

Table 51, **Table 52**, **Table 53** and **Table 54** give an overall overview of TEAEs in Pooled SS 1 and 2, by study and by dose, respectively.

Table 51: *Overview of Treatment-emergent Adverse Events by Study and Overall – Pooled Safety Set 1*

Parameter	LAL-CL01/ LAL-CL04 (N = 9) n (%)	LAL-CL02 (N = 66) n (%)	LAL-CL06 (N = 31) n (%)	Pooled Safety Set 1 (N = 106) n (%)
Any TEAE	9 (100)	65 (98)	31 (100)	105 (99)
Onset during infusion and ≤ 4 hours after end of infusion	7 (78)	36 (55)	14 (45)	57 (54)
Onset during infusion and ≤ 24 hours after end of infusion	9 (100)	54 (82)	27 (87)	90 (85)
Onset > 4 and ≤ 24 hours after end of infusion	9 (100)	43 (65)	22 (71)	74 (70)
Any related TEAE[a]	5 (56)	22 (33)	10 (32)	37 (35)
Onset during infusion and ≤ 4 hours after end of infusion	2 (22)	12 (18)	5 (16)	19 (18)
Onset during infusion and ≤ 24 hours after end of infusion	3 (33)	16 (24)	8 (26)	27 (25)
Onset > 4 and ≤ 24 hours after end of infusion	2 (22)	7 (11)	4 (13)	13 (12)
Any TESAE	1 (11)	13 (20)	10 (32)	24 (23)
Any treatment-related TESAE[a]	0	2 (3)	1 (3)	3 (3)
Any infusion-associated reaction[b]	2 (22)	14 (21)	3 (10)	19 (18)
Any hypersensitivity and anaphylactic reaction[c]	5 (56)	44 (67)	18 (58)	67 (63)
Any TEAE leading to death	0	0	0	0
Any TEAE leading to study discontinuation	0	0	0	0
Any TEAE leading to study drug discontinuation	0	1 (2)	1 (3)	2 (2)

Note: The TEAEs were coded using MedDRA version 21.0. Events that started on placebo, including those that continued during transition to sebelipase alfa, were not included. Percentage (%) was based on N.

[a] Based on Investigator's assessment of whether an event was at least possibly related to study drug.

[b] Includes hypersensitivity (narrow terms) and anaphylactic reactions (broad and narrow terms) by Standardized MedDRA Query.

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

Abbreviations: LAL = lysosomal acid lipase; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified subgroup; n = number of patients with at least 1 TEAE in the category; TESAE = treatment-emergent serious adverse event; TEAE = treatment-emergent adverse event.

Table 52: *Overview of Treatment-emergent Adverse Events by Dose - Pooled Safety Set 1*

	0.35 mg/kg qw (N = 3) n (%)	1 mg/kg qw (N = 5) n (%)	1 mg/kg qow (N = 102) n (%)	3 mg/kg qw (N = 7) n (%)	3 mg/kg qow (N = 26) n (%)	Pooled Safety Set 1 (N = 106) n (%)
Any TEAE	3 (100)	3 (60)	101 (99)	7 (100)	25 (96)	105 (99)
Onset during infusion and ≤ 4 hours after end of infusion	1 (33)	2 (40)	52 (51)	2 (29)	10 (38)	57 (54)
Onset during infusion and ≤ 24 hours after end of infusion	3 (100)	2 (40)	83 (81)	5 (71)	17 (65)	90 (85)
Onset > 4 and ≤ 24 hours after end of infusion	3 (100)	2 (40)	64 (63)	5 (71)	14 (54)	74 (70)
Any related TEAE[a]	1 (33)	0	34 (33)	3 (43)	4 (15)	37 (35)
Onset during infusion and ≤ 4 hours after end of infusion	0	0	18 (18)	0	2 (8)	19 (18)
Onset during infusion and ≤ 24 hours after end of infusion	1 (33)	0	26 (25)	0	3 (12)	27 (25)
Onset > 4 and ≤ 24 hours after end of infusion	1 (33)	0	11 (11)	0	2 (8)	13 (12)
Any TESAE	0	0	19 (19)	0	6 (23)	24 (23)
Any treatment-related TESAE[a]	0	0	3 (3)	0	0	3 (3)
Any infusion-associated reaction[b]	0	0	19 (19)	0	1 (4)	19 (18)
Any hypersensitivity and anaphylactic reaction[c]	0	1 (20)	64 (63)	4 (57)	14 (54)	67 (63)
Any TEAE leading to death	0	0	0	0	0	0
Any TEAE leading to study discontinuation	0	0	0	0	0	0
Any TEAE leading to study drug discontinuation	0	0	1 (1)	0	1 (4)	2 (2)

Note: The TEAEs were coded using MedDRA version 21.0. Events that started on placebo, including those that continued during transition to sebelipase alfa, are not included. Percentage (%) was based on N.

[a] Based on Investigator's assessment of whether an event was at least possibly related to study drug.

[b] Includes hypersensitivity (narrow terms) and anaphylactic reactions (broad and narrow terms) by Standardized MedDRA Query.

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

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified subgroup; n = number of patients with at least 1 TEAE in the category; qw = once weekly; qow = once every other week; TESAE = treatment-emergent serious adverse event; TEAE = treatment-emergent adverse event.

Table 53: *Overview of Treatment-emergent Adverse Events by Study and Overall – Pooled Safety Set 2*

	LAL-CL03 (N = 9) n (%)	LAL-CL08 (N = 10) n (%)	Pooled Safety Set 2 (N = 19) n (%)
Any TEAE	9 (100)	10 (100)	19 (100)
Onset during infusion and ≤ 4 hours after end of infusion	6 (67)	9 (90)	15 (79)
Onset during infusion and ≤ 24 hours after end of infusion	8 (89)	10 (100)	18 (95)
Onset > 4 and ≤ 24 hours after end of infusion	8 (89)	10 (100)	18 (95)
Any related TEAE[a]	6 (67)	8 (80)	14 (74)
Onset during infusion and ≤ 4 hours after end of infusion	5 (56)	7 (70)	12 (63)
Onset during infusion and ≤ 24 hours after end of infusion	5 (56)	8 (80)	13 (68)
Onset > 4 and ≤ 24 hours after end of infusion	3 (33)	6 (60)	9 (47)
Any TESAE	9 (100)	10 (100)	19 (100)
Any treatment-related TESAE[a]	1 (11)	5 (50)	6 (32)
Any infusion-associated reaction[b]	5 (56)	8 (80)	13 (68)
Any hypersensitivity and anaphylactic reaction[c]	8 (89)	9 (90)	17 (89)
Any TEAE leading to death	4 (44)	2 (20)	6 (32)
Any TEAE leading to study discontinuation	0	0	0
Any TEAE leading to study drug discontinuation[d]	2 (22)	0	2 (11)

Note: The TEAEs were coded using MedDRA version 21.0. Percentage (%) was based on N.

[a] Based on Investigator's assessment of whether an event was at least possibly related to study drug.

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

[c] Includes hypersensitivity (narrow terms) and anaphylactic reactions (broad and narrow terms) by Standardized MedDRA Query.

[d] Due to 2 patients who died after the last infusion of sebelipase alfa (ISS Table 14.3.1.7.2.2).

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified subgroup; n = number of patients with at least 1 TEAE in the category; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Table 54: *Overview of Treatment-emergent Adverse Events by Dose - Pooled Safety Set 2*

	0.35 mg/kg qw (N = 8) n (%)	1 mg/kg qw (N = 17) n (%)	3 mg/kg qw (N = 15) n (%)	3 mg/kg qow (N = 3) n (%)	5 mg/kg qw (N = 9) n (%)	7.5 mg/kg qw (N = 1) n (%)	Pooled Safety Set 2 (N = 19) n (%)
Any TEAE	7 (88)	15 (88)	15 (100)	3 (100)	9 (100)	1 (100)	19 (100)
Onset during infusion and ≤ 4 hours after end of infusion	2 (25)	9 (53)	14 (93)	2 (67)	7 (78)	1 (100)	15 (79)
Onset during infusion and ≤ 24 hours after end of infusion	6 (75)	14 (82)	14 (93)	2 (67)	9 (100)	1 (100)	18 (95)
Onset > 4 and ≤ 24 hours after end of infusion	6 (75)	13 (76)	14 (93)	1 (33)	9 (100)	1 (100)	18 (95)
Any related TEAE[a]	1 (13)	9 (53)	12 (80)	2 (67)	7 (78)	1 (100)	14 (74)
Onset during infusion and ≤ 4 hours after end of infusion	0	9 (53)	10 (67)	2 (67)	4 (44)	1 (100)	12 (63)
Onset during infusion and ≤ 24 hours after end of infusion	1 (13)	9 (53)	11 (73)	2 (67)	6 (67)	1 (100)	13 (68)
Onset > 4 and ≤ 24 hours after end of infusion	1 (13)	4 (24)	4 (27)	0	3 (33)	1 (100)	9 (47)
Any TESAE	2 (25)	14 (82)	14 (93)	2 (67)	9 (100)	1 (100)	19 (100)
Any treatment-related TESAE[a]	0	3 (18)	4 (27)	0	2 (22)	1 (100)	6 (32)
Any infusion-associated reaction[b]	0	9 (53)	11 (73)	1 (33)	4 (44)	1 (100)	13 (68)
Any hypersensitivity and anaphylactic reaction[c]	1 (13)	11 (65)	13 (87)	1 (33)	8 (89)	1 (100)	17 (89)
Any TEAE leading to death	2 (25)	2 (12)	1 (7)	0	1 (11)	0	6 (32)
Any TEAE leading to study discontinuation	0	0	0	0	0	0	0
Any TEAE leading to study drug discontinuation	1 (13)	0	1 (7)	0	0	0	2 (11)

Note: The TEAEs were coded using MedDRA version 21.0. Percentage (%) was based on N.

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

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

[c] Includes hypersensitivity (narrow terms) and anaphylactic reactions (broad and narrow terms) by Standardized MedDRA Query.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified subgroup; n = number of patients with at least 1 TEAE in the category; qw = once weekly; qow = once every other week; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Rapporteur's comments

Overall, the safety analysis by dose does indeed seem to indicate that higher dosings do not have a markedly worse safety profile than the currently approved posologies.

4.2.4.2. TEAEs – Children & Adults

The majority of patients (95/106; 90%) experienced at least 1 TEAE in the SOC Infections and infestations. The most frequently reported (> 40% of patients) TEAEs by Preferred Term were nasopharyngitis (52/106 patients; 49%), headache (47/106 patients; 44%), and pyrexia (45/106 patients; 42%).

About 54% of patients experienced a TEAE during or within the 4 hours after infusion, with the TEAEs that were reported by Preferred Term in 5 or more patients being urticaria (6%); pyrexia, abdominal pain, nausea, and vitamin D deficiency (5% each).

A total of 70% of patients experienced at least 1 TEAE between 4 and 24 hours after the infusion, with those events occurring in at least 5 patients being headache (12%); nasopharyngitis (11%); diarrhea (10%); pyrexia (8%); epistaxis, abdominal pain, (8%); upper abdominal pain, vomiting (7%); cough, nausea, oropharyngeal pain (6%); dizziness, and Vitamin D deficiency (5%).

Severe TEAEs were experienced by 13% of subjects, with none being individually reported in 5 or more patients.

A total of 9 patients were found to be ADA positive at one or more timepoints during the respective studies, having a total of 33 events (12.48 PYs of exposure): 5 patients who had low ADA titers (11 events; 13.09 PYs of exposure) and the 4 patients who had high ADA titers (22 events; 12.19 PYs of exposure). This is in comparison with the other 105 patients with ADA negativity, whom reported a combined total of 2517 events (7.29 PYs of exposure).

Rapporteur's comments

Overall, the integrated safety analysis did not expose untoward findings that deviate from the observations made during the analysis of the individual trails.

4.2.4.3. TEAEs – Infants

Most patients experienced a TEAE in the SOCs Gastrointestinal disorders and Investigations (18/19 patients; 95%). The most frequently reported TEAEs (> 50% of patients) by Preferred Term were diarrhea, vomiting, pyrexia (79% each), gastroenteritis, cough (58% each), rhinitis, diaper dermatitis, and tachycardia (53% each). A greater proportion of patients in Study LAL-CL08 were reported with most of these events due to the number of events reported for the 3 patients with dual WGD. However, generally there were marginal differences in the incidence of these events when patients without dual WGD (n = 16) were compared to the overall population (n = 19).

About 79% of infant patients experienced a TEAE during infusion and within 4 hours after the EOI. The TEAEs that were reported by Preferred Term in 2 or more patients were pyrexia (63%); vomiting, tachycardia (47% each); urticaria (32% each); agitation, irritability (26% each); diarrhea, rash (21% each); respiratory distress, tachypnea, pruritus, device-related sepsis (16% each); teething, body temperature increased, device-related infection, rash pruritic, anemia, and pallor (11% each).

In total 95% of subjects experienced at least 1 TEAE between 4 and 24 hours after the infusion. No clear pattern existed in the types of TEAEs that were reported in 2 or more patients.

Severe TEAEs were experienced by 84% of subjects, with those reported in 2 or more patients being tachycardia (21%); anemia, respiratory distress (16% each); dehydration, device-related infection, and sepsis (11% each).

A total of 10 patients presented with ADA positivity, cumulating a total of 883 events (37.19 PYs of exposure). A higher rate of exposure was also reported for the 5 patients who had high ADA titers (601 events; 42.87 PYs of exposure) compared to the 5 patients who had low ADA titers (282 events; 29.01 PYs of exposure). For the remaining 18 patients with ADA negativity, 937 events (39.07 PYs of exposure) were reported.

Note that the rate of exposure for the 3 patients with dual WGD was slightly higher than that of the 7 patients without dual WGD during an ADA positive period; 305 events (39.67 PYs of exposure) compared with 578 events (36.01 PYs of exposure), respectively.

Rapporteur's comments

Overall, the integrated safety analysis did not expose untoward findings that deviate from the observations made during the analysis of the individual trails.

Note that based on the 3 cases of dual WGD patients and associated more complicated immune responses a new safety signal was opened in the latest PSUR (DLP 28 Aug 2019).

4.2.4.4. Treatment-related TEAEs –Children & Adults

Across studies, 35% of patients experienced a treatment-related TEAE. Those that were reported in 5 or more patients were urticaria (7%), abdominal pain (6%), and fatigue (5%).

About 18 % of patients experienced at least 1 treatment-related TEAE during or 4 hours after infusion. The only such TEAE that was reported by 5 or more patients was urticaria (6%).

Around 12% of Pooled SS 1 patients experienced a treatment-related TEAE between 4 and 24 hours after infusion but no treatment-related TEAEs were reported in 5 or more patients.

Of the ADA-positive subjects 11% (n =1) had a TR TEAE at Week 12, a timepoint when the subject had his/her lowest ADA titre measured. At later measurement timepoints the subject had transited to ADA-negativity.

4.2.4.5. Treatment-related TEAEs – Infants

Across studies, 74% of patients experienced a treatment-related TEAE. Those that were reported in 2 or more patients were pyrexia (58%); tachycardia (47%); urticaria (37%); vomiting (32%); agitation, irritability (26%); diarrhea (21%); respiratory distress, tachypnea, pruritus (16%); lip swelling, rash, rash pruritic, body temperature increased, drug-specific antibody present, and pallor (11%).

A total of 63% of patients experienced at least 1 treatment-related TEAE during or within 4 hours after infusion. The TEAEs so reported by 2 or more patients were pyrexia, tachycardia (47% each); urticaria (32%); vomiting, irritability (26% each); agitation (21% each); diarrhea, respiratory distress, tachypnea, pruritus (16% each); rash, rash pruritic, and pallor (11% each).

Around 47% patients experienced a treatment-related TEAE between 4 and 24 hours after infusion with TEAEs reported by 2 or more patients being pyrexia (21%) and drug-specific antibody present (11%).

A total of 80% of patients (n = 8) had an TR TEAE event during ADA-positivity. Those reported by 2 or more patients were pyrexia (70%); tachycardia (60%); urticaria, agitation (40%); diarrhea, lip swelling, rash, rash pruritic, tachypnea, body temperature increased, and drug specific antibody present (20% each).

4.2.4.6. Deaths –Children & Adults

No deaths were reported in the studies that made up the Pooled SS 1.

4.2.4.7. Deaths – Infants

A total of 6 patients, 4 in LAL-CL03 and 2 in LAL-CL08, died in the pooled SS 2. None of the dual WGD patients were part of the fatalities. All deaths were judged not or unlikely related to study IP.

Table 55: *Deaths Occurring While On Study - Pooled Safety Set 2*

Patient Number	Cause of Death (MedDRA Preferred Term)	Last Sebelipase Alfa Dose	Time Since First Dose (days)	Time Since Last Dose (days)[a]	Relationship to Treatment	ADA Positivity[b]
Study LAL-CL03						
01-001	Hepatic failure	0.35 mg/kg qw	6	6	Not related	Negative
05-001	Sudden cardiac death	3 mg/kg qw	279	6	Unlikely related	Negative
06-003	Peritoneal haemorrhage	0.35 mg/kg qw	5	5	Not related	NR
11-001	Cardiac arrest	1 mg/kg qw	26	7	Unlikely related	Negative
Study LAL-CL08						
2001-003	Pericardial effusion	1 mg/kg qw	26	4	Not related	Negative
2001-004	Sepsis	5 mg/kg qw	285	3	Not related	Negative

[a] Dose of sebelipase alfa received prior to the event.
[b] Patients with a positive result on both screening assay and confirmatory assay were considered to be ADA positive.
Abbreviations: ADA = antidrug antibody; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; qw = once weekly.

4.2.4.8. Serious TEAEs –Children & Adults

In the Pooled SS 1 23% of patients experienced a TESAE, but no single event affected more than 5 individual patients and no patient experienced an event during an ADA-positive period.

4.2.4.9. Serious TEAEs – Infants

All subjects in the Polled SS 2 expereinced at least 1 TESAE, with 74% of patients experiencing a serious event in the SOC infections and infestations. TESEAs reported in more than 25% of patients were pyrexia (47%), gastroenteritis, vomiting (42% each), diarrhea (37%), tachycardia (32%), device-related infection, device-related sepsis, and URTI (26% each).

Ten (56%) of the ADA-positive patients had at least a single TESEA, though no hypersensitivity and anaphylactic reactions were reported. There was no difference in the proportion of patients experiencing TESEAs prior or post ADA-positive periods.

4.2.4.10. Treatment-related Serious TEAEs –Children & Adults

A total of 3 (3%) fo the Pooled SS 1 subjects were considered to have experienced a treatment-related TESEA, one of which was an anaphylactoid reaction a two different timepoints in study LAL-CL06. All three subjects had drug interruptions and sometimes concomitant medication administered, and all TESEAs resolved without sequalae. No events occurred during any ADA-positive periods for any of the Pooled SS 1 subjects.

4.2.4.11. Treatment-related Serious TEAEs – Infants

A total of 32% of Pooled SS 2 subjects experienced a TESAE that was judged as related to treatment by the investigator, and this included the three dual WGD subjects in LAL-CL08. Events reported by 2 or more subjects were tachycardia (26%); pyrexia, respiratory distress, urticaria (16%); and vomiting (11%).

Of the infants that presented with at least one period of ADA positivity during treatment (n=10), 40% also experienced at least 1 TESAE judges as related to treatment. Those events experienced by at least 2 patents include tachycardia (30%) and pyrexia (20%), and 3 of the 4 patients were dual WGD subjects whom presented with persistent, high titres of ADA throughout their participation in the study. Only one subject, non-dual WGD, had a treatment interruption at a dose of 3 mg/kg for the events of tachypnea, tachycardia, irritability, and angioedema in order to allow for appropriate management of signs and symptoms associated with the events. Upon resumption of dosing, the patient continued to receive 3 mg/kg qw, which remained unchanged for the remainder of the study.

Rapporteur's comments

The integrated analysis of all and treatment-related TEAEs and TESAEs, in both Pooled SS 1 and 2, did not indicate any new or unknown signals in the aggregated data.

4.2.4.12. AESIs –Children & Adults

Infusion associated reactions

ARs were defined as any TEAE that occurred during or within 4 hours after EOI that were considered by the Investigator to be related to study drug.

In the pooled SS 1 18% of subjects experienced at least 1 IAR, with only urticaria occurring in more than 5 patients total (7%). No events of IAR occurred during any periods of ADA positivity.

Hypersensitivity and Anaphylactic Reactions

Sixty-three percent of the Pooled SS 1 subjects reported at least one event, and 4% had an event classified as being in the SOC immune system disorders: 2 subjects with hypersensitivity and one subject each with anaphylactic reaction and anaphylactic shock. No events occurred during any subject's ADA positive period.

4.2.4.13. AESIs – Infants

Infusion associated reactions

ARs were defined as any TEAE that occurred during or within 4 hours after EOI that were considered by the Investigator to be related to study drug.

In the pooled SS 2 68% of patients had at least one IAR, with those events reported in 2 or more subjects being pyrexia, tachycardia (47% each); urticaria (37); vomiting (32%); agitation, irritability (26% each); diarrhea, pruritus, respiratory distress, tachypnea (16% each) and lip swelling, rash, rash pruritic, and pallor (11% each). Of the infants experiencing ADA positivity, 80% also had at least one IAR during

such period though none were of the SOC Immune system disorder type. Due to the low numbers involved it was not possible to find possible association between ADA status and IAR events.

Hypersensitivity and Anaphylactic Reactions

In the Pooled SS 2 subject pool 89% had at least one event. A total of 16% of subjects had an event classified under the SOC immune system disorders, 2 cases of hypersensitivity, one case of anaphylactic reaction and one case of drug hypersensitivity. About 89% of all patients with ADA positive results also had events during such a positive period. Hypersensitivity was reported in 20% of patients with ADA positivity, and anaphylactic reaction and drug hypersensitivity were each reported in 10% of patients with ADA positivity.

Rapporteur's comments

The integrated AESI analysis generally confirmed the previously knowledge, with infants having generally more adverse events that are of the special interest type.

4.2.4.14. Clinical Laboratory Evaluations

Liver function – Children & adults

Platelet counts were reported for 96.2% of the Pooled SS 1 population at baseline for which the median value was 227.75 × 10^9/L. Median changes from baseline remained consistent through Month 24 and decreased slightly through Month 36. The median platelet count at the last assessment on study was 226 × 10^9/L.

The median leukocyte count at baseline was 6 × 10^9/L. Median changes from baseline remained consistent (with slight fluctuations) through Month 36. The median leukocyte count at the last assessment on study was 5.66 × 10^9/L.

There were no clinically meaningful changes observed in platelet and leukocyte counts over time.

Liver function – Infants

Platelet counts were reported for 16/19 (84.2%) infants at baseline for which the median was 159.5 × 10^9/L. Median values markedly increased at Week 2 and at Week 48 where it was 309 × 10^9/L. Following this timepoint, median changes from baseline remained consistent (with small fluctuations) through Week 144. The median platelet count at the last assessment on study was 310.5 × 10^9/L.

The median leukocyte count at baseline was 6.95 × 10^9/L. Median changes fluctuated slightly through Week 144, but values generally increased over time. The median leukocyte count at the last assessment on study was 8.25 × 10^9/L.

The observed changes in platelet and leukocyte counts were consistent with an improvement in the underlying disease of LAL-D in infants.

Liver injury – Children & adults

Alanine aminotransferase results were reported for all children and adults at baseline for which the median value was 83.17 U/L. Median changes from baseline markedly decreased by Month 6 and were maintained through Month 36. The median ALT value for the last assessment on study was 38 U/L.

Aspartate aminotransferase results were reported for all children and adults at baseline for which the median value was 66.25 U/L. Median changes from baseline decreased by Month 6 and further decreased gradually through Month 36. The median AST value for the last assessment on study was 35 U/L.

The observed changes in serum transaminases were consistent with an improvement in the underlying disease of LAL-D in children and adults.

Gamma glutamyl transferase results were reported for all children and adults at baseline for which the median value was 33.83 U/L. Median changes from baseline decreased by Month 6 and were maintained through Month 36. The median GGT value for the last assessment on study was 19 U/L.

Serum albumin results were reported for all children and adults at baseline for which the value was 42.17 g/L. Median changes from baseline remained consistent through Month 36. The median serum albumin value for the last assessment on study was 44 g/L.

Serum bilirubin results were reported for all children and adults at baseline for which the median value was 12.5 µmol/L. Median changes from baseline generally remained consistent through Month 36. The median serum bilirubin value for the last assessment on study was 11 µmol/L.

The observed changes in GGT were consistent with an improvement in the underlying disease of LAL-D in children and adults. There were no clinically meaningful changes observed in serum albumin and bilirubin over time.

Activated partial thromboplastin time was reported for 91.5% of children and adults at baseline for which the median time was 30.6 sec. Median changes from baseline remained consistent through Month 36. The median aPTT time for the last assessment on study was 30 sec.

The INR was reported for 96.2% of children and adults at baseline for which the median ratio was 1.1. Median changes from baseline remained consistent through Month 36. The median INR at for the last assessment on study was 1.06.

Prothrombin time was reported for 78.3% of children and adults at baseline for which the time was 12.7 sec. Median changes from baseline remained consistent through Month 30 (after this time data were only available for 1 or 2 patients. The median prothrombin time for the last assessment on study was 12.255 sec.

For children and adults, the coagulation parameters (PT, INR, and aPTT) for the last assessment on study were similar to that of the values reported at Baseline.

Liver injury – Infants

Alanine aminotransferase results were reported for 94.7% of infants at baseline for which the median value was 62.5 U/L. Median changes from baseline fluctuated but generally decreased through Week 48 and further, generally decreased through Week 144. The median ALT value for the last assessment on study was 38 U/L.

Aspartate aminotransferase results were reported for 89.5% of infants at baseline for which the median value was 101 U/L. Median changes from baseline markedly decreased at Week 2 and continued to fluctuate, yet generally decreased through Week 48. Following this timepoint, median changes from baseline slightly fluctuated through Week 144. The median AST value for the last assessment on study was 53 U/L.

The observed changes in serum transaminases were consistent with an improvement in the underlying disease of LAL-D in infants.

Gamma glutamyl transferase results were reported for 89.5% of infants at baseline for which the median value was 95 U/L. Median changes from baseline markedly increased at Week 2. Following this timepoint, median changes from baseline fluctuated, yet generally decreased though Week 48. After this time, median changes from baseline gradually decreased through Week 144. The median GGT value for the last assessment on study was 22 U/L.

Serum albumin results were reported for 94.7% of infants at baseline for which the median value was 23.5 g/L. Median changes from baseline fluctuated, yet generally increased through Week 48. Thereafter median changes were maintained through Week 144. The median serum albumin value for the last assessment on study was 33.3 g/L.

Serum bilirubin results were reported for 89.5% of infants at baseline for which the median value was 12 µmol/L. Median changes from baseline fluctuated, yet generally decreased through Week 48. Following this timepoint, there were incremental increases through Week 144 (although values did not reach the levels reported at Baseline; 3 µmol/L). The median serum bilirubin value for the last assessment on study was 5.13 µmol/L.

The observed changes in the discussed parameters were consistent with an improvement in the underlying disease of LAL-D in infants.

Activated partial thromboplastin time was reported for 78.9% of infants at baseline for which the median time was 28 sec. Median changes from baseline fluctuated slightly through Week 120. The median aPTT time for the last assessment on study was 28.1 sec.

The INR was reported for 8 of the 19 infants at baseline for which the median ratio was 1.1. No conclusions can be made due to limited number of patients with available data at the postbaseline timepoints.

Prothrombin time was reported for 78.9% of infants at baseline for which the median (min, max) time was 12.1 sec. Median changes from baseline were consistent through Week 120. No data were available for the Week 144 timepoint. The median prothrombin time for the last assessment on study was 14.2 sec.

For infants, the coagulation parameters (PT, INR, and aPTT) for the last assessment on study were similar to that of the values reported at Baseline.

Acute Phase Reaction – Children & adults

Serum ferritin results were reported for 99% of children and adults at baseline for which the median value was 44.70 µg/L. Median changes from baseline fluctuated, but generally decreased through Week 48. The median serum ferritin value for the last assessment on study was 40.7 µg/L.

For children and adults, no clinically meaningful changes were observed in serum ferritin values over time.

Acute Phase Reaction – Infants

Serum ferritin results were reported for 47.4% of infants at baseline for which the median was 586.3 µg/L. Median values markedly decreased at the first postbaseline timepoint (Week 2) and further decreased to
57.7 µg/L by Week 48. Following this timepoint, median changes from baseline fluctuated but generally decreased until Week 144 when the median serum ferritin value was 43 µg/L. The median serum ferritin value for the last assessment on study was 83.85 µg/L.

The observed changes in serum ferritin were consistent with an improvement in the underlying disease of LAL-D in infants.

Rapporteur's comments

Overall no specific new issues regarding clinical laboratory events could be seen in the integrated data analysis.

4.2.4.15. Immunogenicity

ADA positivity – Children & Adults

In the Pooled SS 1 patient group 98% of subjects had baseline ADA testing done, and 8% became positive during the respective studies with a median duration until first titre peak (median 37) of 57 days. Of the latter 9% of patients 3 were heterozygous for the common mutation, 1 was homozygous for the common mutation, and 4 were documented with "other" mutations.

Generally ADA positivity was transient in the Pooled SS 1 group and overall low titres of ADAs were reported. Two of the 9 ADA+ patients went on to develop Nabs that had an impact on efficacy, but neither was forced to discontinue due to this evolution.

ADA positivity – Infants

In the Pooled SS 2 group, 68% of subjects had baseline ADA testing results, and 10 (>50%) patients became ADA positive during the respective studies with a median duration until first positivity of 57 days and until median peak titre (median 3839) of 792 days. Of these 10 patients, 1 was heterozygous for the common mutation and 6 were documented with "other" mutations.

Persistence of ADA positivity was observed for all 10 patients. Further, 9 patients were positive for NAbs that inhibited LAL activity and/or cellular uptake. Nonetheless, the development of ADAs and/or NAbs was not correlated with either an increased incidence of TEAEs or suboptimal clinical response, respectively. For the overall population, IARs were reported for patients with both ADA positivity and ADA negativity and were similar in type and severity.

Three LAL-CL08 patients whom reported with the high titers of ADAs and NAbs were discovered to have a homozygous deletion affecting both alleles of genes *LIPA* and the neighboring Cholesterol, 25-Hydroxylase gene, and these 3 patients required more medical attention, including infusions of higher dosage regimens of sebelipase alfa. Two of the 3 patients received immunomodulatory therapy, 1 patient later underwent a bone marrow transplant (BMT), and 1 patient received a HSCT. Both latter patients required a lower dosage regimen of sebelipase alfa once dosing was resume and their ADA titers and NAbs decreased thereafter.

The third patient is currently receiving sebelipase alfa 5 mg/kg qw and continues to have high titers of ADAs. This patient exhibits progressive liver fibrosis (Ishak fibrosis score = 3) but has improved clinically with bortezomib treatment and is scheduled for an eventual BMT or HSCT. The patient's laboratory workup indicated very high levels of anti-drug Immunoglobulin G, which significantly inhibit cellular uptake of LAL.

Mean time to the first ADA positive result was shorter for the patients with dual WGD than in patients without dual WGD, median peak titre was considerably higher (260,476 versus 578) and time to peak was shorter 728 days versus 927 days.

While patients with dual WGD had the highest levels of ADAs and NAbs, this is most likely related to the lack of enzyme and immune intolerance. The role that the additional deletion of the Cholesterol, 25-Hydroxylase gene plays is unknown. For the 2 patients with dual WGD who underwent successful BMT and HSCT, the presence of enzyme resulted in a decrease in ADAs and NAbs which in turn lowered the need for higher doses of sebelipase alfa.

A review of data for these patients with high titer ADAs did not show a clear relationship between ADA titer and the risk of IARs and more likely represented the underlying disease.

Rapporteur's comments

The aggregated observations confirm earlier findings, with infants having a proportionally higher ADA development.

Development of anti-sebelipase antibodies is associated with a reasonable chance to also develop Nabs, as was known before, but generally the Nab-positive status was not associated with complete response failure or increased safety issues, neither in children/adults nor in infants.

One new observation made in LAL-CL08 regarded three infant patients whom developed a strong immunogenic response and required extensive and persistent dose escalation to maintain effectiveness. These three patients turned out to have a dual WGD phenotype, and this led to the opening of a new safety signal in the latest PSUR (DLP 28 Aug 2019).

4.2.4.16. Vital Signs

Vital signs – Children & Adults

Any vital sign TEAEs that were reported, the majority of which were drops in blood pressure, in Pooled SS 1 were generally mild and unrelated to treatement. Due to the small number of patients experiencing changes in vital signs no conclusions could be made thereupon.

Vital signs – Infants

Across clinical studies conducted in infants, over 50% of patients had an increase or decrease in blood pressure and around 47% had transient increases in heart rate while on study. The abnormalities in vital sign results that were reported as TEAEs in infants were mainly characterized as mild and not related to sebelipase alfa. Due to the small number of patients experiencing changes in vital signs no conclusions could be made thereupon.

4.2.4.17. Subanalyses

Subanalyses– Children & Adults

Overall no significant differences of interest in either age or gender stratified analyses could be discerned. Likewise, no meaningful differences in safety could be discerned along a LLM usage stratification axis.

Subanalyses – Infants

No subanalyses based on age was undertaken, and gender did not seem to induce any difference in the safety outcomes of treatment. Likewise, no meaningful differences in safety could be discerned along a LLM usage stratification axis.

4.2.4.18. Incidence Summary

ADR tables were generated for both Pooled SS 1 and 2 sets using standard methodologies, with the following caveats:

Three ADR terms represent a grouping of multiple Preferred Terms:

- The incidence of ADRs of "infusion site reaction" was calculated based on the following group of Preferred Terms: infusion site extravasation, infusion site pain, infusion site reaction, and infusion site urticaria.
- The incidence of ADRs of "hypersensitivity" was calculated based on the number of patients with Preferred Term(s) that met the SMQ for hypersensitivity (narrow), see Table 38. Of the 281 Preferred Terms in this SMQ, the Preferred Terms included in ADRs of hypersensitivity reported for patients in the sebelipase alfa clinical program are presented by pooled safety set in Table 1. Similarly, t
- The incidence of ADRs of "anaphylactic reaction" was calculated based on the number of patients with Preferred Term(s) that met the SMQ for anaphylactic reaction (broad and narrow), see Table 38. Of the 92 Preferred Terms in this SMQ, the Preferred Terms included in ADRs of anaphylactic reaction reported for patients in the sebelipase alfa clinical program are presented by pooled safety set in Table 1.

  The incidence of ADRs of hypersensitivity and anaphylactic reaction encompass all cases identified by the respective SMQs, regardless of causality or seriousness.

For Pooled Safety Set 1, events that had an onset during treatment with placebo in the Double-blind Period of Study LAL-CL02, including those that continued after the transition to open-label treatment with sebelipase alfa, were not included in the calculation of the incidence of ADRs.

Rapporteur's comments

Given that the ADR tables should only include AEs that are clearly related to the treatment this is acceptable.

Table 56: *Preferred Terms Included in the Adverse Drug Reactions of Hypersensitivity and Anaphylactic Reaction Reported for Patients in the Sebelipase Alfa Clinical Program, by Pooled Safety Set*

Pooled Safety Set 1 (Children and Adults)		Pooled Safety Set 2 (Infants)	
Preferred Terms in ADRs of Hypersensitivity[a]	**Preferred Terms in ADRs of Anaphylactic Reaction**[b]	**Preferred Terms in ADRs of Hypersensitivity**[a]	**Preferred Terms in ADRs of Anaphylactic Reaction**[b]
Allergic cough	Anaphylactic reaction	Anaphylactic reaction	Anaphylactic reaction
Anaphylactic reaction	Anaphylactic shock	Angioedema	Angioedema
Anaphylactic shock	Asthma	Catheter site rash	Asthma
Bronchospasm	Bronchospasm	Drug hypersensitivity	Cardiac arrest
Catheter site rash	Chest discomfort	Eczema	Cough
Conjunctivitis allergic	Choking	Eyelid oedema	Cyanosis
Dermatitis	Cough	Face oedema	Erythema
Dermatitis acneiform	Dyspnoea	Hypersensitivity	Eyelid oedema
Dermatitis allergic	Erythema	Lip swelling	Face oedema
Dermatitis atopic	Eye pruritus	Rash	Flushing
Dermatitis contact	Eyelid oedema	Rash erythematous	Hypotension
Dermatitis infected	Flushing	Rash generalised	Lip swelling
Eczema	Generalised erythema	Rash macular	Ocular hyperaemia
Eye allergy	Hypotension	Rash maculo-papular	Oedema
Eyelid oedema	Laryngeal oedema	Rash pruritic	Pruritus
Gingival swelling	Lip swelling	Rash pustular	Pruritus generalised
Hypersensitivity	Nasal obstruction	Red man syndrome	Rash
Infusion related reaction	Ocular hyperaemia	Swelling face	Rash erythematous
Infusion site urticaria	Oedema	Urticaria	Rash generalised
Laryngeal oedema	Pruritus		Rash pruritic
Lip swelling	Pruritus allergic		Respiratory distress
Pruritus allergic	Rash		Respiratory failure
Rash	Rash pruritic		Sneezing
Rash macular	Shock		Swelling
Rash pruritic	Sneezing		Swelling face
Rash pustular	Tachypnoea		Tachypnoea
Rhinitis allergic	Urticaria		Urticaria
Shock	Urticaria papular		Wheezing
Skin reaction	Wheezing		
Urticaria			
Urticaria papular			

[a] The subset of Preferred Terms in the SMQ for hypersensitivity (narrow) that were included in ADRs of hypersensitivity reported for patients in the indicated pooled safety set.

[b] The subset of Preferred Terms in the SMQ for anaphylactic reaction (broad and narrow) that were included in ADRs of anaphylactic reaction reported for patients in the indicated pooled safety set.

Abbreviations: ADR = adverse drug reaction; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA query.

Table 57 presents the incidence and frequency category of ADRs for Pooled Safety Set 1 (children and adults), whereas **Table 58** does the same for infants.

Table 57: *Incidence and Frequency Category of Adverse Drug Reactions in Sebelipase Alfa Clinical Studies – Pooled Safety Set 1*

System Organ Class Preferred Term	Pooled Safety Set 1 (N = 106) n (%)	Frequency Category
Immune system disorders	67 (63.21)	
Anaphylactic reaction[a, b]	60 (56.60)	Very common
Hypersensitivity[b, c]	46 (43.40)	Very common
Gastrointestinal disorders	55 (51.89)	
Diarrhoea	41 (38.68)	Very common
Abdominal pain	34 (32.08)	Very common
Abdominal distension	3 (2.83)	Common
General disorders and administration site conditions	55 (51.89)	
Pyrexia	45 (42.45)	Very common
Fatigue	12 (11.32)	Very common
Infusion site reaction[d, b]	5 (4.72)	Common
Chest discomfort	4 (3.77)	Common
Nervous system disorders	13 (12.26)	
Dizziness	13 (12.26)	Very common
Skin and subcutaneous tissue disorders	12 (11.32)	
Rash	9 (8.49)	Common
Rash papular	5 (4.72)	Common
Respiratory, thoracic and mediastinal disorders	7 (6.60)	
Dyspnoea	7 (6.60)	Common
Investigations	6 (5.66)	
Body temperature increased	6 (5.66)	Common
Vascular disorders	4 (3.77)	
Hyperaemia	2 (1.89)	Common
Hypotension	2 (1.89)	Common
Cardiac disorders	3 (2.83)	
Tachycardia	3 (2.83)	Common

[a] Refer to Table 1 for Preferred Terms included in the ADRs of anaphylactic reaction reported for children and adults.

[b] All ADRs of hypersensitivity and anaphylactic reaction were reported under the SOC of Immune system disorders regardless of the SOC in which the Preferred Terms appeared in MedDRA version 21.0.

[c] Refer to Table 1 for Preferred Terms included in the ADRs of hypersensitivity reported for children and adults.

[d] Infusion site reactions included Preferred Terms of infusion site extravasation, infusion site pain, infusion site reaction, and infusion site urticaria.

Notes: The TEAEs were coded using MedDRA version 21.0.

The incidence (and frequency category) of ADRs was calculated based on the percentage of patients experiencing an ADR. A patient with more than 1 event for a particular ADR was counted only once for that ADR.

Frequency categories were defined as follows: Very Common: ≥ 1/10, Common: ≥ 1/100 to < 1/10, Uncommon: ≥ 1/1000 to < 1/100, Rare: ≥ 1/10000 to < 1/1000, Very Rare: < 1/10000.

Events that had an onset during treatment with placebo in the Double-blind Period of Study LAL-CL02, including those that continued during transition to open-label treatment with sebelipase alfa, were not included.

Abbreviations: ADR = adverse drug reaction; % = Percentage based on N; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified group; n = number of patients with available data; SOC = System Organ Class.

Table 58: *Incidence and Frequency Category of Adverse Drug Reactions in Sebelipase Alfa Clinical Studies – Pooled Safety Set 2*

System Organ Class Preferred Term	Pooled Safety Set 2 (N = 19) n (%)	Frequency Category
Gastrointestinal disorders	17 (89.47)	
Diarrhoea	15 (78.95)	Very common
Vomiting	15 (78.95)	Very common
Immune system disorders	17 (89.47)	
Anaphylactic reaction[a, b]	17 (89.47)	Very common
Hypersensitivity[c, b]	13 (68.42)	Very common
General disorders and administration site conditions	15 (78.95)	
Pyrexia	15 (78.95)	Very common
Hyperthermia	2 (10.53)	Very common
Cardiac disorders	10 (52.63)	
Tachycardia	10 (52.63)	Very common
Investigations	8 (42.11)	
Body temperature increased	4 (21.05)	Very common
Respiratory rate increased	4 (21.05)	Very common
Heart rate increased	3 (15.79)	Very common
Blood pressure increased	2 (10.53)	Very common
Drug specific antibody present	2 (10.53)	Very common
Oxygen saturation decreased	2 (10.53)	Very common
Respiratory, thoracic and mediastinal disorders	8 (42.11)	
Respiratory distress	8 (42.11)	Very common
Skin and subcutaneous tissue disorders	7 (36.84)	
Rash	7 (36.84)	Very common
Rash maculo-papular	2 (10.53)	Very common
Eye disorders	3 (15.79)	
Eyelid oedema	3 (15.79)	Very common

[a] Refer to Table 1 for Preferred Terms included in the ADRs of anaphylactic reaction reported for infants.
[b] All ADRs of hypersensitivity and anaphylactic reaction were reported under the SOC of Immune system disorders regardless of the SOC in which the Preferred Terms appeared in MedDRA version 21.0.
[c] Refer to Table 1 for Preferred Terms included in the ADRs of hypersensitivity reported for infants.
Notes: The TEAEs were coded using MedDRA version 21.0.
The incidence (and frequency category) of ADRs was calculated based on the percentage of patients experiencing an ADR. A patient with more than 1 event for a particular ADR was counted only once for that ADR.
Frequency categories were defined as follows: Very Common: ≥ 1/10, Common: ≥ 1/100 to < 1/10, Uncommon: ≥ 1/1000 to < 1/100, Rare: ≥ 1/10000 to < 1/1000, Very Rare: < 1/10000.
Abbreviations: ADR = adverse drug reaction; % = Percentage based on N; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in specified group; n = number of patients with available data; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Rapporteur's comments

The proposed ADR tables are incomplete. And and all adverse event that has at least a suspicion of causal origin should be included by preferred term. Based on the sources quoted, namely ISS Tables 14.3.1.23.1.1.1 and 14.3.1.23.2.1.2, not all treatment-related preferred term event shave been quoted in the new ADR tables.

4.3. Discussion

4.3.1. Integrated Efficacy Discussion

In this grouped variation the MAH provided both the final study results of the expanded access programme EA01 that ran in the US and which allowed patients that weren't eligible for trial participation to be treated until commercial product would become available. Additionally, this variation also provided an integrated analysis of the efficacy and safety results of all post-approval studies that were set up and have now finished. Each of these studies was assessed separately prior, but the current exercise does provide a cross-study analysis of outcomes, with all benefits and drawbacks that this entails.

For what concerns the expanded access study, efficacy follow-up was not an objective in this programme, but nonetheless certain safety parameters that were gathered also allow a certain measure of clinical benefit follow-up.

In the 6 patients, 5 children and 1 adult, that participated in this programme there was a clear improvement in parameters such as liver function and dyslipidaemia, the latter which occurred without any concomitant LLMs, alongside improvements in serum transaminases. Five out of six patients had a baseline palpable liver which became smaller over the course of treatment.

Thus in general the improvements in clinical status of these subjects generally mirrors the effects seen during the clinical development programme as well as in the post-approval study settings.

The Integrated analysis of post-approval studies aggregated the results of six studies: LAL-CL01, CL04, CL02, CL06, CL03 and CL08. The latter two studies, CL03 and CL08, were studies in infant subjects with rapid onset LA-D, whereas the other studies were done in a mixed children, adolescents and adults setting for CL02 and CL06 and a strictly adult setting for CL01 and CL04.

For the integrated analysis the aggregation of data was done in two large pools, based on the fact that the disease severity and lethality is different in infants; Pooled FAS 1 which contained all children and adults that participated the trails and Pooled FAS 2 which included all infant subjects.

Given the fact that the integrated analysis is a cross-study heterogenic data aggregation it should come as no surpise that for different efficacy endpoints different degrees of data paucity may exist, as well as a difference in dosing regimens, but overall the majority of endpoints were sufficiently congruent as to allow meaningful analysis.

Another issue to take into account specifically for Pooled FAS 2 is the fact that even in this aggregated form only very few subjects were included (n = 19), which immediately makes it exceedingly difficult to consider the clinical significance of or draw any firm conclusions from any new findings that would emerge from this integrated analysis.

Overall the efficacy results in both Pooled FAS groups are congruent with the observations made in both the clinical development leading up to market authorization, as well as the observations made in the individual studies that lake up the aggregated data body for this analysis. No new worrying signs of lack of efficacy or inadequacy of dosing were discovered, though the Applicant set forth three new points to consider:

- It is suggested based on the fact that a sizable exposure of 3 mg/kg qow was observed to be used in the aggregated data of children and adults that had a less-than-optimal response on the standard dose, and that this did not result in any new safety issues, to allow the option of said dose in the SmPC approved posology in case warranted by clinical response. Generally this

suggestion is supported based on the data as seen in the integrated analysis and the clinical reality which some of these patients find themselves in.

- Likewise, according to the Applicant there was a sizeable use of the 5 mg/kg qw dose in the infant population, for much the same reasons as above. Thus the applicant proposes to also alter the max dose escalation in the SmPC approved posology accordingly. However, in contrast to the previous point there are a few issues to consider here. First is the fact that the aggregated data only cover a total of 19 patients (13 of which made it to their respective studies' end) and of those only 7 were administered a doses of 5 mg/kg qw or higher. Moreover, of these 7 patients 3 were the dual WGD patients whose situation is slightly outside the norm, thus leaving only 4 'non-exceptional' patients with high dose use. This is considered far too few to normally allow a substantive alteration to the posology as proposed. However, one should also take into account the clinical reality of early-onset LAL-D which is characterised by a rapid onset and higher severity of pathophysiologic processes and characteristics, as well as a markedly higher mortality. Thus based on the observations made, the fact that no major safety issues were noted related by the higher dosing (with the caveat that the actual number of patients is exceedingly low) and the clinical reality of early-onset LAL-D the proposed change to the approved posology could be accepted if the MAH also provides a guidance in the SmPC that clearly outlines when and how dose-escalation and –de-escalation should be undertaken and in addition provide information on how to proceed if even the highest allowed dose does not alleviate disease burden.
- Three infant subjects in study LAL-CL08 showed continuous high ADA titres with efficacy-impacting NAb development with required high dosing treatment for limited effect, with one patient even escalating to 7.5 mg/kg qw. Eventually the patients' situation could be alleviated using BMT and HSCT. Genetic analysis showed that these three patients had a dual WGD (a homozygous deletion affecting both alleles of the genes *LIPA* and Cholesterol 25-Hydroxylase). In the process of study LAL-CL08 assessment the MAH was asked to potentially provide a retrospective integrated analysis of immunology with specific focus on the disease-underlying genetic mutations, but unfortunately most trails did not collect genetic data thus making this type of exercise impossible. Dual WGD and associated risks have however been flagged as a new safety signal in the updated RMP following the last renewal procedure for Kanuma®.

4.3.2. Integrated Safety Discussion

In the results of the US expanded access Programme LAL-AE01 no deaths or serious adverse events were noted, nor were there any discontinuations. Of the 6 patients 5 had post-baseline immunogenicity data available and none showed ADA development, and in general no worrisome or untoward safety issues were noted in these patients.

The integrated analysis of the 6 PA studies was done on the so-called Pooled SS 1 and 2 groups, aggregating data from respectively children/adults and infants, which for all intents and purposes were functionally identical to the Pooled FAS 1 & 2 groups used for the efficacy assessment and which carries the same limitations in regards to potential data heterogeneity and paucity.

Overall the safety and immunogenicity findings of this integrated analysis did not find any new or untoward safety parameters and outcomes were congruent with findings during the clinical development for MA and the individual PA studies.

No impact of dose escalation on the safety profile was apparent either, though caution should be taken given that, especially in infants, the data was very limited given the lower numbers of subjects on higher dose treatments.

One important combined efficacy-safety finding, as already discussed in the previous section, was the clue that dual whole genome deletion in the form of a homozygous deletion affecting both alleles of the genes LIPA and Cholesterol 25-Hydroxylase may impact the underlying disease in in such a way that patients are at elevated risk of having efficacy-impacting immunogenic responses to treatment. Based on this data a new safety signal has been incorporated in the RMP.

After further clarification on the method of ADR inclusion eligibility and a restructuring of the ADR table, said table is now considered acceptable.

4.3.3. Conclusions

Overall, the integrated analysis as provided here, in combination with the final results of the LAL-EA01 expanded access programme, confirm the clinical safety and efficacy of sebelipase alfa as determined in the clinical development program for MA as well as the individual post-authorisation studies that make up the aggregated data body of this analysis.

Based on the results the MAH proposed to update the approved posology to allow escalation of dosing in children and adults up to 3 mg/kg qow and in infants up to 5 mg/kg qw in function of clinical response. Sufficient data is available to agree with the change of adult and children's posology, but the change in infant posology cannot be accepted based solely on the very limited clinical data available. However, based on the clinical knowledge on the graveness of infant LAL-D the proposed dose escalation could be acceptable if the MAH also provides a cleat guidance on how and when to escalate and de-escalate doses in infants, as well as providing guidance on what should be done if a patient's situation can still not be controlled even at the new upper treatment limit.

As already discussed during the evaluation of the LAL-CL08 individual study results and during the renewal procedure for Kanuma®, three infant patients identified whom suffered efficacy-impacting immunogenic responses and for whom the disease was difficult to control even at sebelipase doses of 5 mg/kg qw and higher. Genetic typing of these three subjects revealed that they had a homozygous deletion affecting both alleles of the genes *LIPA* and Cholesterol 25-Hydroxylase, which may have contributed to a more severe disease characteristic. Based on these findings a new safety signal was put into the update RMP following the latest renewal procedure.

Finally, as a result of this procedure the MAH wishes to delete one of the PAMs in the Annex II to the SmpC:

> *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 overtime up to 3 years and survival at 12 months. The safety objectives should focus on hypersensitivity reactions, particularly anti-drug antibodies development impacting response to drug.*

Based on the fact that the final LAL-CL08 report has been submitted and providedand the fact that all questions raised thereupon have been adequately addressed by the MAH,the deletion of this Annex II PAM can be accepted.

5. PRAC advice

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6. Risk management plan

The MAH submitted an updated RMP version 4.0 with this application. The (main) proposed RMP changes were the following:

Part II: Safety specification:

- Module SIII and Module SIV were updated with the patient exposure from Pooled Safety Set 1 and Set 2.
- Module SV was update with available post-marketing data on patient exposure.
- Module SVII was updated with available safety data from Pooled Safety Set 1 and Set 2.

Part III: Pharmacovigilance plan

- Part III.1 was updated with information on pregnancy follow-up questionnaire.
- Part III.2/III.3 was revised to reflect on ongoing (LAL Deficiency Registry) and completed post-authorisation safety studies (LAL-CL06 and LAL-CL08).
- Part IV was updated with available milestone for the post-authorisation efficacy study.

Annex 2 and 3

Annexes were updated to reflect the information on ongoing (LAL Deficiency Registry) and completed post-authorisation safety studies (LAL-CL06 and LAL-CL08).

6.1. Safety Specification

Clinical trial exposure

The tables have been updated with detailed information on patient exposure.

Populations not studied in clinical trials

The tables have been updated to reflect the patients included in the completed clinical trials.

Post-authorisation experience

The tables have been updated with available post-marketing data.

Identified and potential risks

The identified and potential risks remain unchanged, but the section has been updated with data from the clinical trials and post-marketing experience.

Missing information

Topics considered missing information remain unchanged, but the section has been updated with data from the clinical trials and post-marketing experience.

PRAC Rapporteur's comment

The updates to the safety specification are accepted.

6.2. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of 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

All safety concerns and missing information except "*use in patients with egg allergy*" are subject to further investigation within the Category 1 PASS, LAL Deficiency Register.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

The final conclusion is however pending the CHMP assessment of the new safety data submitted with this variation.

6.3. Pharmacovigilance plan

The section on routine PhV activities has been updated with information on pregnancy follow-up questionnaire.

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study/status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
The LAL Deficiency Registry (non-interventional ~~imposed~~ PASS) Ongoing	~~The objective of the LAL Deficiency Registry is to use uniform methodology to collect longitudinal data over an extended period to provide information to:~~ • Further understand the disease, its progression and any associated complication.	Hypersensitivity reactions including anaphylaxis; ADA development impacting response to drug; Safety and efficacy in patients older than 65 years of age;	~~Final report~~ ***Interim reports***	~~The final report will be submitted 12 months after completion of the registry period.~~ ~~Interim reports will be submitted annually.~~ ***Submitted annually***

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	• Evaluate the long-term effectiveness 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-D and access to care.	Safety and efficacy in a paediatric population 2-4 years of age; Use in pregnant or lactating women; Long-term safety and effectiveness data.	***Final report***	***The final report will be submitted 12 months after completion of the registry period.*** ***Estimated date 30 January 2027***
~~LAL-CL08~~	~~Efficacy and safety; pharmacokinetics~~	~~Long-term safety and efficacy data ADA development impacting response to drug~~	~~Final report~~	~~July 2019~~
~~**Category 2** – imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances~~				
~~Not applicable~~	~~Not applicable~~	~~Not applicable~~	~~Not applicable~~	~~Not applicable~~
~~**Category 3** – required additional pharmacovigilance activities~~				
~~LAL-CL06 Completed~~	~~Efficacy and safety; pharmacokinetics~~	~~Safety and efficacy in a paediatric population 2-4 years of age ADA development impacting response to drug~~	~~Final report~~	~~Final CSR 144 weeks Dec 2018~~

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PhV plan has been updated to reflect that studies LAL-CL08 (Cat 1) and LAL-CL06 (Cat 3) have now been completed.

Overall conclusions on the PhV Plan

There are still outstanding issues regarding the RMP but a preliminary view is that:

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

The final conclusion is however pending the CHMP assessment of the new safety data submitted with this variation.

Plans for post-authorisation efficacy studies

This section was updated with available milestone for the post-authorisation efficacy study.

Table Part IV.1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study/status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are conditions of the marketing authorisation				
The LAL Deficiency Registry Ongoing	~~The objective of the LAL Deficiency Registry is to use uniform methodology to collect longitudinal data over an extended period to provide information to:~~ • Further understand the disease, its progression and any associated complication. • Evaluate the long-term effectiveness 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-D and access to care.	Hypersensitivity reactions including anaphylaxis; ADA development impacting response to drug; Safety and efficacy in patients older than 65 years of age; Safety and efficacy in a paediatric population 2-4 years of age; Use in pregnant or lactating women; Long-term safety and effectiveness data.	~~Final~~ ***Interim*** report	~~The final report will be submitted 12 months after completion of the registry period.~~ ***Submitted*** annually
			Final report	***The final report will be submitted 12 months after completion of the registry period.*** ***Estimated date 30 January 2027***

6.4. Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reactions including anaphylaxis	Routine risk minimisation measures: SmPC sections 4.3, 4.4, and 4.8 PL sections 2 and 4 Need for availability of appropriate medical support during administration stated in SmPC section 4.4 Patient observation for one-hour post initial/dose-escalated infusion stated in SmPC section 4.4 Recommendations for management of hypersensitivity listed in SmPC section 4.4 Recommendation for ADA testing in case of severe infusion-related reactions included in SmPC section 4.4 Restricted medical prescription Additional risk minimisation measures: Guide for healthcare professionals	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: None Additional pharmacovigilance activities: The LAL Deficiency Registry ***(final study report: estimated 30 January 2027)***
ADA development impacting response to drug	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 Recommendation for ADA testing in case of severe infusion-related reactions is included in SmPC section 4.4. Restricted medical prescription Additional risk minimisation measures: Guide for healthcare professional	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: None Additional pharmacovigilance activities: The LAL Deficiency Registry ***(final study report: estimated 30 January 2027)***
Use in patients with egg allergy	Routine risk minimisation measures: SmPC sections 2, 4.3, and 4.4	Routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL section 2 Additional risk minimisation measures: None	
Safety and efficacy in patients older than 65 years of age	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: None Additional pharmacovigilance activities: The LAL Deficiency Registry ***(final study report: estimated 30 January 2027)***
Safety and efficacy in paediatric population 2-4 years of age	Routine risk minimisation measures: SmPC section 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: None Additional pharmacovigilance activities: The LAL Deficiency Registry ***(final study report: estimated 30 January 2027)***
Use in pregnant and lactating women	Routine risk minimisation measures: SmPC sections 4.6 and 5.3 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: None Additional pharmacovigilance activities: The LAL Deficiency Registry ***(final study report: estimated 30 January 2027)***
Long-term safety and efficacy data	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: None Additional pharmacovigilance activities: The LAL Deficiency Registry ***(final study report: estimated 30 January 2027)***

The table has been updated to include the estimated time point for the submission of the final study report for the LAL Deficiency Registry.

Overall conclusions on risk minimisation measures

There are still outstanding issues regarding the RMP but a preliminary view is that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The final conclusion is however pending the CHMP assessment of the new safety data submitted with this variation.

6.5. Elements for a public summary of the RMP

The elements for a public summary of the RMP has been updated to reflect the new data submitted with the variation as well as the removal of the completed studies from the RMP. The updates are accurate and generally acceptable.

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

Further changes may be needed pending the final conclusions of the procedure.

6.6. Annexes

The annexes have been updated appropriately.

6.7. Overall conclusion on the RMP

The final conclusion is pending the CHMP assessment of the new safety data submitted with this variation.

☒ The changes to the RMP and the changes to the conditions and obligations of MA are acceptable.

7. Changes to the Product Information

As a result of this group of variations, section(s) 4.2, 4.4, 4.6, 4.7, 4.8, 5 and 6.6 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly. See Annexed SPC and PIL proposals with inline assessment/comments.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

8. Request for supplementary information

8.1. Major objections

Clinical aspects

1. It is observed that at least 287 samples from 4 clinical studies (studies LAL-CL02, LAL-CL03, LAL-CL06 and LAL-CL08) were impacted by data integrity issues, i.e. 19% of the total number of samples for these 4 studies (287/1510) or 14% out of all PK samples collected in the six clinical studies with PK sampling (287/2122). The sponsor proposes to report these results as 'non reportable'. The disqualification of this substantial number of results raises concerns about the validity of the entire set of PK data reported and may warrant an inspection. The MAH is required to justify that the conclusions drawn on the pharmacokinetics of sebelipase can be considered reliable.

2. The population pharmacokinetic analyses has been conducted to support the proposed posology and pharmacokinetic characteristics of sebelipase alpha in sections 4.2 and 5.2 of the SmPC. There are, however, issues with the current population pharmacokinetic analyses.

   Therefore,

   a. The applicant is requested to confirm the proposed posology and pharmacokinetic statements of the SmPC. The applicant is asked to perform additional simulations using an updated final PK model to identify alternative dosing weight ranges leading to comparable exposure as observed in adults. Further, exposure comparison between paediatrics and adults should also be conducted in different age ranges of paediatrics to evaluate the current posology,

   b. The assessment of bodyweight effect on clearance and volume of distribution with an estimated exponent is not supported in view of the limited data in the lower age subgroup; data from only 9 patients of < 4 years old were available. Bodyweight should be implemented in the model using allometric scaling with fixed exponents of 0.75 and 1 for all CL and V parameters, respectively. Additional effect of age/maturation should be tested on this model, including body weight. It is noticed that the current methodology of allometric scaling with estimated model parameters is incorrect. All clearance and volume of distribution parameters need to be scaled if allometric scaling is applied (irrespective of estimated or fixed allometric scaling exponents), which is most likely resulting in the high RSE observed for Vp and the high amount of unexplained between-subject variability in the model. As a result, the influence of body weight and age cannot be assessed.

RMP aspects

None

8.2. Other concerns

Clinical aspects

Immunogenicity and PK

3. Concerning the immunogenicity assays, the Applicant is requested to determine the cut-points of the target populations using the pre-treatment samples from the completed studies LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06 and LAL-CL08 to confirm the assay cut points determined with samples from healthy drug-naïve subjects. A statistical comparison is expected.

4. Concerning immunogenicity, the MAH has investigated the impact of ADA on exposure using a covariate analysis methodology on the final Pop-PK model. But the total number of patients with samples with measurable concentrations of sebelipase alfa and an ADA status used in this analysis is limited in comparison to the totality of data provided (3 ADA+ on 19 ADA+ in total; 72 ADA- on 106 ADA- in total). The effect of NAb was not formally tested in the population PK model due to the low number of samples with both a measurable concentration and a positive NAb (ie, a total of 1 positive NAb in 1 patient). Thus no conclusion can be currently drawn due to the limited information available. The SmPC should be updated in that sense, unless otherwise justified.

<u>POPPK modelling</u>

5. The final POPPK model was conducted on 714 samples on 880 considered PK samples. The reasons for not including 116 reportable samples in the POPPK analysis were: pre- or post-dose blank, a measurable concentration before the first dose, TAD>10 and not BLQ, missing sampling time and amount of previous dose imputed. The MAH is requested to clarify why a total of 1122 study samples with reportable results (as calculated based on Table 5 Module 2.7.1 and excluding the samples excluded from LAL-CL01 due to data integrity issues and from study LAL-CL08 due to errors in dosing records) has not been considered for inclusion in the POPPK analysis. In addition, the exclusion criteria 'TAD>10' should be clarified.

6. In view of the identified issues with data integrity and related data exclusion, the applicant is asked to provide the distribution of the data used for POPPK modelling by age group and to discuss whether there were enough data in the different age subgroups (2-4, 4-6, 6-12, and 12-18 y.o) to allow adequate PK characterization in the different age groups.

7. Nonlinear clearance should also be tested in the POPPK model using individual predicted concentrations as exposure marker.

8. It is noted that Vp parameters was poorly estimated using the updated POPPK model with RSE of 66%, this should be discuss in particular in light of data exclusion.

9. Model misspecifications are observed on the IPRED vs OBS and the pcVPC graphic: this should be further discussed. Moreover, model fitting performances (GOF nad pcVPC) should also be provided by age subgroups.

10. For adequate graphical evaluation, some missing plots should be provided. NPDEs distribution should also be provided as well as NPDE vs PRED and vs time plots. In addition, the applicant could present ETA plots versus bodyweight and age for:

    - model without bodyweight or age as covariates,

    - model with bodyweight as covariate,

- model with age as covariate.

PK/PD modelling

11. The choice of the 2 PD markers for the modelling exercise need to be better substantiated, as well as acceptance criteria and target levels to be reached for the selected dosing regimens.

12. The exclusion of placebo arm data from the PK/PD analysis is not acceptable given that these data could be informative for adequate description of the time course of the 2 biomarkers. The MAH is asked to address this issue.

13. The selection of the structural model in particular absence of testing alternative structural model with drug clearance from the central compartment and outside the effect compartment need to be justified for both ALT and LDL-cholesterol.

14. Key parameters (e.g. IC50 and EC50) were fixed without justifications of the source and the plausibility of the values used.

15. Pc VPC should be provided.

16. Model fitting performances (GOF nad pcVPC) should also be provided by age subgroups.

17. NPDEs distribution should also be provided as well as NPDE vs PRED and vs time plots.

Clinical Efficacy

18. The Applicant's proposed increase of the maximum dosage in infants to 5mg/kg qw does not have sufficient data to unequivocally support this change. However, given the clinical knowledge on the aggressiveness of early-onset LAL-D and the overall trend that seems to emerge from the limited data that there are indeed patients that benefit from higher doses, a higher maximal dose in case of insufficient response could be accepted if the MAH provides a guidance in the SmPC on how and when to escalate or de-escalate the dose, and what to do in case an infant's situation does not become controlled even at the higher maximal dose. Details on the format and content of this guidance is left to the MAH to devise and propose.

SmPC

19. The Applicant should update the ADR tables in section 4.8 of the SmPC as to provide frequency information for each preferred term instead of for the MeDRa SOC as a whole. Additionally, **all** causally related or reasonably considered as potentially causally related events should be listed by preferred term.

20. Regarding the modifications in the section 5.2, some updates are already proposed :

    a. It should be clarified in the title of the table 5 that the parameters were simulated after multiple dose.

b. The table 5 is not in line with the table 8 of the PK/PD simulation report. As an example, the total number N for overall subjects is discrepant (N=72 vs N=4).

c. The conclusions on the linearity of sebelipase alpha PK and accumulation over time are drawn based on the non-compartmental analysis in study LAL-CL04 and in study LAL-CL04 and LAL-CL06, respectively. But the number of patients in each category of age was limited and should be reflected in the SmPC. In addition, the lack of sign of accumulation for the 3 mg/kg qow dosing is not reported in the SmPC. Instead, lack of accumulation at 3 mg/kg once weekly is mentioned. It should be clarified if the source of this information is the study LAL-CL01 while all the PK samples from this study were disqualified. The SmPC should be updated accordingly.

21. The MAH should consider providing revised Product Information based on all the comments included in attachment to this Request for Supplementary Information.

RMP aspects

22. The elements for a public summary of the RMP should be slightly revised to include an explanation to the term "patients with dual WGD", e.g. "patients who lack the enzyme completely".

9. Assessment of the responses to the request for supplementary information

9.1. Major objections

Clinical aspects

Question 1

It is observed that at least 287 samples from 4 clinical studies (studies LAL-CL02, LAL-CL03, LAL-CL06 and LAL-CL08) were impacted by data integrity issues, i.e. 19% of the total number of samples for these 4 studies (287/1510) or 14% out of all PK samples collected in the six clinical studies with PK sampling (287/2122). The sponsor proposes to report these results as 'non reportable'. The disqualification of this substantial number of results raises concerns about the validity of the entire set of PK data reported and may warrant an inspection. The MAH is required to justify that the conclusions drawn on the pharmacokinetics of sebelipase can be considered reliable.

Summary of the MAH's response

Alexion is committed to assuring the quality and integrity of our study data, and for that reason we have disqualified data that did not meet applicable standards. An investigation was conducted, and actions were taken to ensure the accuracy and reliability of the results we have reported and ability to reconstruct the studies. A summary of those events, decisions and justification for the validity of the reported data is discussed herein.

In 2013, the CRO was contracted to validate an "Enzymatic Method to Determine the Activity of SBC-102 in Human Serum" (ELISA-0558-007) and perform sample analysis for the Studies LAL-CL01, LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06, and LAL-CL08. In early 2017, Alexion was notified by CRO that a Health Authority had performed a directed inspection of the in December 2016 that did not involve Alexion studies, but did result in the issuance of observations related to data integrity. It was also communicated that similar issues impacted some of the Alexion study data. Alexion immediately initiated an investigation into the nature and extent of the issues, resulting in both corrective and preventive actions as well as the disqualification of impacted study data.

Summary of investigation

Investigation and review of audit trails found that in the course of analyzing PK samples, single analytical plates had been read multiple times. In some instances, plates were read up to 5 times. When a re-read of a plate occurred, the original data were overwritten and only data from the final plate read were captured and subsequently reported. This activity was not documented anywhere in the associated study data. Original and intermediate plate reads were not captured by backup systems connected to the instrument; however, the audit trails for Softmax Pro did record the activity. This overwriting of original data was limited to a single analyst working on Alexion studies.

Investigation highlights:

• Alexion bioanalytical scientists and quality group personnel performed an onsite data review and onsite audit, respectively.

• Policies and standard operating procedures (SOPs) associated with data integrity were reviewed.

• Electronic system configuration, access, and permissions were assessed.

• All audit trails for Alexion studies were 100% reviewed (including supporting validations) identifying all impacted analytical runs.

• Analytical run performance and acceptance were reviewed.

• Study incurred sample reanalysis (ISR) data were reviewed and specifically ISR data where at least 1 value was from a run associated with data overwriting.

Root cause assessment:

• System access rights allowed replacement and overwriting of data for analysts who were also method developers.

• A single analyst failed to follow policies and SOPs designed to address data integrity.

• Review of data by supervising staff, Quality Control and Quality Assurance did not consistently involve review of system audit trails.

Highlights of actions:

• All data from runs involving overwriting of original results were disqualified.

• Any samples within established stability were reanalyzed.

• The analyst responsible for the overwriting practice was removed from global system access.

• The ability to overwrite/delete data in SoftMax Pro was removed from all users (except administrators).

• SoftMax Pro SOP's were updated.

• Increased review of user access to regulated systems was implemented.

• Data integrity training was conducted for staff.

• Specific requirements for review of system audit trails as part of any QA review was put in place.

Conclusion of the investigation:

All samples impacted by these events were identified and reanalyzed when possible or the data were disqualified. Without the disqualified results, the rest of the reported results (86% of total number of samples) met the criteria recommended by EMA (2/3 [66.67%] of samples are within 30% Diff) in the incurred sample reanalysis (ISR), thus demonstrating the reproducibility of the data. Therefore, from our investigation, the actions taken by both CRO and Alexion, and the performance of method, we have concluded that the reported Kanuma PK data are free of data integrity issues and reliable for use.

The actions that lead to the subsequent data disqualification in this program were limited to a single analyst who is no longer employed by the CRO. The laboratory has taken appropriate steps to prevent these actions from reoccurring in the future through procedural and technical controls.

Assessment of data reliability

Despite exclusion of these data, the final Pop-PK model incorporated 25% more PK data than in the original regulatory application model, ie, the final Pop-PK modeling was conducted on 714 samples compared with 570 samples in the original Marketing Authorization application (Original Sebelipase Alfa Pop-PK Report Section 8.2.1).

For the PK/PD modeling, exploratory graphical analysis and a model-based sensitivity analysis (Sebelipase Alfa PK/PD Report Appendix 4) suggested that the PD data from Studies LAL-CL04 and LAL-CL06 were uninformative to improve the PK/PD model. Therefore, the Pop-PK analysis was conducted on the reportable data from Studies LAL-CL02, LAL-CL03, LAL-CL04, and LAL-CL06 only, and the PK/PD modeling was conducted on the reportable data from Studies LAL-CL02 and LAL-CL03 only.

The analytical methods used to generate the reported PK dataset are fully validated. The ISR analysis, a mandated measure of a bioanalytical methods accuracy and reliability in the table below, meet the acceptance criteria as recommended by EMA (2/3 [66.67%] of the samples are within 30%), demonstrating the reliability of the reported bioanalytical results.

Table 59 – Summary of ISR across Kanuma studies

Study:	LAL-CL02	LAL-CL03	LAL-CL04	LAL-CL06	LAL-CL08
Number of samples analyzed for ISR	76	4	15	22	10
Samples meeting acceptance criteria	62	4	15	16	7
Pass rate	81.6%	100.0%	100.0%	72.7%	70.0%

Abbreviation: ISR = incurred sample reanalysis
Source: Bioanalytical study reports: 8291-767 (LAL-CL02), 8291-768 (LAL-CL03), 8291-766 (LAL-CL04), 8299-224 (LAL-CL06), and 8308-665 (LAL-CL08)

As such, Alexion has confidence in the data that were included in the PAM PK analyses, and that these data are sufficiently reliable to support the conclusions drawn on the PK of sebelipase alfa. The results from the final PK/PD model, which includes 25% more PK data than in the original MAA confirms the initial conclusions drawn on the PK of sebelipase alfa.

Assessment of the MAH's response

In answer to the major objection raised at the first round of assessment of this variation questioning the validity of the PK data, the MAH has described the corrective and preventive action plan taken to address the data integrity issues detected as part of a Health Authority inspection carried out in 2016. In general, this is deemed acceptable in terms of GCP and are expected to prevent a similar problem in the future :

- An investigation was conducted, and actions were taken to ensure the accuracy and reliability of the reported results and ability to reconstruct the studies. The ability to overwrite/delete data in SoftMax Pro was removed from all users (except administrators). This is considered as a crucial correction in their systems and quality control management to prevent similar data issues for future analysis.
- The laboratory has taken appropriate steps to prevent these actions from reoccurring in the future through procedural and technical controls.
- All audit trails for Alexion studies were 100% reviewed (including supporting validations) identifying all impacted analytical runs.
- All samples impacted by these events were identified and reanalyzed when possible or the data were disqualified. Based on the information provided in the original dossier submitted for this variation, it was understood that at the time of data disqualification these samples were beyond the validated long-term storage stability for the study results for KANUMA and could not be reanalysed. These samples were, therefore, unreportable. The Applicant should clarify if PK samples collected in the KANUMA studies were included in the 86% of total number of samples reanalysed and reported as meeting the criteria recommended by EMA in the incurred sample reanalysis.**(OC)**

Regarding the inspection report, it has not been provided by the MAH. It should be provided in order to see the initial findings and issues. In addition the MAH should give a list of GCP/GCLP inspections performed by European or other authorities outside EU during the same periods as the KANUMA studies periods at the CRO. The inspection results and the corresponding outcome should be discussed.**(OC)**

Conclusion

Partly resolved

Question 2

The population pharmacokinetic analyses has been conducted to support the proposed posology and pharmacokinetic characteristics of sebelipase alpha in sections 4.2 and 5.2 of the SmPC. There are, however, issues with the current population pharmacokinetic analyses.

Therefore,

a. The applicant is requested to confirm the proposed posology and pharmacokinetic statements of the SmPC. The applicant is asked to perform additional simulations using an updated final PK model to identify alternative dosing weight ranges leading to comparable exposure as observed in adults. Further, exposure comparison between paediatrics and adults should also be conducted in different age ranges of paediatrics to evaluate the current posology,

b. The assessment of bodyweight effect on clearance and volume of distribution with an estimated exponent is not supported in view of the limited data in the lower age subgroup; data from only 9 patients of < 4 years old were available. Bodyweight should be implemented in the model using allometric scaling with fixed exponents of 0.75 and 1 for all CL and V parameters, respectively. Additional effect of age/maturation should be tested on this model, including body weight. It is noticed that the current methodology of allometric scaling with estimated model parameters is incorrect. All clearance and volume of distribution parameters need to be scaled if allometric scaling is applied (irrespective of estimated or fixed allometric scaling exponents), which is most likely resulting in the high RSE observed for Vp and the high amount of unexplained between-subject variability in the model. As a result, the influence of body weight and age cannot be assessed.

Summary of the MAH's response

Part a:

Exploration of an improved Pop-PK model was performed as requested in Questions 2b and 7. This Pop-PK model is referred to as the "current best model" (CBM) in these responses, and includes the PAM Pop-PK model plus addition of data from patients who received placebo and then switched to sebelipase alfa. None of the evaluated model changes (see the table below) resulted in a better model compared to the existing PAM Pop-PK model.

It should be noted that the previously submitted PAM PK/PD report (2019 Sebelipase Alfa PK/PD Report) highlighted that exposure does not inform the PD response (eg, ALT and LDL-C) levels, given the short half-life and long dosing interval for sebelipase alfa. Thus, acceptance criteria and target levels of these endpoints were not prespecified for selecting the dosing regimens. Across the Alexion clinical studies in LAL-D, dose modifications were based on clinical response and not systemic drug concentrations or drug exposure (PK) parameters. Per the assorted clinical protocols, dose increases were permitted for patients who exhibited a suboptimal clinical response, as determined based on protocol-specified criteria reflecting the key disease manifestations. Dose reductions were also permitted in the event of poor tolerability.

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) that binds to cell surface receptors via glycans expressed on the protein (Sands, 2001; Sly, 2006), which facilitate its uptake into lysosomes, the drug's site of action. 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 (Stahl, 1978; Coutinho, 2012).

Sebelipase alfa is an ERT that exhibits a nonsystemic site of drug action; the previously submitted PAM PK/PD report confirms that exposure does not inform the PD response, indicating that systemic drug exposure does not inform dosing or dosing recommendations for sebelipase alfa. This is supported by Kanuma dosing once every 2 weeks for a compound with mean predicted terminal elimination half-life of approximately 3 hours and is consistent with dosing recommendations for other ERTs for lysosomal

storage disorders (eg, Cerezyme®, Fabrazyme®, Replagal™, and VPRIV® SmPCs). The reason for characterizing the PK of sebelipase alfa is mainly to assess systemic availability following dosing.

Considering the above, ALT and LDL-C simulations comparing exposure and response between pediatric and adult patients in the PAM PK/PD report (2019 Sebelipase Alfa PK/PD Report Figures 7 and 9), and completing the requested modeling work in these responses, Alexion believes that the 2019 adult versus pediatric simulations are sufficient to support the proposed PK statements and proposed posology in the EU SmPC.

Part b:

To address this request, it is necessary to consider the following: 1) if the data are sufficient for the lower age patients, and 2) if the model building approach was correct. Based on previous Alexion submissions and goodness-of-fit (GOF) plots from Pop-PK modelling of sebelipase alfa (see response to Question 6), sufficient PK data are available for younger patients.

To test the different Pop-PK models requested (M1, M2, and M3), each model was compared with the CBM (see the table below) to assess if a requested model was better and should be used as the final Pop-PK model.

Table 60 - Requested Model Evaluations – Current Best Model

CBM	MOFV	Test Model	MOFV	ΔMOFV	Result
Estimated Allometry on CL and Vc only	8323.69	M1, Estimated Allometry on CL/Q and Vc/Vp	8329.35	5.66	CBM better
Estimated Allometry on CL and Vc only	8323.69	M2, Fixed Allometry on CL and Vc Only	8351.9	28.21	CBM better
Estimated Allometry on CL and Vc only	8323.69	M3, Fixed Allometry on CL and Vc Only + Maturation	8384.12	60.43	CBM better

Note: ΔMOFV = M1, M2, or M3 – CBM. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CBM = current best model; CL = clearance; MOFV=minimum objective function value; Q = intercompartmental volume of distribution; Vc = central volume of distribution; Vp = peripheral volume of distribution
Source: Appendix Section 4.1

The M1 model applied body weight based allometric scaling to all clearance and volume parameters (CL, Q, Vc, and Vp). The M2 model applied body weight based allometric scaling to CL/Vc fixing the allometric exponents to 0.75 and 1.0 for CL and Vc, respectively. The M3 model added a maturation covariate to M2. The CBM was found to be a better model than M1, M2 and M3 models. For sebelipase alfa Pop-PK model development, M1 and M2 were tested previously, but were not included in the PK/PD report (2019 Sebelipase Alfa PK/PD Report) as the focus of the report was to answer the specific PAM questions. The M3 model structure was tested during model development as well; however, the allometric exponents were estimated and not fixed.

Comparison of the parameter estimates for the CBM versus M1, M2, and M3 is provided in the tables below. In these tables, it should be noted, for the CBM, relative standard error (RSE)% for Vp improved from 66% (see response to Question 8) to 29.7%. This is likely due to including the PK data from the patients who received placebo and then switched to active treatment, and not because of incorrect modelling of body weight-based allometry. Additional Pop-PK models were requested to be tested (see response to Question 10), and these models were not found better compared with the CBM either, especially for Vp, the RSE was 34.2% when allometry was fixed to 1 for V and to 0.75 for CL.

In conclusion, the model submitted as part of the post authorization measure (ie, the 2019 PAM model) is still the best Pop-PK model structure, and it was technically improved by including PK data from patients who received placebo and then switched to active treatment (ie, the CBM).

Table 61 - Population PK Parameter Estimate Comparison Between Current Best Model and M1

Parameter	CBM (MOFV: 8323.69) Estimated Allometry on CL and Vc Only			M1 (MOFV: 8329.35) Estimated Allometry on CL/Q and Vc/Vp		
	Estimate	RSE%	95% CI	Estimate	RSE%	95% CI
CL	36.1	8.43	30.1 – 42.1	38.0	9.96	30.6 – 45.4
Q	1.50	13.1	1.11 – 1.89	2.05	17.0	1.36 – 2.73
Vc	4.21	12.4	3.19 – 5.24	4.51	12.8	3.38 – 5.63
Vp	4.07	29.7	1.70 – 6.43	6.59	47.0	0.515 – 12.7
Weight on CL	0.480	17.2	0.319 – 0.642	0.589	16.6	0.398 – 0.780
Weight on Vc	0.460	34.6	0.148 – 0.772	0.508	28.3	0.226 – 0.789
IIV on CL	0.391	12.7	0.294 – 0.488	0.380	12.3	0.289 – 0.472
IIV on Vc	0.737	10.4	0.587 – 0.886	0.721	10.2	0.578 – 0.865
Correlation CL, Vc	0.0842	165	-0.188 – 0.356	0.151	88.9	-0.112 – 0.414
ETA scaling factor (Q:CL)	1.41	18.0	0.913 – 1.91	1.33	20.5	0.797 – 1.87
IOV on Vc	0.241	6.68	0.210 – 0.273	0.243	7.07	0.209 – 0.276
Proportional Error	52.8	2.93	49.8 – 55.8	52.8	3.03	49.7 – 56.0
Additive Error	0.0447	Fixed	Fixed	0.0447	Fixed	Fixed

Note: CBM ETA shrinkage: CL = 19.7%, Vc = 24.8%. M1 ETA shrinkage: CL = 21.2%, Vc = 22.6%.
Abbreviations: CBM = current best model; CI = confidence interval; CL = clearance; ETA = random effect; IIV = inter-individual variability; IOV = inter-occasion variability; MOFV = minimum objective function value; PK = pharmacokinetic; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment
Source: Appendix Section 4.2

Table 62 - Population PK Parameter Estimate Comparison Between Current Best Model and M2

Parameter	CBM (MOFV: 8323.69) Estimated Allometry on CL and Vc Only			M2 (MOFV: 8351.9) Fixed Allometry on CL/Vc Only		
	Estimate	RSE%	95% CI	Estimate	RSE%	95% CI
CL	36.1	8.43	30.1 – 42.1	41.7	6.13	36.7 – 46.7
Q	1.50	13.1	1.11 – 1.89	1.69	15.2	1.18 – 2.19
Vc	4.21	12.4	3.19 – 5.24	5.53	11.0	4.34 – 6.72
Vp	4.07	29.7	1.70 – 6.43	5.41	34.2	1.78 – 9.03
Weight on CL	0.480	17.2	0.319 – 0.642	0.750	Fixed	Fixed
Weight on Vc	0.460	34.6	0.148 – 0.772	1.00	Fixed	Fixed
IIV on CL	0.391	12.7	0.294 – 0.488	0.405	12.3	0.307 – 0.503
IIV on Vc	0.737	10.4	0.587 – 0.886	0.791	10.7	0.625 – 0.957
Correlation CL, Vc	0.0842	165	-0.188 – 0.356	0.0806	162	-0.176 – 0.337
ETA scaling factor (Q:CL)	1.41	18.0	0.913 – 1.91	1.27	18.4	0.814 – 1.74
IOV on Vc	0.241	6.68	0.210 – 0.273	0.253	6.51	0.220 – 0.285
Proportional Error	52.8	2.93	49.8 – 55.8	53.2	2.77	50.3 – 56.1
Additive Error	0.0447	Fixed	Fixed	0.0447	Fixed	Fixed

Note: CBM ETA shrinkage: CL = 19.7%, Vc = 24.8%. M2 ETA shrinkage: CL = 19.8%, Vc = 23.5%.
Abbreviations: CBM = current best model; CI = confidence interval; CL = clearance; ETA = random effect; IIV = inter-individual variability; IOV = inter-occasion variability; MOFV = minimum objective function value; PK = pharmacokinetic; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment
Source: Appendix Section 4.3

Table 63 - Population PK Parameter Estimate Comparison Between Current Best Model and M3

Parameter	CBM (MOFV: 8323.69) Estimated Allometry on CL and Vc Only			M3 (MOFV: 8384.12) Fixed Allometry on CL/Vc Only+ Maturation		
	Estimate	RSE%	95% CI	Estimate	RSE%	95% CI
CL	36.1	8.43	30.1 – 42.1	44.0	6.76	38.1 – 49.8
Q	1.50	13.1	1.11 – 1.89	2.15	20.3	1.30 – 3.01
Vc	4.21	12.4	3.19 – 5.24	5.92	10.9	4.65 – 7.18
Vp	4.07	29.7	1.70 – 6.43	9.54	44.1	1.29 – 17.8
Weight on CL	0.480	17.2	0.319 – 0.642	0.750	Fixed	Fixed
Weight on Vc	0.460	34.6	0.148 – 0.772	1.00	Fixed	Fixed
IIV on CL	0.391	12.7	0.294 – 0.488	0.486	11.4	0.378 – 0.595
IIV on Vc	0.737	10.4	0.587 – 0.886	0.776	10.8	0.612 – 0.940
Correlation CL, Vc	0.0842	165	-0.188 – 0.356	0.223	58.2	-0.0311 – 0.476
ETA scaling factor (Q:CL)	1.41	18.0	0.913 – 1.91	1.17	16.6	0.788 – 1.55
IOV on Vc	0.241	6.68	0.210 – 0.273	0.254	6.58	0.221 – 0.287
Proportional Error	52.8	2.93	49.8 – 55.8	53.7	2.82	50.7 – 56.6
Additive Error	0.0447	Fixed	Fixed	0.0447	Fixed	Fixed
Age_{50} on CL	NA	NA	NA	1.00	Fixed	Fixed
Age on CL Hill constant	NA	NA	NA	1.51	37.9	0.388 – 2.62

Note: CBM ETA shrinkage: CL = 19.7%, Vc = 24.8%. M3 ETA shrinkage: CL = 16.0%, Vc = 24.3%.
Abbreviations: CBM = current best model; CI = confidence interval; CL = clearance; ETA = random effect; IIV = inter-individual variability; IOV = inter-occasion variability; MOFV = minimum objective function value; NA = not applicable; PK = pharmacokinetic; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment
Source: Appendix Section 4.4

Assessment of the MAH's response

The applicant has provided model with fixed allometric components. Even if statistically less performing than the CBM model, this model is considered more reliable given the limited amount of data in the paediatric population. Given the very close values of all the remaining parameters of the model, no important impact is expected on the predicted exposure levels and the starting dose recommendation.

In the absence of PK exposure comparison between the adults and the different age groups, it cannot be concluded that the POPPK data are supportive of the recommended starting dose.

Conclusion

Issue not pursued

9.2. Other concerns

Clinical aspects

Immunogenicity and PK

Question 3

Concerning the immunogenicity assays, the Applicant is requested to determine the cut-points of the target populations using the pre-treatment samples from the completed studies LAL-CL02, LAL-CL03,

LAL-CL04, LAL-CL06 and LAL-CL08 to confirm the assay cut points determined with samples from healthy drug-naïve subjects. A statistical comparison is expected.

Summary of the MAH's response

At this stage, Alexion is unable to calculate population or disease specific cut-points for the neutralizing antibody (NAb) assays due to a lack of pretreatment sample data from the study, and the samples now being outside long term stability limits. Samples were only tested for NAb status when they were determined to be antidrug antibody (ADA) positive, and no patients were at baseline. Pretreatment samples are all 4 to 9 years old currently, and no longer valid for analysis.

For the ADA assay, Alexion will use the combined pretreatment data from Studies LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06, and LAL-CL08 to evaluate specific cut-points for children (< 18 years old) and adult (≥ 18 years old) populations. Due to the small number of infants included in the sebelipase alfa clinical development program, infants will be included with the population of children. A statistical comparison based upon the 95% confidence intervals of the validation and newly established cut-points will be conducted to identify any significant differences. This analysis is ongoing and Alexion commits to providing the results to the EMA by July 2020.

Assessment of the MAH's response

For the NAb assay, the MAH is reporting that no pre-treatment samples are available anymore (out-of-stability) and the samples were only tested in case of ADA positive results. This is acknowledged. Since the investigation of the impact of the immune response to sebelipase on PK, efficacy and safety has been investigated at NAb level and ADA level as well, this issue is **not pursued**.

For the ADA assay, the MAH has committed to provide the statistical comparison of the validation cut-point (healthy subjects) and the newly established cut points (target population) by July 2020. The observed false positive error rate of the clinical study baseline samples, after excluding the samples with pre-existing ADA, using the validation cut point should also be taken into account in the discussion on the reliability of the validation cut point in the study population.**(OC)**

Conclusion

Unresolved issue

Question 4

Concerning immunogenicity, the MAH has investigated the impact of ADA on exposure using a covariate analysis methodology on the final Pop-PK model. But the total number of patients with samples with measurable concentrations of sebelipase alfa and an ADA status used in this analysis is limited in comparison to the totality of data provided (3 ADA+ on 19 ADA+ in total; 72 ADA- on 106 ADA- in total). The effect of NAb was not formally tested in the population PK model due to the low number of samples with both a measurable concentration and a positive NAb (ie, a total of 1 positive NAb in 1 patient). Thus no conclusion can be currently drawn due to the limited information available. The SmPC should be updated in that sense, unless otherwise justified.

Summary of the MAH's response

Alexion acknowledges EMA's feedback and agrees to update the EU SmPC to reflect this position. As such, the EU SmPC text has been updated (below in bold underlined).

Section 4.4 Special warnings and precautions for use

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In the sebelipase alfa clinical program, patients were routinely tested for anti-sebelipase alfa antidrug antibodies (ADAs) to determine the immunogenicity potential of sebelipase alfa. Patients who tested positive for ADAs were also tested for inhibitory antibody activity. The presence of inhibitory activity has been detected at some postbaseline timepoints in clinical studies (see section 4.8). Overall, ~~**there is no clear relationship between either development of ADAs/inhibitory antibody activity and associated hypersensitivity reactions or suboptimal clinical response**~~ **no conclusion on the relationship between development of ADAs/NAbs and associated hypersensitivity reactions or suboptimal clinical response can be made.**

During clinical studies, a decrease in clinical response associated with the development of inhibitory antibody activity was only observed in 3 patients with a homozygous deletion affecting both alleles of genes Lipase A, lysosomal acid (LIPA) and Cholesterol, 25-Hydroxylase (see section 4.8).

Section 4.8 Undesirable effects

Immunogenicity

There is potential for immunogenicity (see section 4.4). Patients have developed anti-drug antibodies (ADA) to sebelipase alfa. Compared to children and adults, an increased occurrence of ADA positivity was observed within the infant population (10/19 patients).

Among 125 patients with LAL Deficiency enrolled in the clinical studies, 19/125 (15.0%) patients tested positive for anti-drug antibodies (ADAs) at some timepoint after starting treatment with KANUMA. Among those 19 patients, 11 (58%) also showed the presence of inhibitory antibody activity (NAbs) at some postbaseline timepoint.

Overall, ~~**there is no clear relationship between development of ADAs/NAbs and associated hypersensitivity reactions or suboptimal clinical response**~~ **no conclusion on the relationship between development of ADAs/NAbs and associated hypersensitivity reactions or suboptimal clinical response can be made**. In clinical studies, 3 patients homozygous for a deletion affecting both alleles of genes Lipase A, lysosomal acid [LIPA] and Cholesterol 25-Hydroxylase developed inhibitory antibody activity associated with a suboptimal clinical response (see section 4.4). These patients underwent either immunomodulatory therapy alone or in combination with hematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT), resulting in improved clinical response to KANUMA.

Section 5.2 Pharmacokinetic properties

Immunogenicity

As with all therapeutic proteins, there is the potential for the development of immunogenicity. Nineteen of 125 (15%) patients with LAL Deficiency had at least 1◦postbaseline antidrug antibody (ADA) positive result, 9 of which were children and adult patients. For children and adult patients with LAL Deficiency,

ADA positivity was transient with generally low titers of ADAs reported. No ~~**apparent correlation of antibody development to altered sebelipase alfa pharmacokinetics was observed**~~ **conclusion on the impact of immunogenicity on sebelipase alfa exposure can be made.**

Assessment of the MAH's response

The limited information available hampers the assessment of the impact of ADA/NAb on sebelipase exposure. The MAH has adequately updated the section 5.2 as requested to reflect that no conclusion can be currently drawn regarding the impact of ADAs/NAbs on sebelipase exposure. The proposed changes in the sections 4.4 and 4.8 are also accepted. However, to avoid redundant statement, the detailed information on the ADA incidence should only be provided in the section 4.8 with a cross-reference to the section 4.8 in the section 5.2 : "As with all therapeutic proteins, there is the potential for the development of immunogenicity. Nineteen of 125 (15%) patients with LAL Deficiency had at least 1◦postbaseline antidrug antibody (ADA) positive result, 9 of which were children and adult patients. For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported".**(OC)** In addition, to give a full overview of all patient populations to the healthcare provider, the following statement on the ADA incidence in infants provided in the document 2.7.2 should be reported in the section 4.8: "On the other hand, persistence of ADA positivity was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants." **(OC)**

Conclusion

Partly resolved

POPPK modelling

Question 5

The final POPPK model was conducted on 714 samples on 880 considered PK samples. The reasons for not including 116 reportable samples in the POPPK analysis were: pre- or post-dose blank, a measurable concentration before the first dose, TAD>10 and not BLQ, missing sampling time and amount of previous dose imputed. The MAH is requested to clarify why a total of 1122 study samples with reportable results (as calculated based on Table 5 Module 2.7.1 and excluding the samples excluded from LAL-CL01 due to data integrity issues and from study LAL-CL08 due to errors in dosing records) has not been considered for inclusion in the POPPK analysis. In addition, the exclusion criteria 'TAD>10' should be clarified.

Summary of the MAH's response

For clarification, Module 2.7.1 Table 5 contains accounting of unreportable samples for the reasons of the data integrity issue and of exceeding long-term stability, but not for analytical reasons such as insufficient sample volume. Additionally, this Module 2.7.1 Table 5 contained typographical errors, which are now corrected and updated below to include samples unreportable for analytical reasons to complete the accounting of samples (see the table below). Most of the discrepancy noted in the number of PK samples comes from Study LAL-CL02, where, as discussed above, Module 2.7.1 Table 5 had indicated that 291 of 973 PK samples were non-reportable for this study, which was incorrect due to a typographical error (actual number of non-reportable samples 203/973; bioanalytical study report 8291-767; Table 6), while the Pop-PK analyses indicated that there were 444 reportable PK samples (Module

2.7.2 Table 18). This has no impact on the total number of PK samples considered in the PAM pop-PK analysis (714 samples, Module 2.7.2 Table 5).

Table 64 - Summary of Non-Reportable Sample Results (correcting Module 2.7.1 Table 5)

Clinical Study	Bioanalytical Study Report	Non-reportable/Total PK Samples	Reportable samples
LAL-CL01[a]	8299-266	270/270	0
LAL-CL02	8291-767	203/973[b]	770
LAL-CL03[c]	8291-768	15/44[d]	29
LAL-CL04[a]	8291-766	107/342[e]	235
LAL-CL06	8299-224	282/456[f]	174
LAL-CL08	8308-665	13/33[g]	20
Total:	NA	890/2118	1228

[a]Sebelipase alfa concentrations for study LAL-CL01 and for a portion of Study LAL-CL04 were analysed using ELISA-0558 but were determined to be unreportable due to lack of long term stability.

b Correcting 291/973 as mentioned in Module 2.7.1 Table 5, source: bioanalytical study report 8291-767.
c Study LAL-CL03 sample numbers also include samples taken under the Study LAL-CL05 protocol (Reported in bioanalytical study report 8299-267), which were merged with the Study LAL-CL03 dataset.
d Correcting 21/47 as mentioned in Module 2.7.1 Table 5, source: bioanalytical study report 8291-768.
e Correcting 106/342 as mentioned in Module 2.7.1 Table 5, source: bioanalytical study report 8291-766.
f Correcting 278/456 as mentioned in Module 2.7.1 Table 5, source: bioanalytical study report 8299-224.
g Correcting 13/34 as mentioned in Module 2.7.1 Table 5, source: bioanalytical study report 8308-665.
Abbreviation: ELISA = enzyme-linked immunosorbent assay; NA = not applicable; PK = pharmacokinetic

For the submitted PAM Pop-PK analysis (2019 Sebelipase Alfa PK/PD Report), extension data from all studies were excluded due to a higher variability in PK data typically resulting from fewer visits and reduced sample collection. This resulted in exclusion of PK data from 30 patients in Study LAL-CL02 who received placebo (no treatment) during the treatment period and then switched to active treatment during the extension period (2019 Sebelipase Alfa PK/PD Report). The table below shows the counts when these 30 patients are included in the PK dataset. With inclusion of these 30 patients, the PK data used in the Pop-PK analysis increase from 714 to 850 PK samples.

Table 65 - Updated Summary of Dataset Available for the Population PK Analysis

Study	Number (%) of Patients	Total Number (%) of Sebelipase Alfa PK Samples	Number of Samples			Total Number (%) of Samples Included in Pop-PK Analysis
			Pre-dose BLQ	Post-dose BLQ	Excluded	
LAL-CL02[a]	65 (61.9)	772 (63.9)	167	87	22	496 (41.1)
LAL-CL03	5 (4.8)	28 (2.3)	0	7	0	21 (1.7)
LAL-CL04	8 (7.6)	235 (19.5)	0	43	1	191 (15.8)
LAL-CL06	27 (25.7)	173 (14.3)	4	20	7	142 (11.8)
Total[b]	105 (100.0)	1208 (100.0)	171 (14.16%[c])	157 (13.00%[c])	30 (2.48%[c])	850 (70.36)

Note: All PK data from Study LAL-CL08 were omitted as described in Module 2.7.2.3.2.1.
[a] There were 30 patients randomized to placebo in Study LAL-CL02 who received active treatment in the Open-label Extension Phase and were included in the current analysis.
[b] Total here includes 3 adult patients who received the 3 mg/kg dose and were excluded from the final model. The final Pop-PK model included 102 patients and 757 PK samples.
[c] Percent of the total number of sebelipase alfa PK samples, 1208 samples.
Abbreviations: BLQ = below the limit of quantification; PK = pharmacokinetics; Pop = population
Source: Appendix 5.1

Also, high PK levels late in the dosing interval (time after dose [TAD] > 10 hours) were considered

biologically implausible based on the mean predicted terminal elimination half-life of sebelipase alfa of approximately 3 hours and a once every 1 or 2 week dosing frequency and, thus, were removed from the dataset both in the PAM analyses and in the current analyses. All patients who met the criteria for TAD > 10 hours had biologically implausible drug concentrations > 335 hours (ie, approximately 2 weeks) after the last dose (see the table below).

Table 66 - List of Patients With PK Levels Late in the Dosing Interval (TAD > 10 Hours)

Subject ID	Visit	Timepoint	TAD (h)	Observed Value (µg/mL)	Comment
LAL-CL02-1101-089	Week 22	NA	335.5	635.735	TAD > 10 h and not BLQ
LAL-CL02-1704-085	Week 22	NA	358.6	541.419	TAD > 10 h and not BLQ
LAL-CL01-06-001	Week 104	Pre-dose	336.1	1722.472	TAD > 10 h and not BLQ
LAL-CL06-1502-034	Week 24	Pre-dose	335.9	38.303	TAD > 10 h and not BLQ

Abbreviations: BLQ = below level of quantitation; h = hours; NA = not applicable; PK = pharmacokinetic; TAD = time after dose

Source: Sebelipase Alfa PK/PD Report Section 10.1.4

Assessment of the MAH's response

The applicant has provided the requested clarification for data exclusion.

Conclusion

Issue not pursued.

Question 6

In view of the identified issues with data integrity and related data exclusion, the applicant is asked to provide the distribution of the data used for POPPK modelling by age group and to discuss whether there were enough data in the different age subgroups (2-4, 4-6, 6-12, and 12-18 y.o) to allow adequate PK characterization in the different age groups.

Summary of the MAH's response

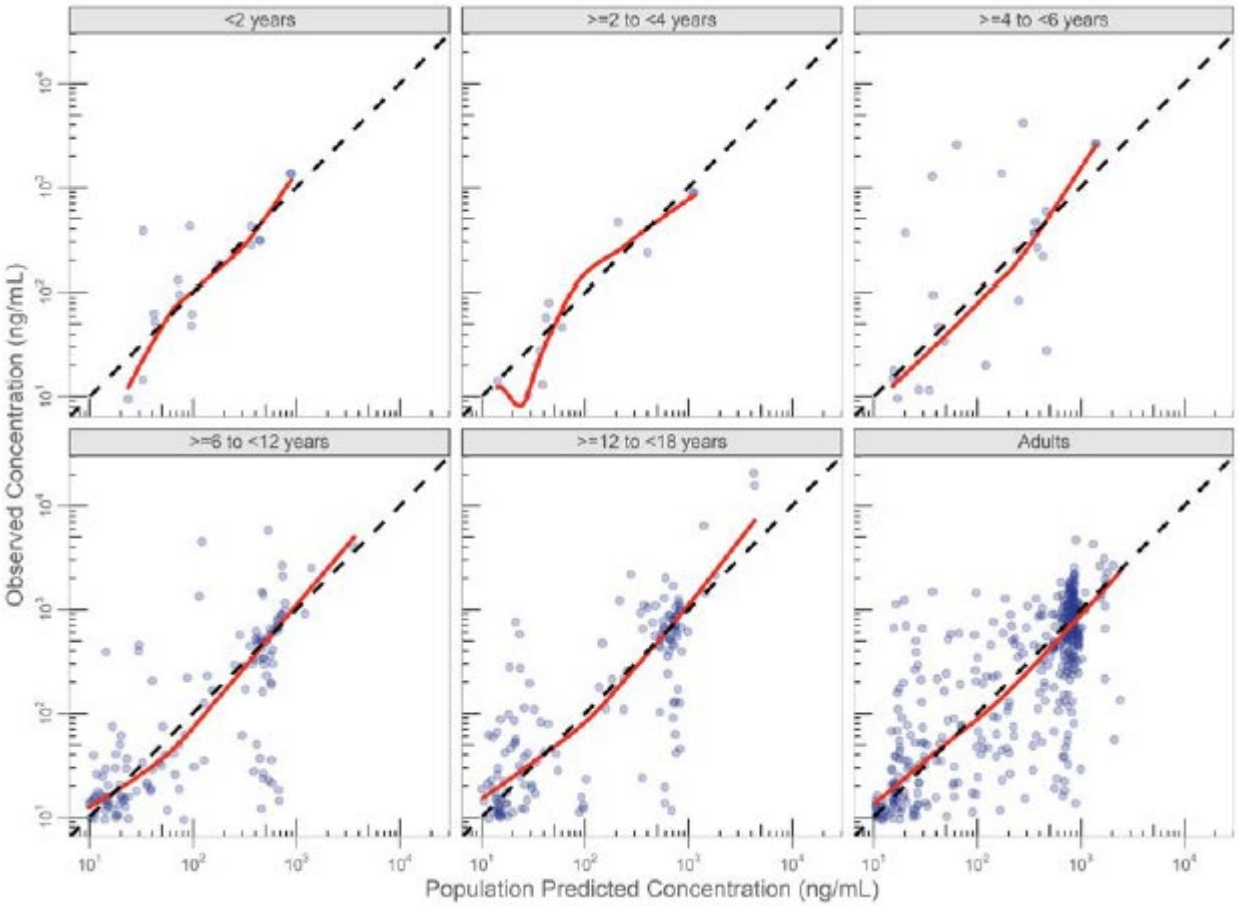
Limited PK data in pediatric patients with an ultra-rare disease is not unusual. Alexion has previously submitted Pop-PK models for eculizumab (aHUS 10-003 PK/PD Report Table 8) and ravulizumab (aHUS Pop-PK-PD Report Section 14.2) for the treatment of pediatric patients with atypical hemolytic uremic syndrome (aHUS); N = 10 < 5 years of age and N = 6 < 4 years of age, respectively. The distribution of sebelipase alfa concentrations by age group are presented in the table below. The adequacy of PK characterization can be assessed using goodness-of-fit (GOF) plots (see the figures below). For patients 6 years of age and older, the Pop-PK model characterizes the data well. For patients less than 6 years of age, the GOF plots indicate that the Pop-PK model still characterizes the sparse PK data well. Overall, age stratified GOF plots concluded that there were enough data in the different age subgroups (2-4, 4-

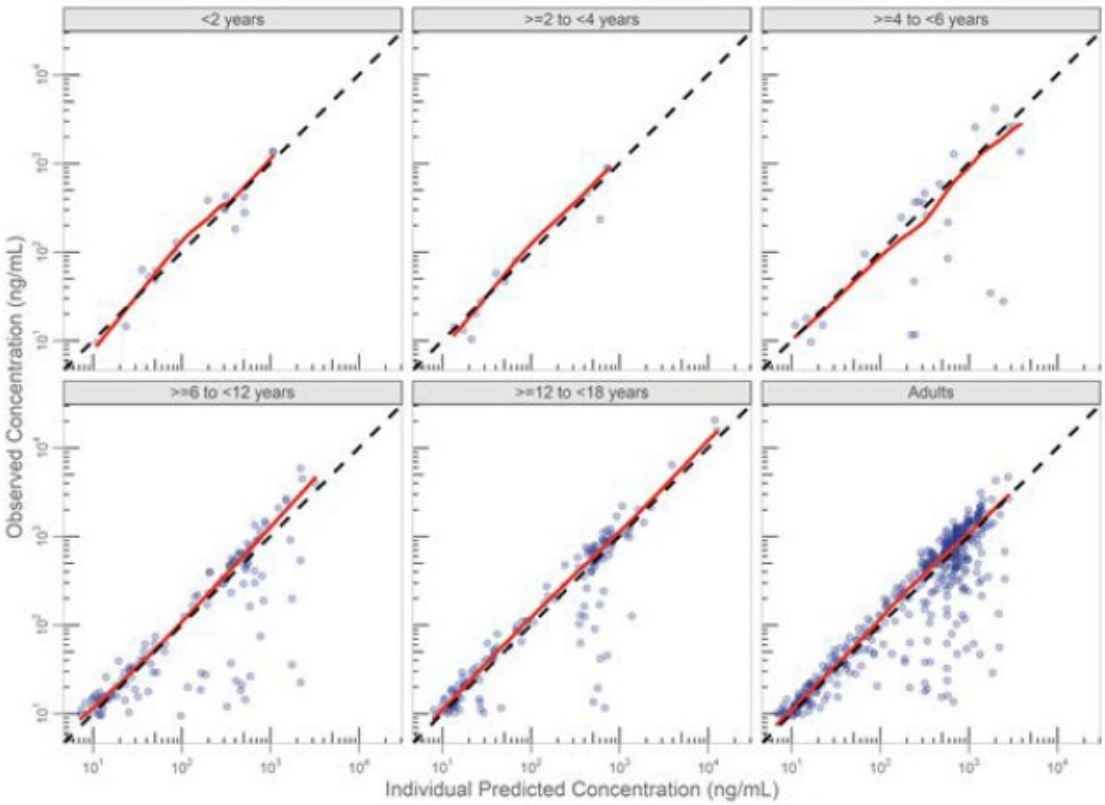
6, 6-12, and 12-18 years old) to allow adequate PK characterization in the different age groups.

Table 67 - Distribution of PK Samples by Age Group

Age Group (years)	Number of Patients (% of Total)	Number of Sebelipase Alfa PK Samples (% of Total)	Number of Predose BLQ Samples	Number of Postdose BLQ Samples	Number of Excluded Samples	Number of Samples Included in the Population PK Analysis (% of Overall Total[a])
< 2	5 (4.8)	22 (1.8)	0	5	0	17 (1.4)
2 to < 4	2 (1.9)	15 (1.2)	0	3	0	12 (1.0)
4 to < 6	6 (5.7)	42 (3.5)	4	12	0	26 (2.2)
6 to < 12	30 (28.6)	201 (16.6)	32	27	7	135 (11.2)
12 to < 18	29 (27.6)	228 (18.9)	46	19	14	149 (12.3)
Adults (≥ 18)	33 (31.4)	700 (57.9)	89	91	9	511 (42.3)
Total	105 (100.0)	1208 (100.0)	171 (14.16%[a])	157 (13.00%[a])	30 (2.48%[a])	850 (70.36)

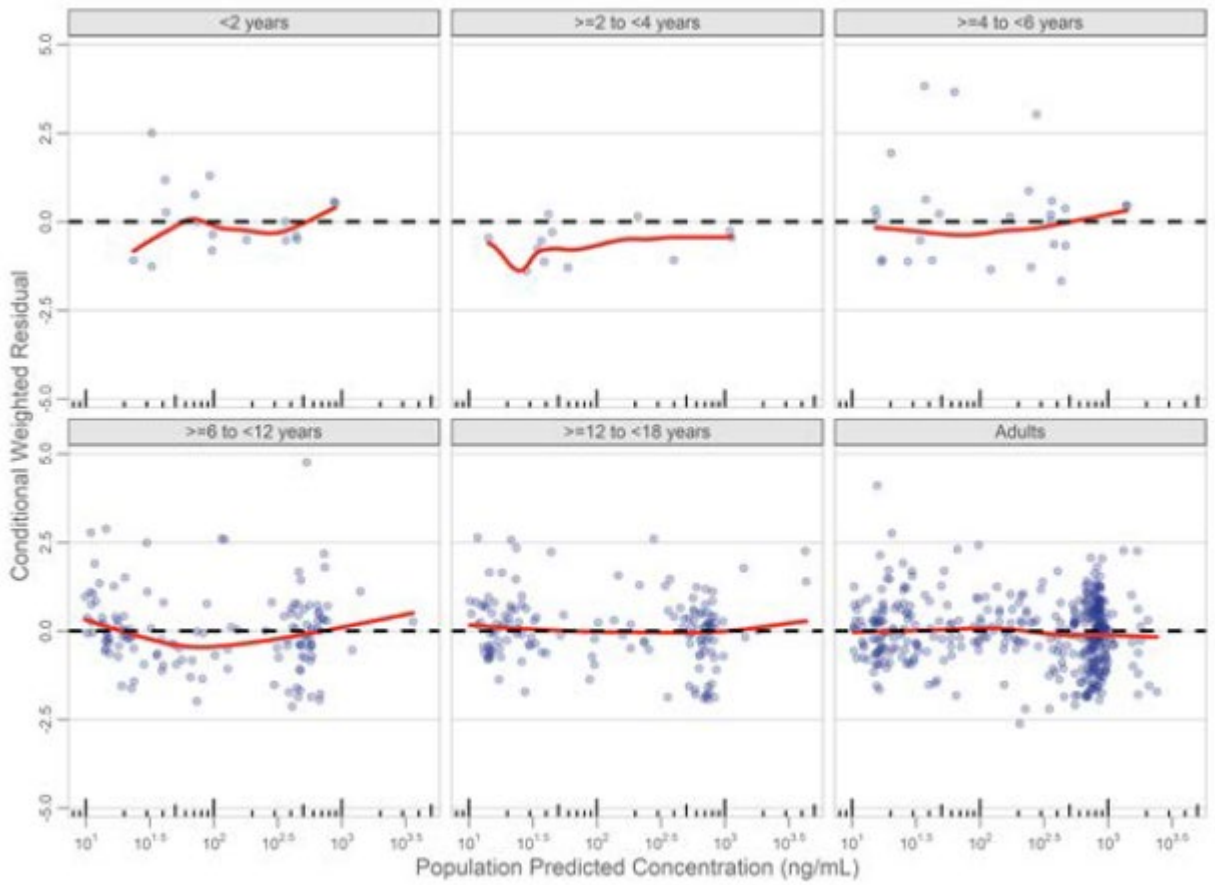
[a] Percentage of overall total number of samples, ie, 1208 samples.
Abbreviations: BLQ = below level of quantitation; PK = pharmacokinetic
Source: Appendix Section 6.1

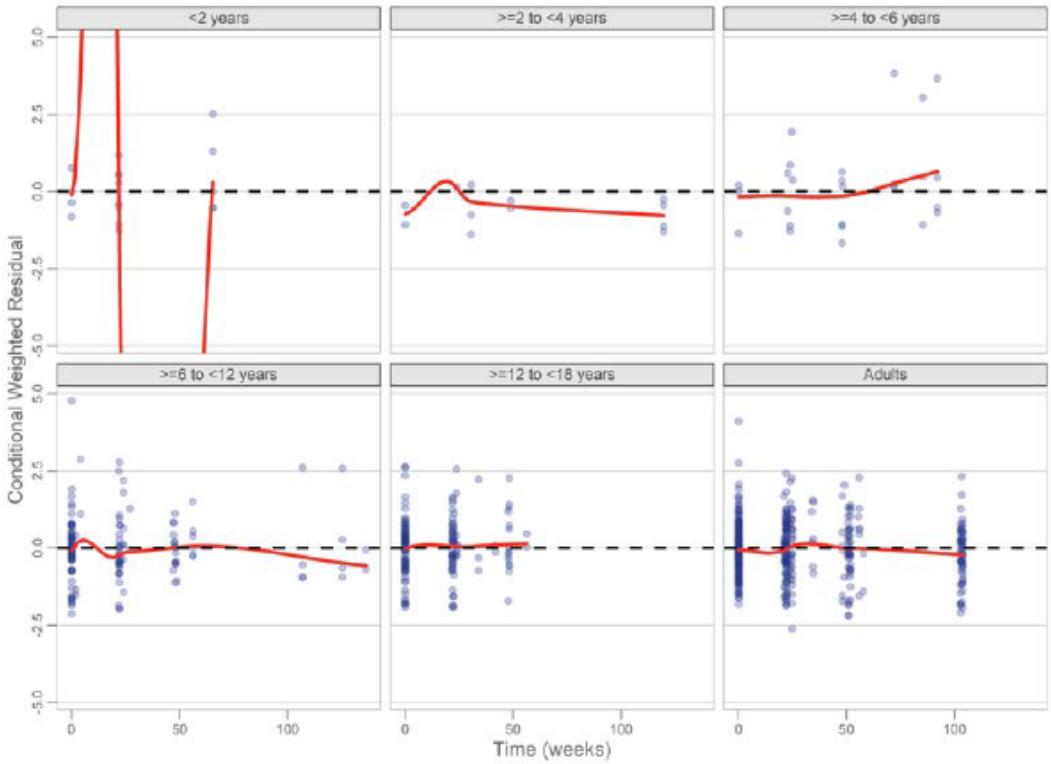




Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviation: LOESS = locally weighted scatter-plot smoothing
Source: Appendix Section 6.2

Figure 6 - Goodness-of-Fit – Population and Individual Predicted Concentrations by Age Group – Current Best Model


<2 years
>=2 to <4 years
>=4 to <6 years
>=6 to <12 years
>=12 to <18 years
Adults
Conditional Weighted Residual
Population Predicted Concentration (ng/mL)



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviation: LOESS = locally weighted scatter-plot smoothing
Source: Appendix Section 6.3

Figure 7 - Goodness-of-Fit – Conditional Weighted Residuals Versus Time by Age Group – Current Best Model

Assessment of the MAH's response

No bias was graphically detectable across the different age groups. However the data are not considered very informative given the limited number of patients in the different age subgroups (5 vs 2 vs 6 in the 3 age subgroups).

Use of fixed allometric exponents for the effect of weight on clearance and volume component would be more appropriate for children (see MSWG Q&A on paediatric PK). However, given the values of estimated exponents and the values of other parameters in models CBM and M2, and given the fact that the dose is intended to be adjusted based on clinical benefit-risk assessment, this issue is not pursued (also see our answer to question 2).

However, there are discrepancies between the numbers of patients reported in the different age subgroups in the table provided in AtQ6 and numbers of patients reported in the table 4 provided in the SmPC. They should be clarified.**(OC; see also question 20)**

Conclusion

Issue not pursued

Question 7

Nonlinear clearance should also be tested in the POPPK model using individual predicted concentrations as exposure marker.

Summary of the MAH's response

As requested by the Agency, nonlinear elimination was tested in the Pop-PK model (Appendix Section 7.1). A model including parallel linear and nonlinear clearance mechanism was used for assessing potential target-mediated drug disposition (TMDD). The Michaelis–Menten approximation of the TMDD model assumes quasi steady-state and rapid binding/dissociation between the target and sebelipase alfa (Gabrielsson, 2016; Gibiansky, 2008). These models have traditionally been used to describe nonlinear elimination of large molecules at low concentrations (eg, monoclonal antibodies). The above model was used to assess the concentration-time profiles of sebelipase alfa. The model did not successfully converge and was most likely over-parameterized considering the small number of samples collected during the elimination phase. As part of an exploratory analysis, a model including only a nonlinear (Michaelis-Menten) clearance was used to assess the concentration-time profiles of sebelipase alfa. These models, including only a nonlinear clearance, have traditionally been used to assess nonlinearity at high concentrations for small molecules (eg, ethanol, phenytoin) (Gabrielsson, 2016). While this model successfully converged, and achieved a minimum objective function value of ~50 units better compared with the linear model (see table below), there were problems with the minimization indicating instability in the model and, thus, the parameter estimates should be interpreted cautiously. Typically, initial estimates, over parameterization, the number of PK samples collected, and the distribution of sample times over the PK profile are sources that may cause a model to become unstable. While the model including only a nonlinear clearance was associated with a lower objective function value, it is important to underscore that the concentrations of sebelipase alfa declined in a linear manner on a semi-log scale, suggesting that the elimination of sebelipase alfa was linear (ie, first order) and not concentration dependent.

Table 68 - Comparison of Linear and Nonlinear Elimination Clearance for the Current Best Model

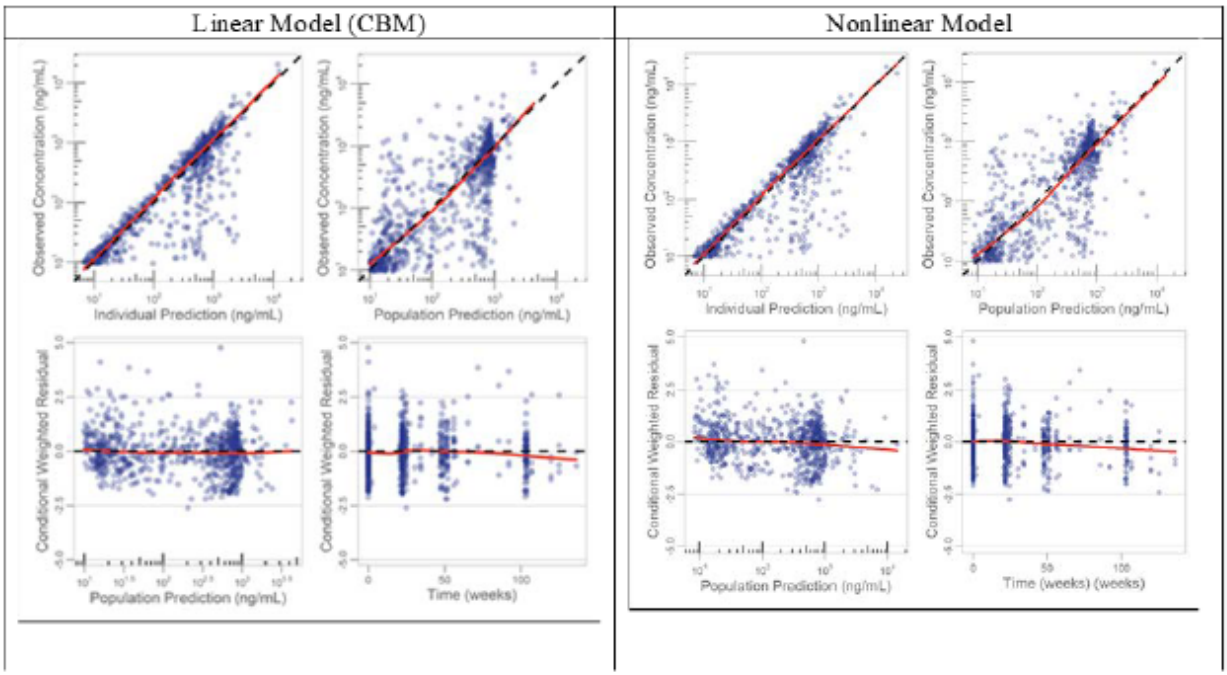
Parameter (Unit)	Linear Model (OFV: 8323.69)			Nonlinear Model (OFV: 8270.99)		
	Estimate	RSE %	95% CI	Estimate	RSE %	95% CI
CL (L/h)	36.1	8.43	30.1 – 42.1	NA	NA	NA
V_{max} (µg/h)	NA	NA	NA	80.3	10.1	64.4 – 96.3
K_m (µg/mL)	NA	NA	NA	1.39	15.7	0.962 – 1.81
Q (L/h)	1.50	13.1	1.11 – 1.89	2.23	10.6	1.77 – 2.70
Vc (L)	4.21	12.4	3.19 – 5.24	5.03	10.9	3.96 – 6.11
Vp (L)	4.07	29.7	1.70 – 6.43	4.39	14.3	3.16 – 5.62
Weight on CL	0.480	17.2	0.319 – 0.642	0.545	10.5	0.433 – 0.656
Weight on Vc	0.460	34.6	0.148 – 0.772	0.467	28.6	0.206 – 0.729
IIV on CL	0.391	12.7	0.294 – 0.488	0.199	15.2	0.140 – 0.259

Parameter (Unit)	Linear Model (OFV: 8323.69)			Nonlinear Model (OFV: 8270.99)		
	Estimate	RSE %	95% CI	Estimate	RSE %	95% CI
IIV on Vc	0.737	10.4	0.587 – 0.886	0.674	9.83	0.544 – 0.804
Correlation CL, Vc	0.0842	165	-0.188 – 0.356	0.125	123	-0.176 – 0.425
ETA scaling factor (Q:CL)	1.41	18.0	0.913 – 1.91	1.69	36.1	0.493 – 2.88
IOV on Vc	0.241	6.68	0.210 – 0.273	0.211	6.64	0.183 – 0.238
Proportional Error	52.8	2.93	49.8 – 55.8	51.8	3.02	48.7 – 54.9
Additive Error	0.0447	Fixed	Fixed	0.0447	Fixed	Fixed

Abbreviations: CI = confidence interval; CL = clearance; ETA = random effect; IIV = inter-individual variability; IOV = inter-occasion variability; K_m = Michaelis-Menten constant; MOFV = minimum objective function value; NA = not applicable; PK = pharmacokinetic; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; V_{max} = maximum velocity; Vp = volume of distribution in the peripheral compartment

Source: Appendix Section 7.1

Additionally, comparison of GOF plots (see figure below) for the linear and nonlinear Pop-PK models demonstrate the results are almost identical, further supporting that the linear model is the right choice.



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.

Abbreviation: LOESS = locally weighted scatterplot smoothing

Source: Appendix Sections 7.2 and 9.1

Figure 8 - Comparison of Goodness-of-Fit Between Linear and Nonlinear Pop-PK Models

Overall, based on the Pop-PK models tested, a GOF comparison between linear and nonlinear models, and the observed terminal elimination phase of sebelipase alfa, first-order elimination (linear) adequately characterized the clearance in the range of concentrations considered in the PAM Pop-PK analysis.

Assessment of the MAH's response

It is understood that a the data available did not support adequate characterization of the nonlinearity of the clearance that could be a more appropriate model for sebelipase (as also shown by lower OFV).

Conclusion

Issue not pursued.

Question 8

It is noted that Vp parameters was poorly estimated using the updated POPPK model with RSE of 66%, this should be discuss in particular in light of data exclusion.

Summary of the MAH's response

Sparse samples were collected over a limited timeframe because of the nature of the population (ie, an ultra-rare disease in pediatric patients) and the short elimination half-life of sebelipase alfa. The data included a significant number of samples with concentrations below the limit of quantitation (BLQ); thus, a limited number of samples were available to robustly characterize the terminal elimination phase.

Based on the above limitations associated with the nature of the population and the short half-life of sebelipase alfa, the estimated Vp was associated with a higher level of uncertainty.

Based on the analysis including patients who received placebo (no treatment) and then switched to active treatment (see response to Question 2b), the Vp of sebelipase alfa was more robustly estimated, with a percent relative standard error (RSE%) of 29.7% (Appendix Section 4.2; Table 3). Pharmacokinetic parameters with RSE% values < 30% are typically recognized as being robustly estimated (Bonate, 2006).

Assessment of the MAH's response

It is understood that a the data available did not support adequate characterization of Vp. It is agreed that this has limited value on dosing recommendation for children.

Conclusion

Issue closed.

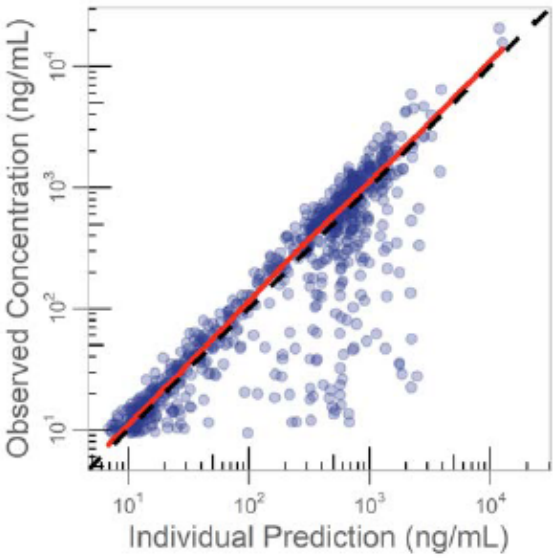
Question 9

Model misspecifications are observed on the IPRED vs OBS and the pcVPC graphic: this should be further discussed. Moreover, model fitting performances (GOF nad pcVPC) should also be provided by age subgroups.

Summary of the MAH's response

Individual predicted versus observed concentrations are presented in the figure below. Please note that the GOF plot presented was from an analysis where the dataset included patients who had received placebo and then switched to active treatment (see response to Question 2b).

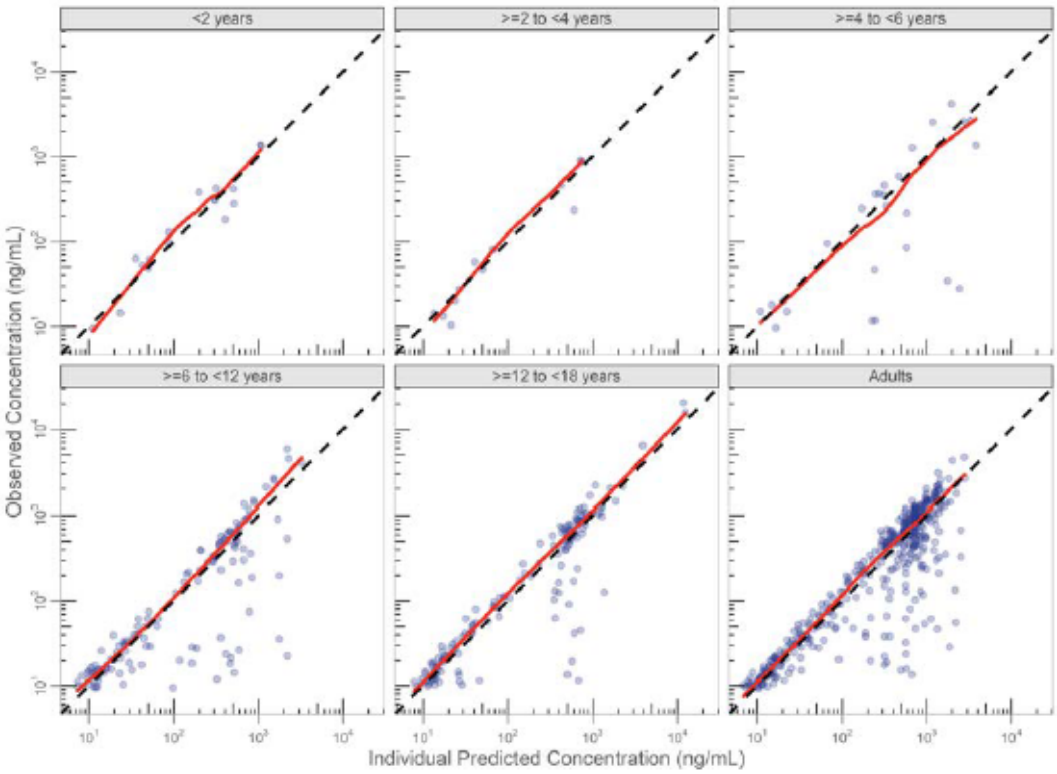
Alexion agrees some individual concentrations were underpredicted with the PAM Pop-PK model. However, the locally weighted scatter-plot smoothing (LOESS) line (red line) was superimposed on the unity line (dashed black line) and suggests that overall the model was associated with a good prediction of the observed data.



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviation: LOESS = locally weighted scatter-plot smoothing
Source: Appendix Section 8.1

Figure 9 - Goodness-of-Fit – Individual Predicted Concentrations – Current Best Model

The GOF plot of individual predictions versus observed concentrations as well as other GOF plots can be found in the response to Question 6. The figure below reproduces the individual prediction versus observed concentration plot by age, from the response to Question 6. As seen in the figure below the LOESS still aligns well with the line of unity, for each age group panel, indicating a good prediction match with the observed data even when the GOF plots are stratified by age.

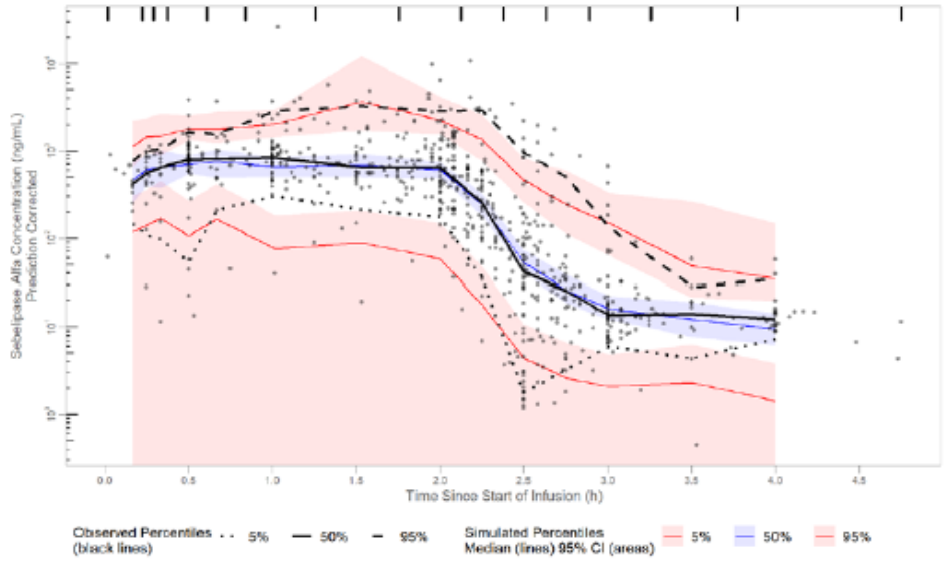


Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviation: LOESS = locally weighted scatter-plot smoothing
Source: Appendix Section 8.2

Figure 10 - Goodness-of-Fit – Individual Predicted Concentrations by Age Group – Current Best Model

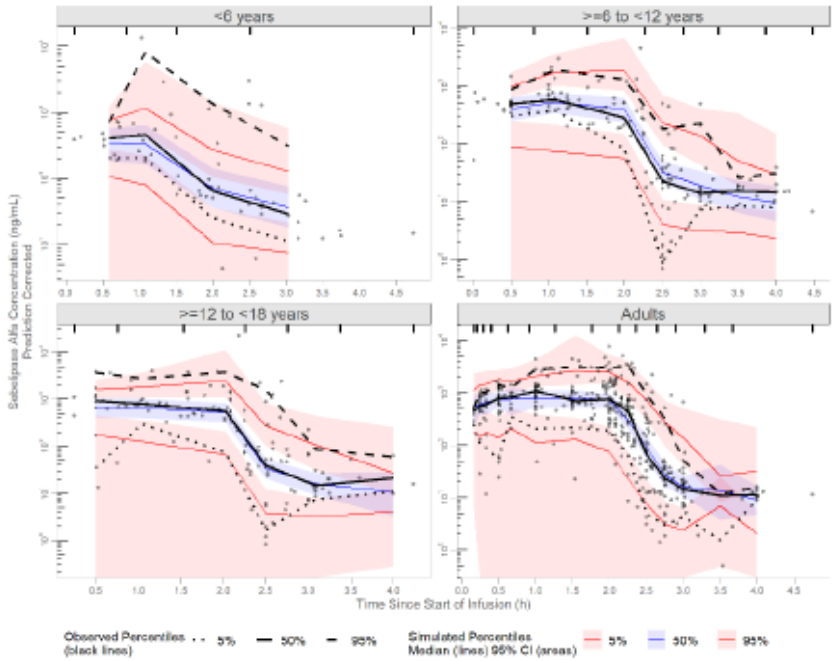
The prediction-corrected visual predictive check (pcVPC) plots are presented for all ages combined in the first figure below and stratified by age group in the second figure below. In the first figure below, the simulated 5th and 95th percentiles are wide (light shading); however, the observed median (black solid line) fell within the simulated 50th percentile (blue shading) indicating the model captured the central tendency for sebelipase alfa concentrations. In the second figure below, the observed versus predicted profiles were similar to that seen in the first figure below indicating that even when stratified by age group, the model captured the central tendency of the sebelipase alfa concentrations.

Overall, the CBM resulted in adequate GOF and pcVPC assessments indicating the PAM Pop-PK model characterizes the observed sebelipase alfa concentrations well.



Note: The pcVPC retains the visual interpretation of the traditional VPC while removing the variability that arises from binning across independent variables by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CI = confidence interval; h = hours; pcVPC = prediction-corrected visual predictive check; VPC = visual predictive check
Source: Appendix Section 8.3

Figure 11 - Prediction-Corrected Visual Predictive Check – Current Best Model



Note: The pcVPC retains the visual interpretation of the traditional VPC while removing the variability that arises from binning across independent variables by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CI = confidence interval; h = hours; pcVPC = prediction-corrected visual predictive check; VPC = visual predictive check
Source: Appendix Section 8.4

Figure 12 - Prediction-Corrected Visual Predictive Check by Age Group – Current Best Model

Assessment of the MAH's response

The pc VPC results show the average concentration values are overall well predicted by the model but not the variability. In particular, the lower limit of the prediction interval is very poorly estimated by the model and therefore unreliable (with very wide CI including zero across the all concentration range). This could be explained by the lack of informative data to adequate estimation of the variability in the data. This is also reflected by the very high value of the proportional component of the residual error.

Conclusion
Issue not pursued.

Question 10

For adequate graphical evaluation, some missing plots should be provided. NPDEs distribution should also be provided as well as NPDE vs PRED and vs time plots. In addition, the applicant could present ETA plots versus bodyweight and age for:

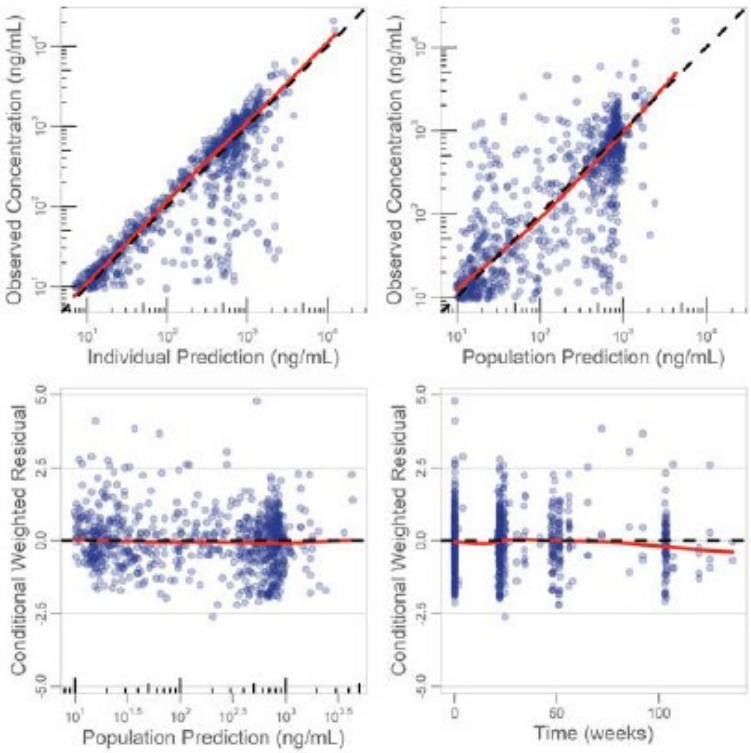
- model without bodyweight or age as covariates,
- model with bodyweight as covariate,
- model with age as covariate.

Summary of the MAH's response

This response addresses 3 requests. First, provide GOF plots for the CBM (Part a). Second, provide normalized prediction distribution error (NPDE) plots for the CBM (Part b). Lastly, using the CBM, test the inclusion/exclusion of body weight and age covariates and show the ETA plots to support the choice of covariate used in the CBM (Part c).

Part a:

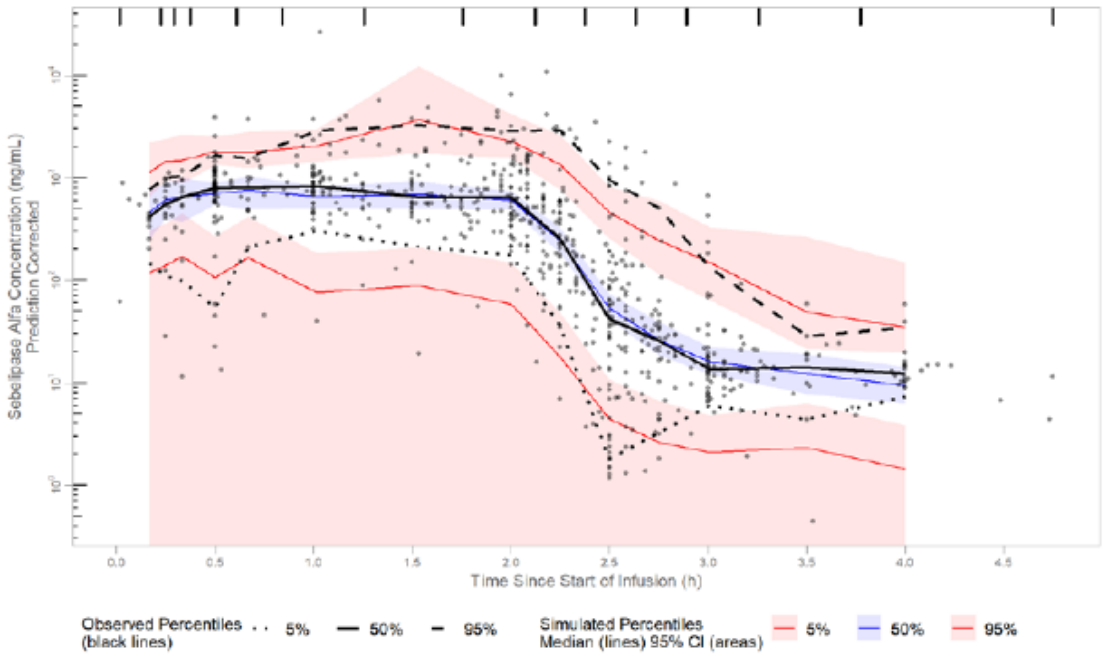
The Figure below shows the GOF plots for the CBM. Some points do deviate from the line of unity (dashed line), but overall, the LOESS fit (red solid line) to the data suggests little to no bias for the overall characterization of the sebelipase alfa predicted concentrations. These GOF plots are also shown broken out by age group in the response to Question 6.



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviation: LOESS = locally weighted scatter-plot smoothing
Source: Appendix Section 9.1

Figure 13 - Goodness-of-Fit Plots for the Current Best Model

The two figures below show the pcVPC, for the CBM, among all age groups and stratified by age group, respectively. In the first figure below, the simulated 5th and 95th percentiles are wide (light shading); however, the observed median (black solid line) fell within the simulated 50th percentile (blue shading) indicating the model captured the central tendency for sebelipase alfa concentrations.



Note: The pcVPC retains the visual interpretation of the traditional VPC while removing the variability that arises from binning across independent variables by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CI = confidence interval; h = hours; pcVPC = prediction-corrected visual predictive check; VPC = visual predictive check
Source: Appendix Section 9.2

Figure 14 - Prediction-corrected Visual Predictive Check – Sebelipase Alfa Concentration Versus Time – Current Best Model

In the figure below, the observed versus predicted profiles were similar to that seen in the previous figure indicating that even when stratified by age group, the model captured the central tendency of the sebelipase alfa concentrations.

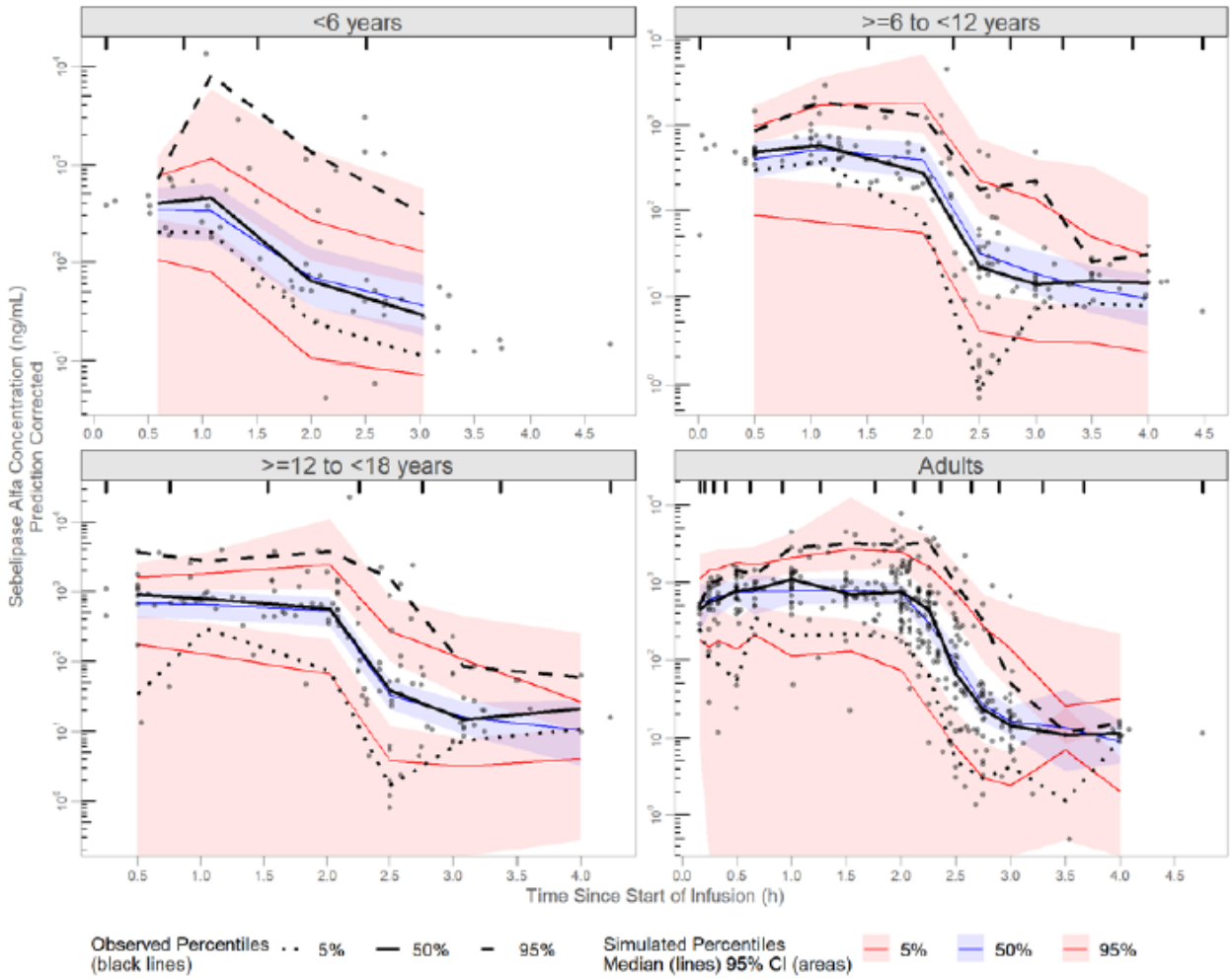
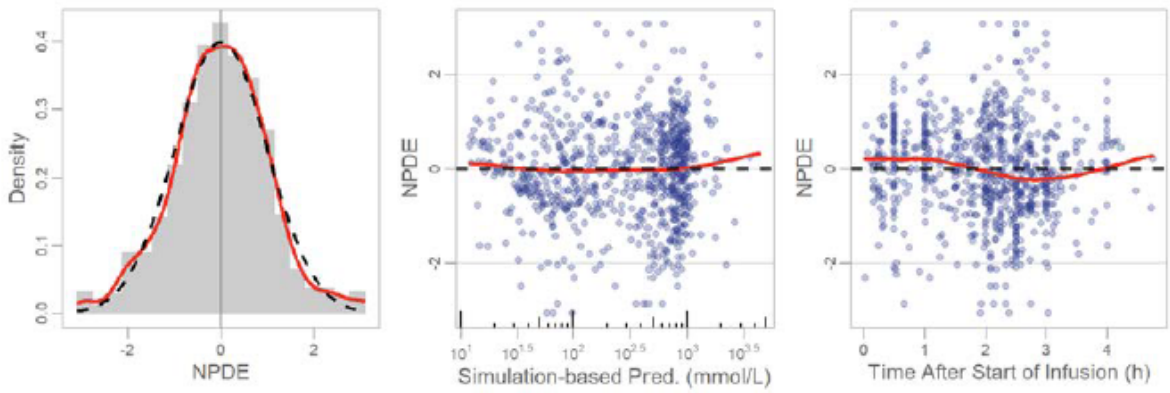


Figure 15 - Prediction-corrected Visual Predictive Check – Sebelipase Alfa Concentration Versus Time-by Age Group – Current Best Model

Part b:

Normalized prediction distribution error plots combing data among all age groups is presented in the figure below. Please note that the NPDE were derived based on the CBM analysis, which includes patients who received placebo and then switched to active treatment (see response to Question 2b).

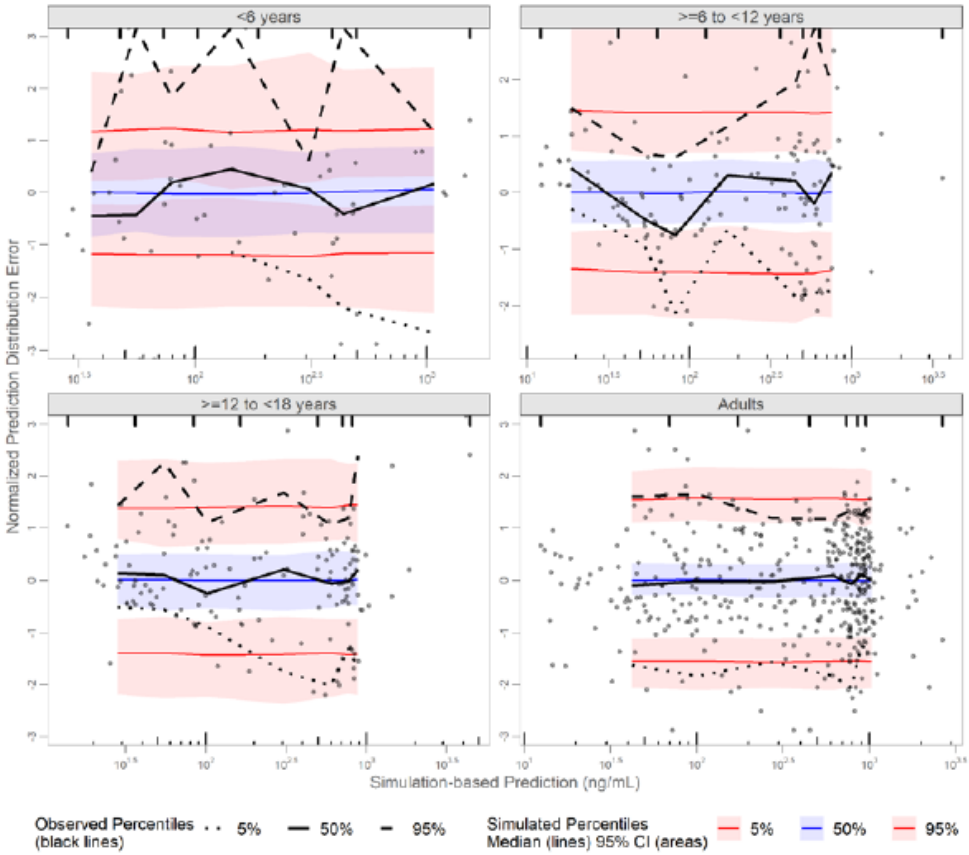
Overall, the model resulted in a homogeneous distribution of NPDE versus population predicted concentration and time.



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: NPDE = normalized prediction distribution error; Pred = predicted concentration
Source: Appendix Section 9.4

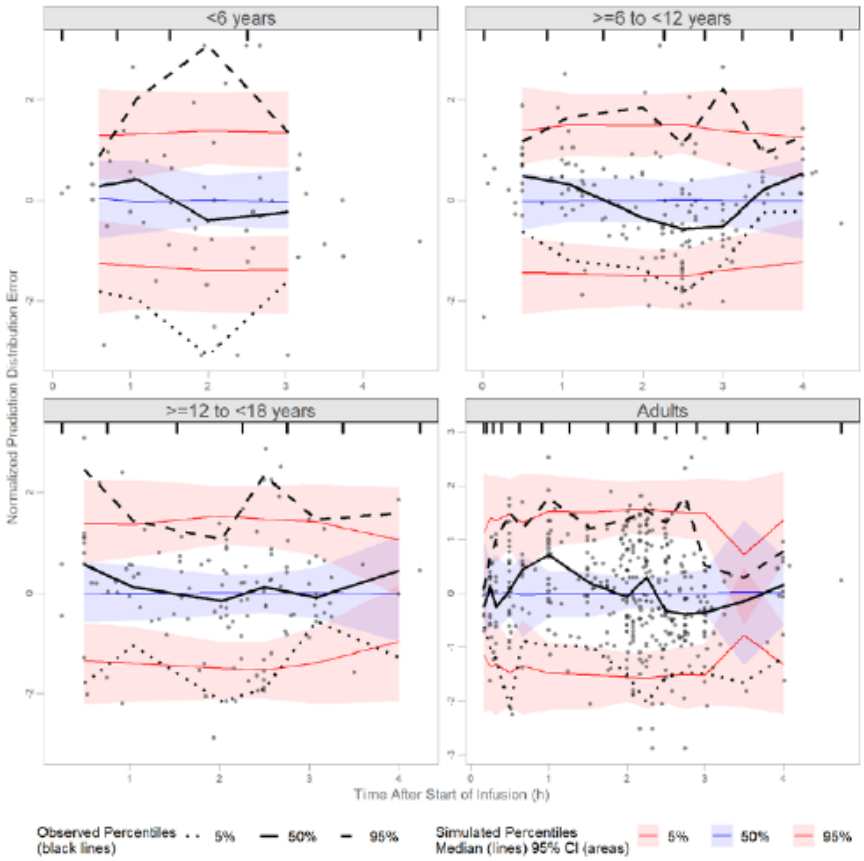
Figure 16 - NPDE Distribution Versus Population Predicted Concentration and Time – Current Best Model

Normalized prediction distribution error versus population predicted concentration stratified by age groups are presented in the first figure below. The observed 50th percentile was contained within the simulated 50th percentile indicating the model captured the central tendency for sebelipase alfa concentration. In the second figure below, the observed versus predicted profiles were similar to that seen in the first figure below indicating that even when stratified by age group, the model captured the central tendency of the sebelipase alfa concentrations.



Note: Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CI = confidence interval; NPDE = normalized prediction distribution error
Source: Appendix Section 9.5

Figure 17 - NPDE Distribution Versus Population Predicted Concentration by Age Group With Ages Less Than 6 Years Combined – Current Best Model



Note: Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CI = confidence interval; NPDE = normalized prediction distribution error
Source: Appendix Section 9.6

Figure 18 - NPDE Distribution Versus Time by Age Group With Ages Less Than 6 Years Combined – Current Best Model

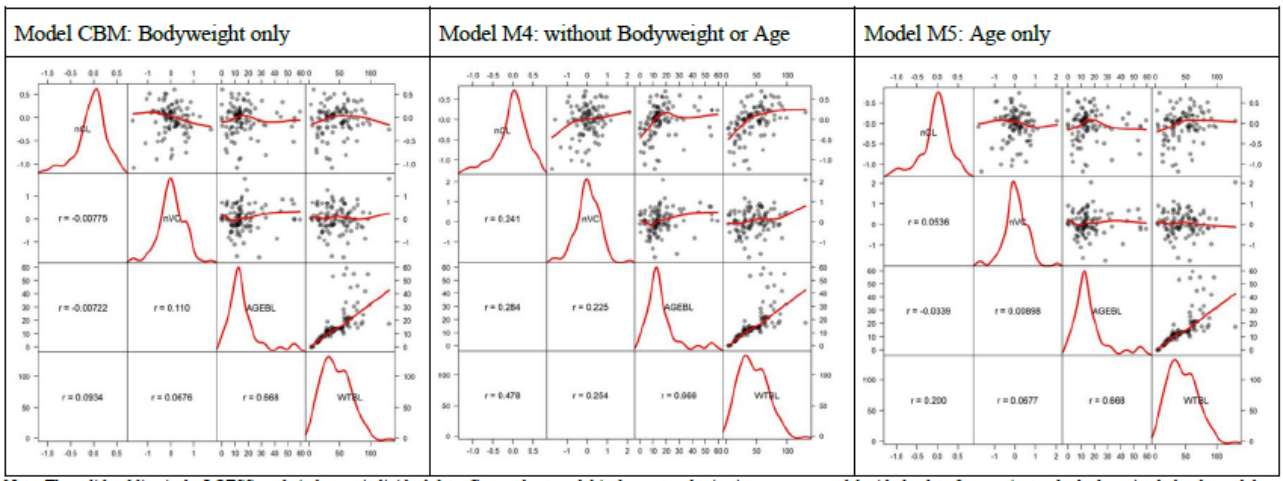
Part c:

The table below shows the Pop-PK modeling results for each of the covariate combinations assessed to determine if age is needed in the model as well as body weight. Question 2b also assessed if age (in the form of a maturation function) should be included in the CBM. Based on the ΔMOF, the CBM was the best model. The figure below provides additional support, in the form of a plot that correlates the ETA values for CL and Vc versus body weight and age.

Table 69 - Requested Model Evaluations – Current Best Model

Model	Reference	Description	MOF	df	ΔMOF
CBM	NA	Model with body weight as covariate	8323.685	11	NA
M4	CBM	Model without bodyweight or age as covariates	8376.291[a]	9	52.606
M5	CBM	Model with age as covariate (but not body weight)	8343.171	11	19.486

Note: Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: Δ = delta, ie, change; CBM = current best model; df = degrees of freedom; MOFV = minimum objective function value; NA = not applicable
Source: Appendix Section 9.7



Note: The solid red line is the LOESS; and circles are individual data. Current best model is the post authorization measure model with the data from patients who had received placebo and then switched to active treatment included.
Abbreviations: CBM = current best model; LOESS = locally weighted scatter-plot smoothing
Source: Appendix Section 9.8

Figure 19 - ETA Plots Comparing Models With Different Combinations of Age and Bodyweight as Covariate – Current Best Model

Assessment of the MAH's response

All the requested information was provided.

Conclusion

Issue closed.

PK/PD modelling

Question 11

The choice of the 2 PD markers for the modelling exercise need to be better substantiated, as well as acceptance criteria and target levels to be reached for the selected dosing regimens.

Summary of the MAH's response

Lysosomal acid lipase deficiency is a lipid metabolism disorder with a strong impact on liver function and LDL-C level. The liver injury parameter ALT was chosen as the more specific liver injury PD parameter because elevations of aspartate aminotransferase (AST) can also be a consequence of other physiological factors (eg, strenuous exercise) and are less specific. Both ALT and LDL-C improved following sebelipase alfa ERT in the patient populations investigated. Other parameters, eg, liver fat content and high-density lipoprotein cholesterol (HDL-C), took longer to respond; however, these responses supported the initial effect observed in ALT and LDL-C.

It is important to highlight that acceptance criteria and target levels of these endpoints were not prespecified for selecting the dosing regimens. There is a knowledge gap in the relationship between the 2 biomarkers and clinical efficacy. In addition, there are large between subject variabilities for the key model parameter estimates (E0, Imax, and Kout) in the developed PK/PD models (see both tables in the response to Question 14). These 2 issues render our ability in setting the acceptance criteria and target levels for ALT and LDL-C in a clinical meaningful manner. Across the sebelipase alfa clinical studies, dose modifications were based on clinical response (a balance between benefit and risk) and not systemic drug concentrations or drug exposure (ie, PK) parameter. Per protocol, dose increases were permitted for patients who exhibited a suboptimal clinical response, as determined based on protocol-specified criteria reflecting the key disease manifestations. Dose reductions were also permitted in the event of poor tolerability.

Sebelipase alfa is a recombinant human lysosomal acid lipase and is approved for the treatment of LAL-D. Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes, the drug's site of action. The initial lipid metabolism is a local phenomenon within the lysosomes of cells, and local drug exposure at cellular level rather than systemic exposure drives the efficacy response to therapy. This ERT, as with other ERTs for lysosomal storage disorders indicated in particular in Gaucher disease, Hunter syndrome and Fabry disease, exhibits a non-systemic site of drug action so systemic drug exposures do not inform dosing or dosing recommendations. This is further supported by dosing of once every 2 weeks for a compound with mean predicted terminal elimination half-life of approximately 3 hours.

Assessment of the MAH's response

It is understood that the 2 biomarkers were chosen based on their sensitivity to the disease status and to the drug effects.

It is also understood that there has been no attempt to quantitatively characterize the link between the 2 biomarkers and the actual meaningful clinical response. The clinical relevance of these biomarkers is therefore not quantitatively characterize. This drastically decrease the value of the PK/PD exercise, which does not have any interest to inform the dose in this context.

Conclusion

Issue closed.

Question 12

The exclusion of placebo arm data from the PK/PD analysis is not acceptable given that these data could be informative for adequate description of the time course of the 2 biomarkers. The MAH is asked to address this issue.

Summary of the MAH's response

Alexion believes that in the setting of treating LAL-D, in patients with aberrantly high PD levels due to enzyme deficiency (ie, ALT and LDL-C), inclusion of PD data for patients not receiving treatment was not expected to be particularly informative. However, in response to review feedback from EMA, the data from the placebo (no-treatment) group were added to the PK/PD models to assess if PD data, when no treatment was given, added meaningful information to the characterization of the PD response or perhaps insight into disease progression for the short time (22 weeks) during which the PD data were collected.

To include the PD data when no treatment was given, the PK/PD models for ALT and LDL-C were further developed to add a no-treatment effect submodel. Because this submodel leveraged PD data collected over time, when treatment was not given, the submodel could also be thought of as a disease progression submodel to the PK/PD models.

Overall, inclusion of PD data, when no treatment was given, and addition of a no-treatment submodel provided a slightly better ALT model (some parameters had lower RSE% and less variability), and a slightly worse LDL-C model, but did not further inform dosing, safety, or efficacy (see examples in response to Question 14).

Assessment of the MAH's response

The requested action was taken by the applicant.

Conclusion

Issue closed.

Question 13

The selection of the structural model in particular absence of testing alternative structural model with drug clearance from the central compartment and outside the effect compartment need to be justified for both ALT and LDL-cholesterol.

Summary of the MAH's response

As noted in the response to Question 11, ERTs often have nonsystemic sites of drug action resulting in systemic drug exposures, which do not inform selection of dose or dose regimen. For sebelipase alfa, the Pop-PK model supported that exposure-response was not directly linked to sebelipase alfa concentration, ie, drug with short half-life (~3 hours) supporting once every week (qw) (or once every

other week [qow]) dosing. Rather than test new features in the Pop-PK model, focus was on modelling the PD data.

For the PK/PD model, an effect compartment overcomes the dose-concentration-response disconnect. Biologically, using a turnover model, sebelipase alfa concentrations in the effect compartment are expected to inhibit the rate of production of ALT (Kin) and stimulate the rate of degradation of LDL-C (Kout). The observed ALT and LDL-C data suggested a delayed response; therefore, an indirect response model was used. Given the original submission work supporting the initial Marketing Authorization Application for Kanuma was not able to develop a PK/PD model, the PK/PD model currently proposed, while limited due to the amount of available data, is a step forward in quantifying our understanding of the dose-response relationship driving efficacy.

Assessment of the MAH's response

This is endorsed.

Conclusion

Issue closed.

Question 14

Key parameters (e.g. IC50 and EC50) were fixed without justifications of the source and the plausibility of the values used.

Summary of the MAH's response

Fixed parameters, in the models, are not identifiable for reasons related to the disconnect between systemic exposure and response (see response to Question 11), ie, short half-life and dosing once every 1 or 2 weeks. Thus, the model is insensitive to some parameters that need to be fixed to a value for the model analysis to complete successfully. The rationale for the fixed values includes: 1) the first-order rate of elimination from the effect compartment (Ke0) needs to be small enough that there is some accumulation in the effect compartment, and 2) the half maximal concentration (IC50, EC50) needs to be small to ensure that the model reflects the clinical response observed in the subjects, ie, response at or near the top of the maximum effect (Emax) curve. The final parameter estimates for the ALT PK/ PD model and for the LDL-C PK/PD model are presented in the tables below, respectively. Goodness-of-fit plots can be found in the responses to Questions 15, 16, and 17.

The first table shows the parameter estimates for the ALT PK/PD model with a no-treatment submodel. The typical value for the no-treatment effect (no-treatment effect [fraction]), while significantly different from 0, is small (-0.0113). This fractional effect is the equivalent of a typical patient at baseline experiencing a 1% increase in the zero-order rate of synthesis, resulting in a small increase from baseline in ALT. The between-subject variability (BSV) adds some flexibility in the model to account for the fact that some subjects do tend to have either a positive or negative change from baseline while on placebo (ie, no treatment). The covariates suggest younger subjects tend to have lower baseline ALT levels followed by larger increases in ALT as compared to older patients (negative placebo effect means ALT goes up instead of down); however, the youngest patient in the no-treatment group was 4 years of age.

The second table shows the parameter estimates for the LDL-C PK/PD model with a no-treatment submodel. The typical value for the no-treatment effect (no-treatment slope), is not statistically significantly different from 0. The point estimate of 0.0823 is the equivalent of a typical subject experiencing a linear increase in the first-order degradation rate of LDL-C of 8.23% over the course of 1 year (52 weeks), resulting in a small decrease from baseline in LDL-C. The between-subject variability (BSV) adds some flexibility in the model to account for the fact that some subjects do tend to have either a positive or negative change from baseline while on no treatment. The covariates suggest younger subjects tended to have lower baseline LDL-C levels followed by a smaller no-treatment (time) effect, leading to slightly larger decreases in LDL-C over time as compared to older subjects; however, the youngest patient in the no-treatment group was 4 years of age.

Overall, inclusion of PD data, when no treatment was given, did not further inform dosing, safety, or efficacy; however, including the data did result in more comprehensive models perhaps capturing disease progression, over a short duration of treatment (22 weeks).

Table 70 - Final Parameter Estimates: ALT PK/PD Model – Current Best Model

Parameter	Point Estimate	RSE%	95% CI
Typical Values			
E_0 (U/L)	86.4	2.36	82.4 – 90.4
no-treatment effect (fraction)	-0.0113	19.5	-0.0156 – -0.00695
I_{max} (fraction)	0.508	3.52	0.473 – 0.543
IC_{50} (ng/mL)	1.00 Fixed	n/a	n/a
K_{out} (h^{-1})	0.00318	14.0	0.00230 – 0.00405
K_{e0} (h^{-1})	0.00400 Fixed	NA	NA
Covariate Effects			
Age on E_0	-0.0161	18.0	-0.0218 – -0.0104
Age on no-treatment effect	-0.126	16.2	-0.166 – -0.0858
Body weight on K_{out}	-0.325	37.0	-0.560 – -0.0891
Between Subject Variability			
On E_0	0.410	8.75	0.340 – 0.481
On no-treatment effect	0.0862	26.8	0.0410 – 0.131
On I_{max}	0.607	15.7	0.420 – 0.794
On K_{out}	0.851	13.7	0.622 – 1.08
Residual Error			
Proportional Error (%)	0.226	5.79	0.200 – 0.252

Note: Objective function value: 9217.382. ETA Shrinkage: E_0 = 6.5%, no-treatment effect = 26.7%, I_{max} = 14.1%, K_{out} = 28.0%.

Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; E_0 = baseline ALT; IC_{50} = half maximal inhibitory concentration; I_{max} = maximum inhibitory effect; K_{out} = first-order rate of degradation of ALT; K_{e0} = first-order rate of elimination from the effect compartment; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; RSE = relative standard error

Source: Appendix Section 10.1

Table 71 - Final Parameter Estimates: LDL-C PK/PD Model – Current Best Model

Parameter	Estimate	RSE%	95% CI
Typical Values			
E_0 (mmol/L)	4.58	8.21	3.84 – 5.32
no-treatment slope (fractional/52 weeks)	0.0823	165	-0.185 – 0.349
E_{max} (fraction)	0.335	46.6	0.0290 – 0.641
EC_{50} (ng/mL)	1.00 Fixed	NA	NA
K_{out} (h^{-1})	0.00381	35.1	0.00119 – 0.00644
K_{e0} (h^{-1})	0.00400 Fixed	NA	NA
K_{pool} (h^{-1})	0.00208	33.4	0.000715 – 0.00344
Pool initial amount (mmol/L)	7.80	22.7	4.33 – 11.3
Covariate Effects			
Age on E_0	-0.0108	45.9	-0.0205 – -0.00107
Age on no-treatment slope	0.00555	47.9	0.000341 – 0.0108
Between Subject Variability			
On E_0	0.383	10.8	0.302 – 0.464
On no-treatment slope	0.223	16.4	0.151 – 0.294
On E_{max}	0.835	12.3	0.633 – 1.04
On K_{out}	1.04	14.8	0.738 – 1.34
Residual Error			
Proportional Error (%)	0.151	6.53	0.132 – 0.170

Note: Objective function value: 562.0762. ETA Shrinkage: E_0 = 2.7%, no-treatment slope = 32.5%, E_{max} = 20.6%, K_{out} = 17.5%.
Abbreviations: CI = confidence interval; E_0 = baseline LDL-C; EC_{50} = half maximal effect concentration; E_{max} = maximum effect; K_{out} = first-order rate of degradation of LDL-C; K_{e0} = first-order rate of elimination from the effect compartment; K_{pool} = first-order rate of LDL-C pool emptying; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; RSE = relative standard error
Source: Appendix Section 10.2

Assessment of the MAH's response

The fact that no-treatment data were including in the modelling dataset is supported. The applicant explained the rationale for imputation of fixed parameter values. This is considered to still partly arbitrary. However, given the limited use of the PK/PD model to inform the dose selection, this issue is not pursued.

Conclusion

Issue is not pursued.

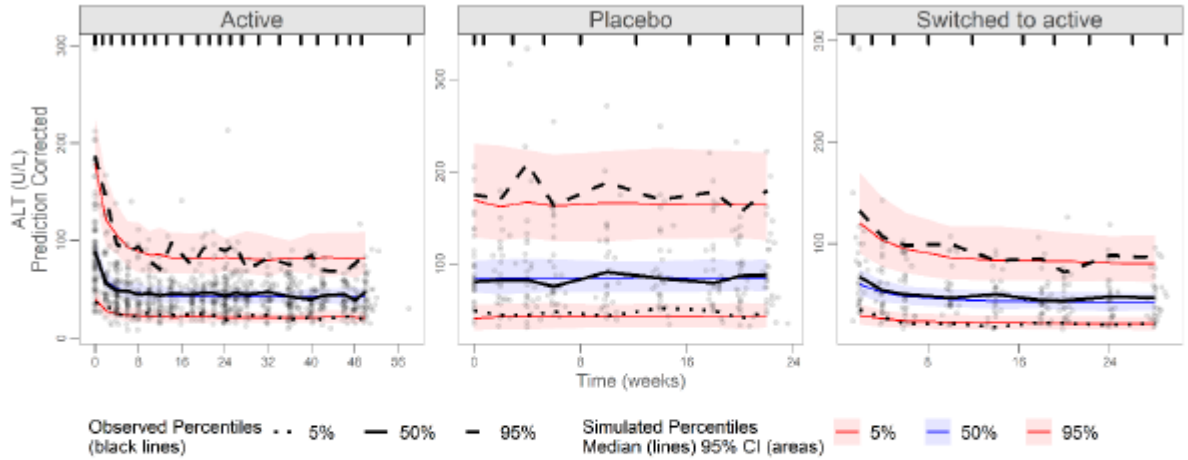
Question 15

Pc VPC should be provided.

Summary of the MAH's response

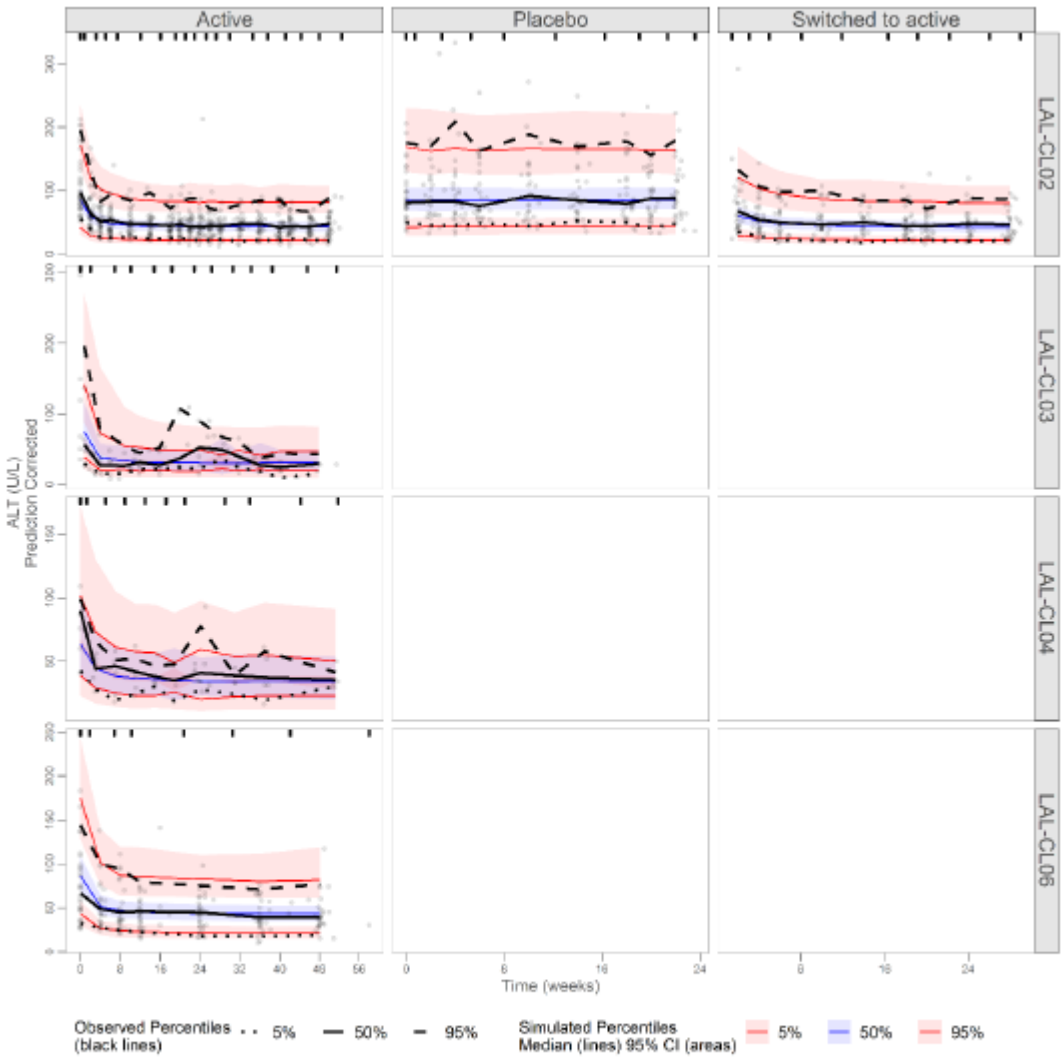
As requested, the first, second and third figures below show pcVPC plots using the ALT PK/ PD CBM and the fourth, fifth and sixth figures show pcVPC plots using the LDL-C PK/PD CBM stratified by treatment status, and either study or age group. For the pcVPC plots, it was necessary to combine ages < 6 years into a single group so binning could be performed to create the plot. Taken together (with responses in Questions 14, 16 and 17), the pcVPCs confirm that the ALT and LDL-C PK/PD CBMs characterize the PD-

time profiles well.



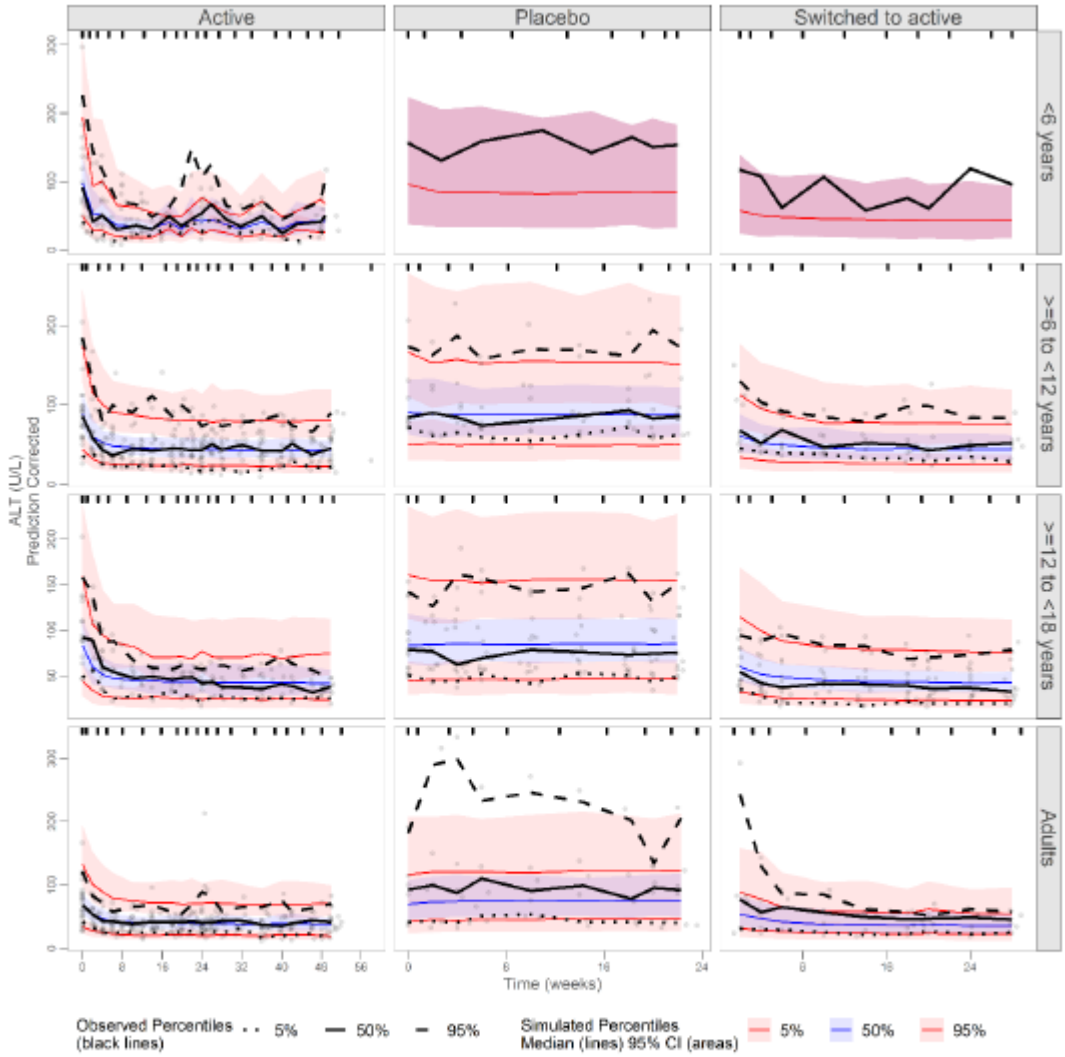
Note: The "Active" panel includes data from patients who received sebelipase alfa except the patients who first received placebo. The "Placebo" and "Switched to active" panels include data from the respective phases of treatment for the patients in Study LAL-CL02 who were randomized to placebo data and then switched to sebelipase alfa during the extension period.
Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 11.1

Figure 20 - Prediction-corrected Visual Predictive Check – ALT Concentration Versus Time – ALT PK/PD Model – Current Best Model



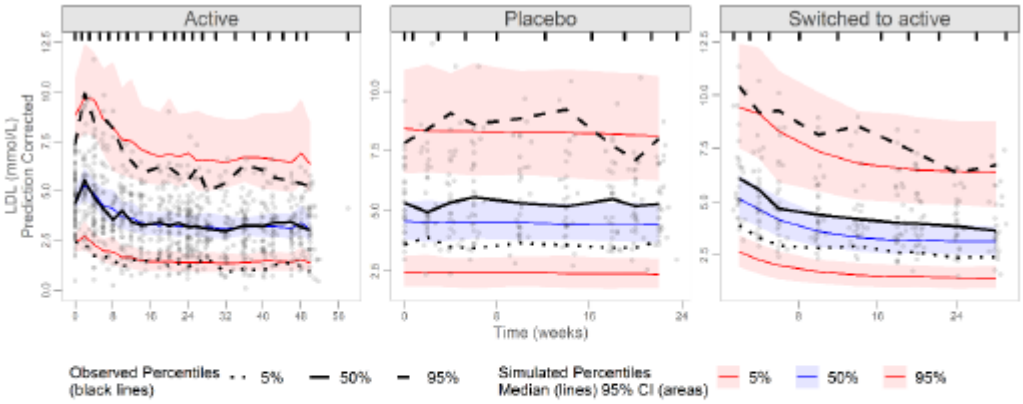
Note: The "Placebo" and "Switched to active" panels include data from the respective phases of treatment for the patients in Study LAL-CL02 who were randomized to placebo data and then switched to sebelipase alfa during the extension period.
Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 11.2

Figure 21 - Best Model Prediction-corrected Visual Predictive Check – ALT Concentration Versus Time by Study – ALT PK/PD Model – Current Best Model



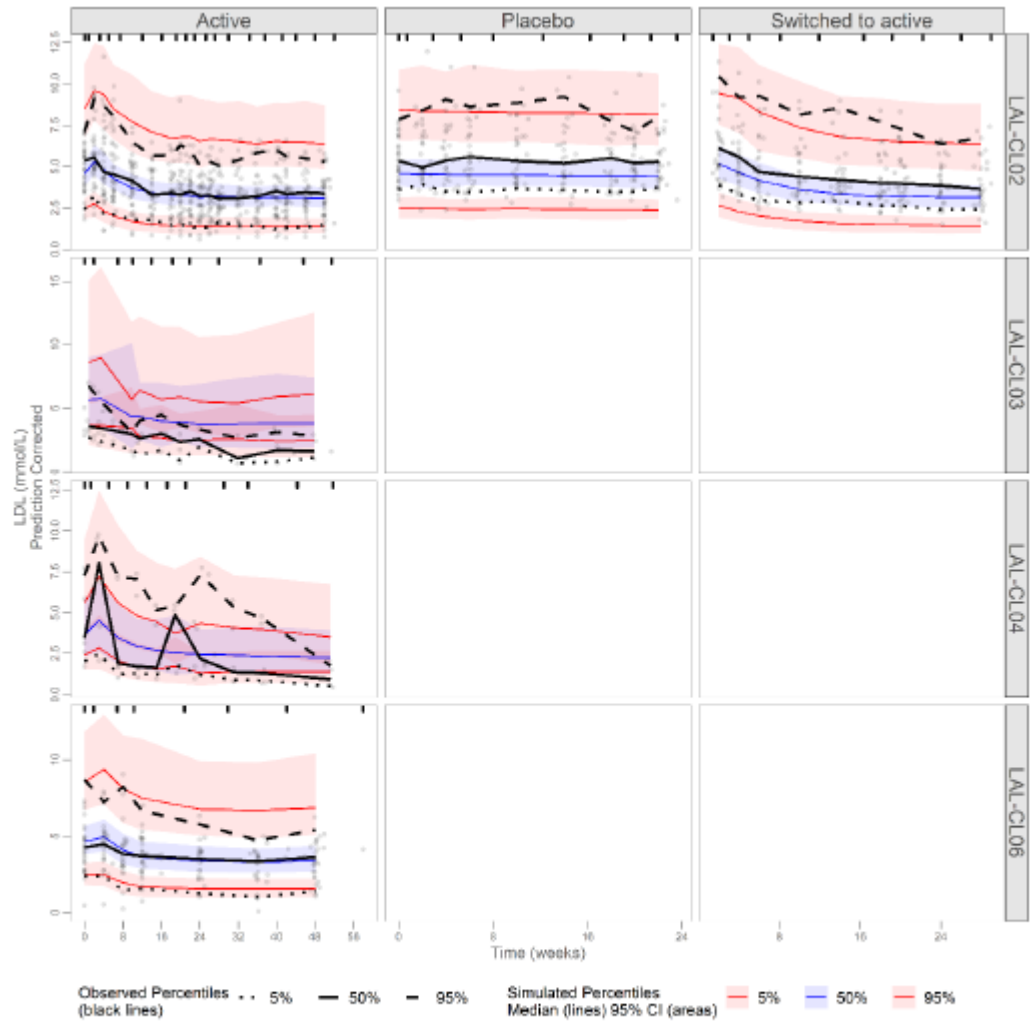
Note: The "Placebo" and "Switched to active" panels include data from the respective phases of treatment for the patients in Study LAL-CL02 who were randomized to placebo data and then switched to sebelipase alfa during the extension period.
Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 11.3

Figure 22 - Prediction-corrected Visual Predictive Check – ALT Concentration Versus Time by Age Group With- Ages Less Than 6 Years Combined – ALT PK/PD Model – Current Best Model



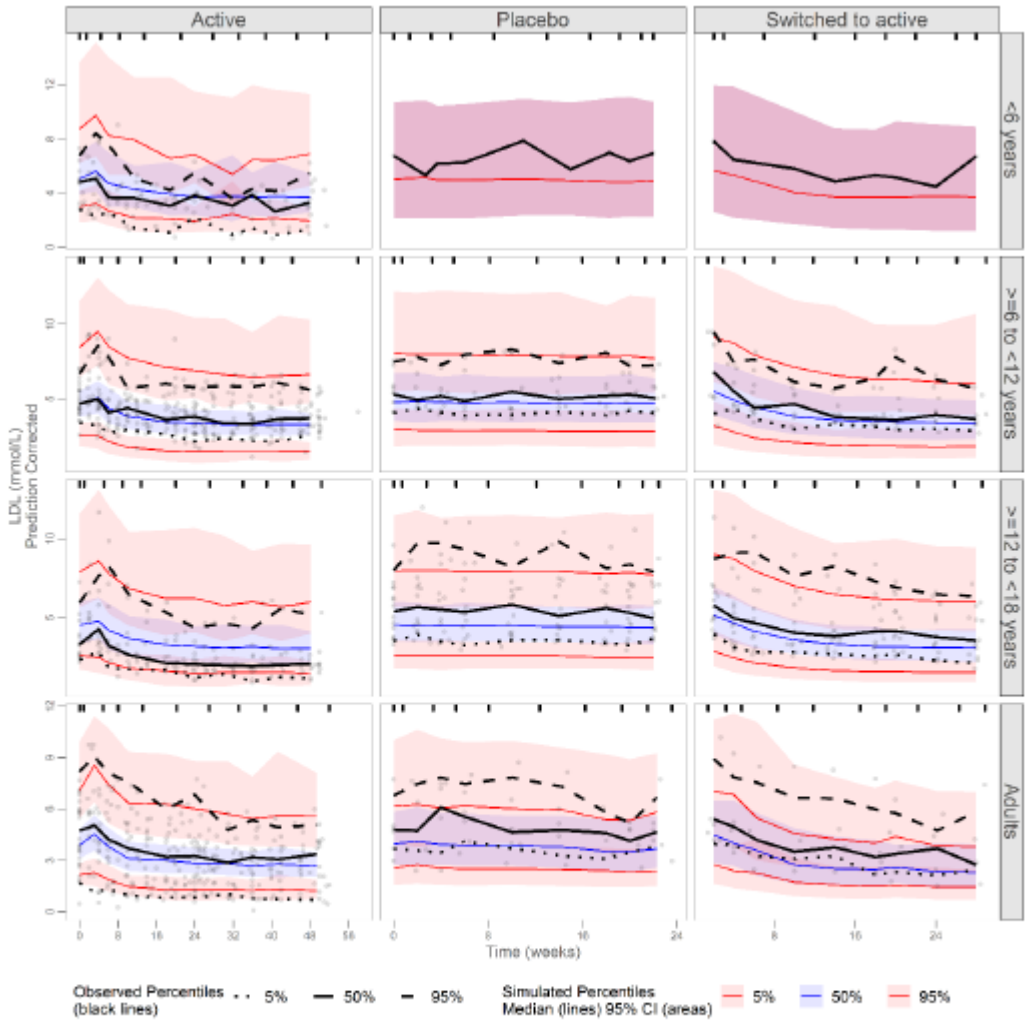
Note: The "Placebo" and "Switched to active" panels include data from the respective phases of treatment for the patients in Study LAL-CL02 who were randomized to placebo data and then switched to sebelipase alfa during the extension period.
Abbreviations: CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 11.4

Figure 23 - Prediction-corrected Visual Predictive Check – LDL-C Concentration Versus Time – LDL-C PK/PD Model – Current Best Model



Note: The "Placebo" and "Switched to active" panels include data from the respective phases of treatment for the patients in Study LAL-CL02 who were randomized to placebo data and then switched to sebelipase alfa during the extension period.
Abbreviations: CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 11.5

Figure 24 - Prediction-corrected Visual Predictive Check – LDL-C Concentration Versus Time by Study – LDL-C PK/PD Model – Current Best Model



Note: The "Placebo" and "Switched to active" panels include data from the respective phases of treatment for the patients in Study LAL-CL02 who were randomized to placebo data and then switched to sebelipase alfa during the extension period.
Abbreviations: CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 11.6

Figure 25 - Prediction-corrected Visual Predictive Check – LDLC Concentration Versus Time by Age Group With- Ages Less Than 6 Years Combined – LDL-C PK/PD Model – Current Best Model

Assessment of the MAH's response

Endorsed.

Conclusion

Issue closed.

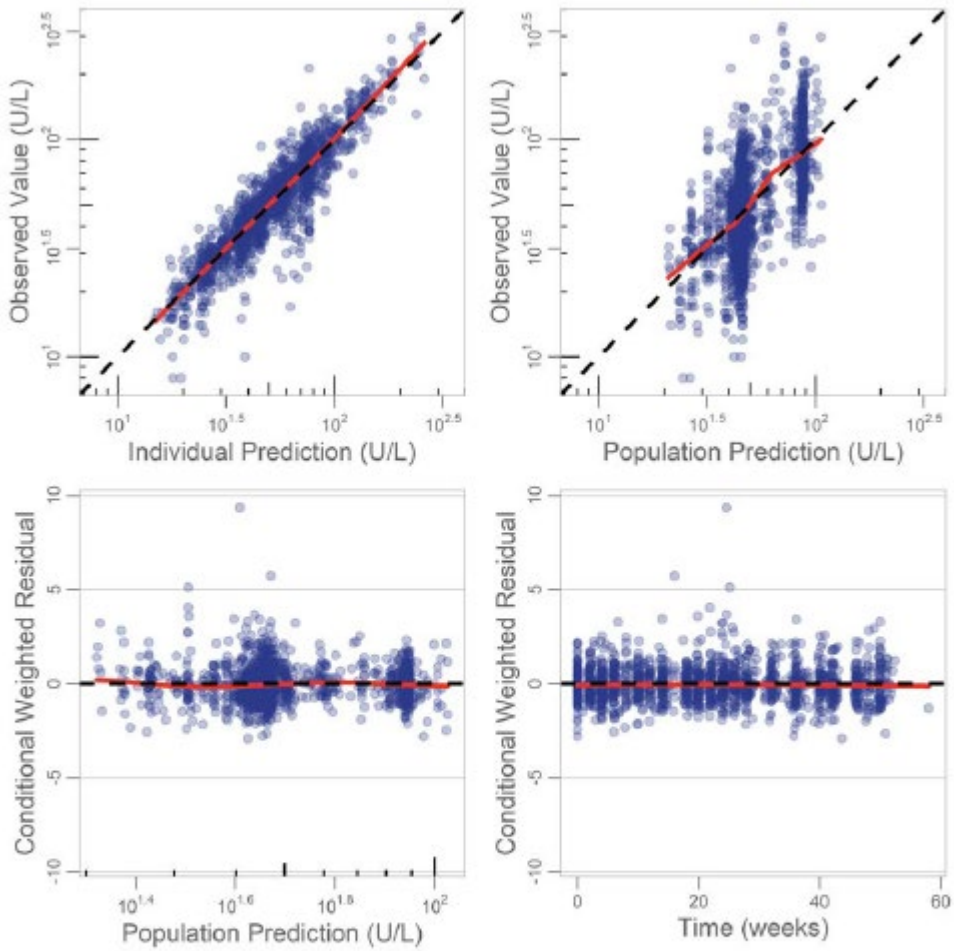
Question 16

Model fitting performances (GOF nad pcVPC) should also be provided by age subgroups.

Summary of the MAH's response

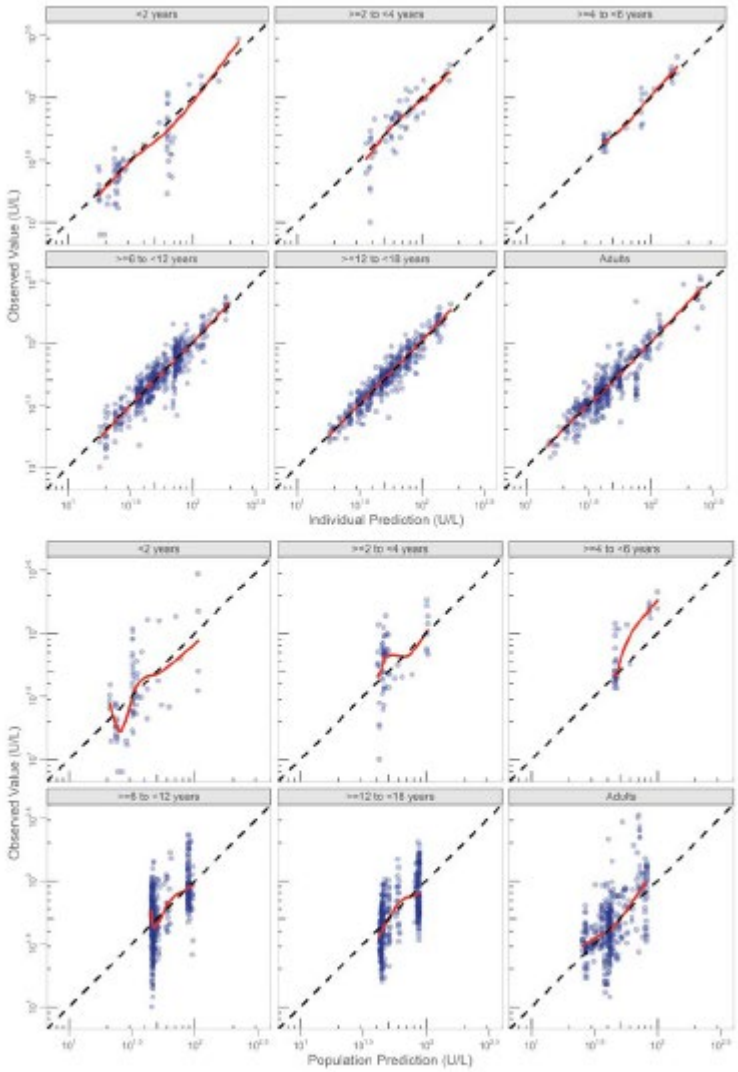
Goodness-of-fit plots are shown in the first, second and third figures or the ALT PK/ PD model and in the fourth, fifth and sixth figures for the LDL-C PK/PD model. The dataset used for the PK/PD modeling included PD measurements for patients who did not receive treatment (the CBM, ie, PAM + no-treatment submodel). The plots are organized into "all data" or "stratified by age group," and show that model predictions and residuals characterize the observed ALT and LDL-C data well even when stratified by age.

Taken together (with results in Questions 14, 15, and 17), the GOF plots characterize the PD data well. The pcVPC plots for the ALT and LDL-C PK/PD CBMs are shown in the response to Question 15.



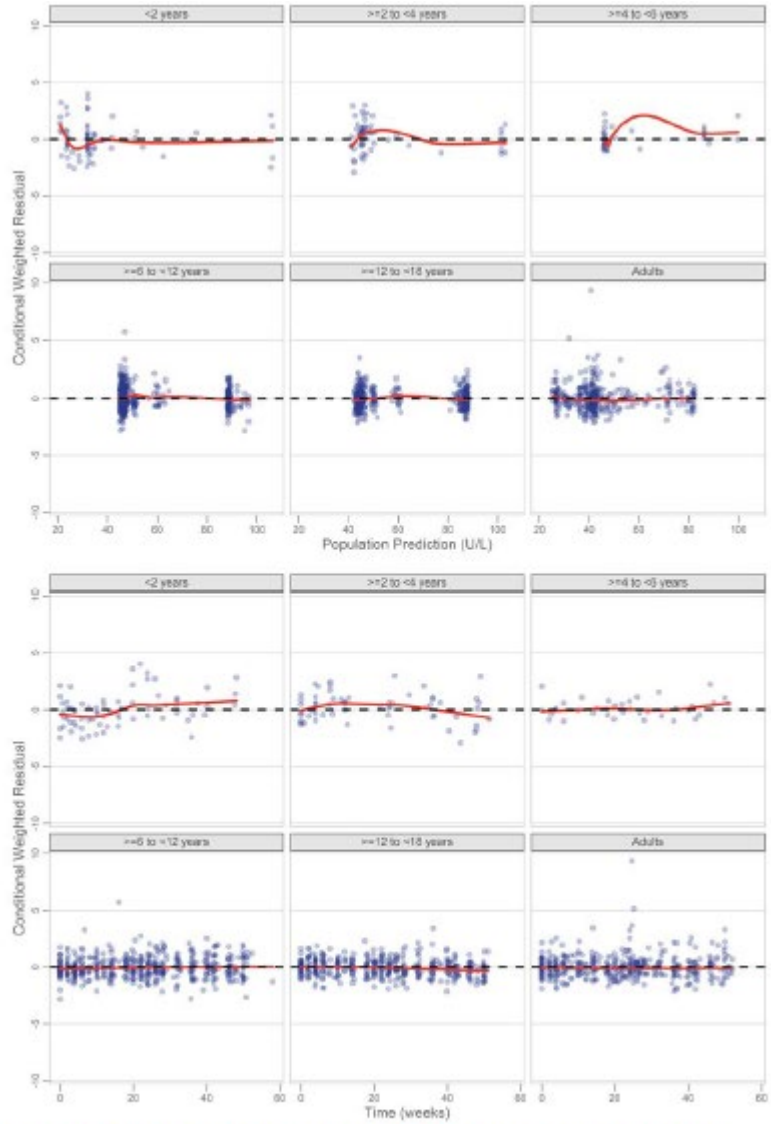
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing;
PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 12.1

Figure 26 - Goodness-of-Fit Plots – ALT PK/PD Model – Current Best Model – All Data



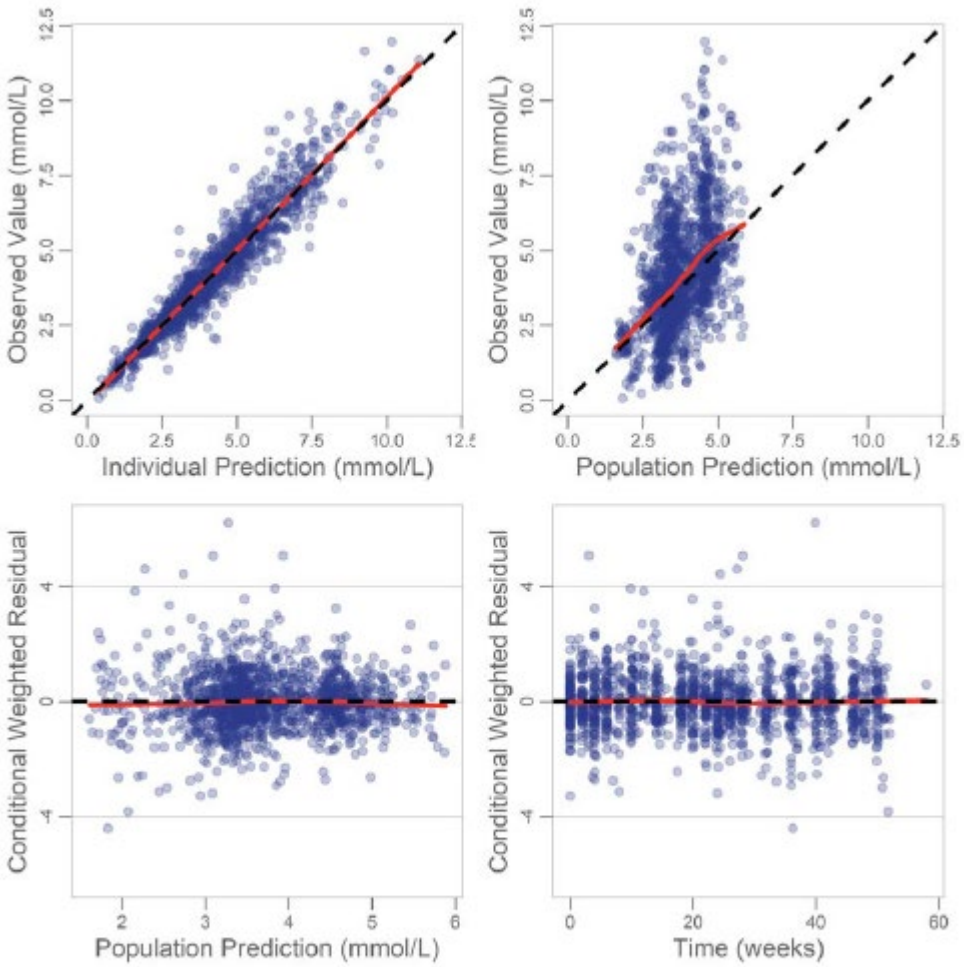
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing;
PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 12.2

Figure 27 - Individual and Population Predicted Concentrations by Age Group – ALT PK/PD Model – Current Best Model



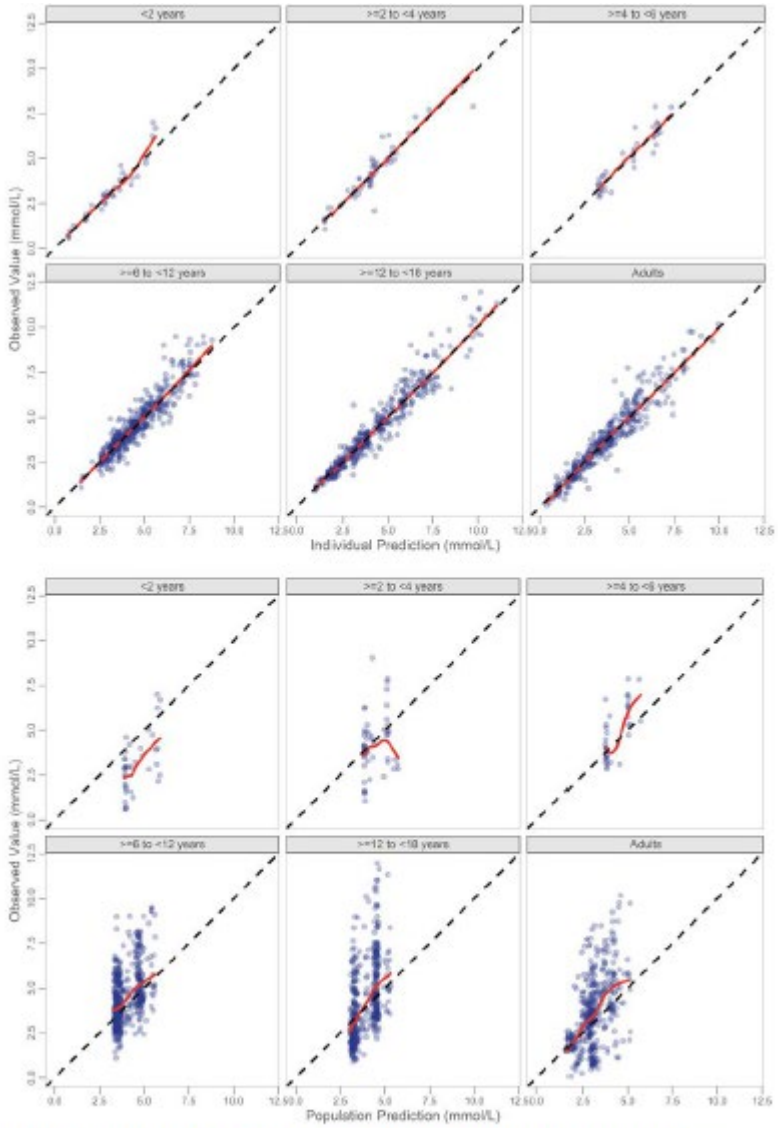
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 12.3

Figure 28 - Population Predicted Concentration and Time by Age Group – Conditional Weighted Residuals – ALT PK/PD Model – Current Best Model



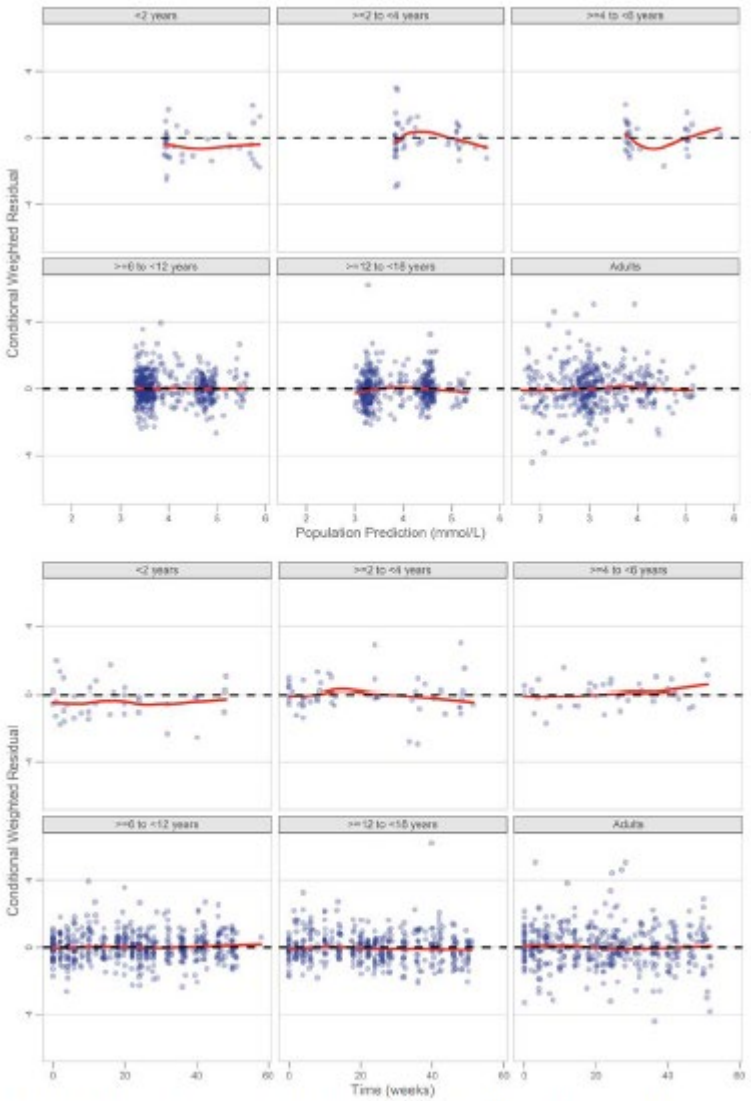
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 12.4

Figure 29 - Goodness-of-Fit Plots – LDL-C PK/PD Model – Current Best Model – All Data



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 12.5

Figure 30 - Individual and Population Predicted Concentrations by Age Group – LDL-C PK/PD Model – Current Best Model



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 12.6

Figure 31 - Population Predicted Concentration and Time by Age Group – Conditional Weighted Residuals – LDL-C PK/PD Model – Current Best Model

Assessment of the MAH's response

Endorsed.

Conclusion

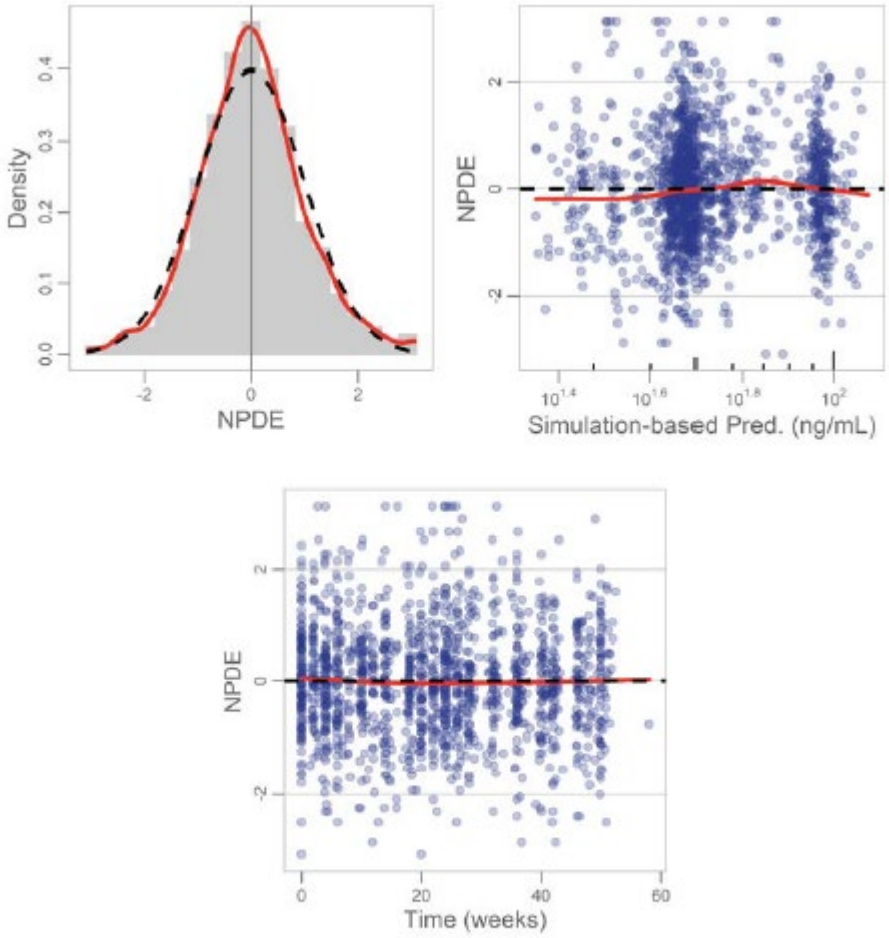
Issue closed.

Question 17

NPDEs distribution should also be provided as well as NPDE vs PRED and vs time plots.

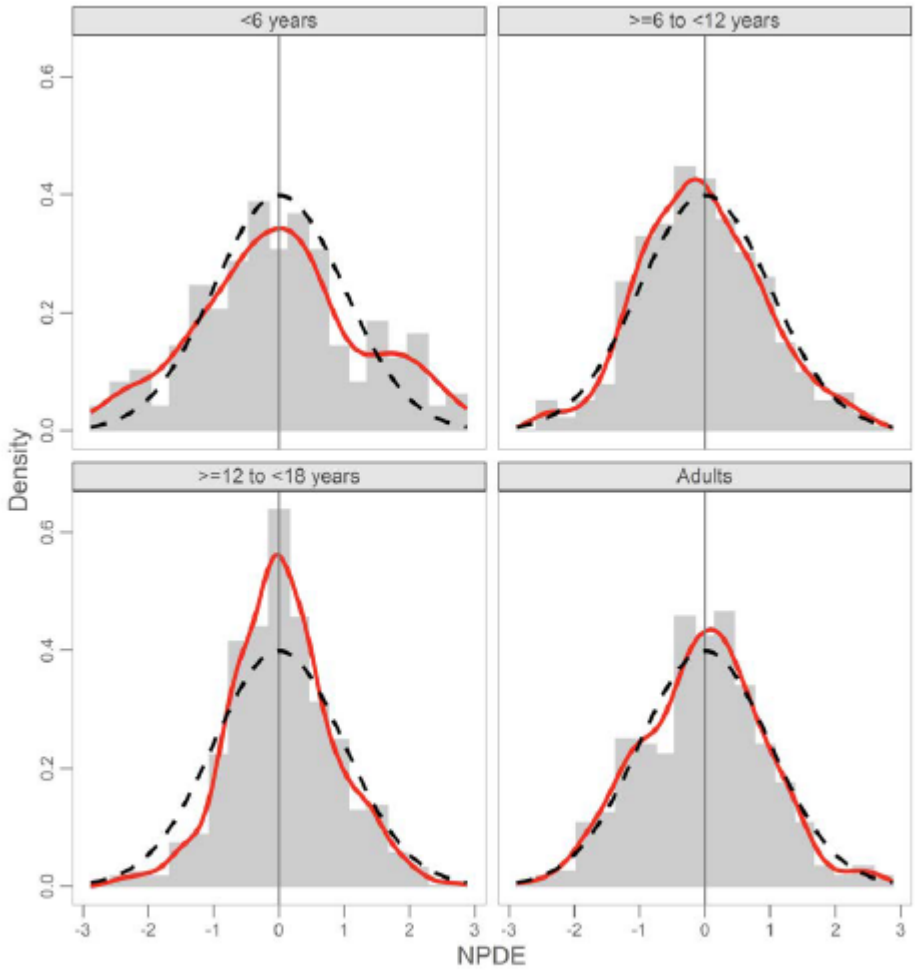
Summary of the MAH's response

As requested, NPDE plots are presented in the five first figures for the ALT PK/ PD model and the next figures for the LDL-C PK/PD model. All data displayed together and stratified by age group show that the ALT and LDL-C PK/ PD CBMs describes the PD data well.



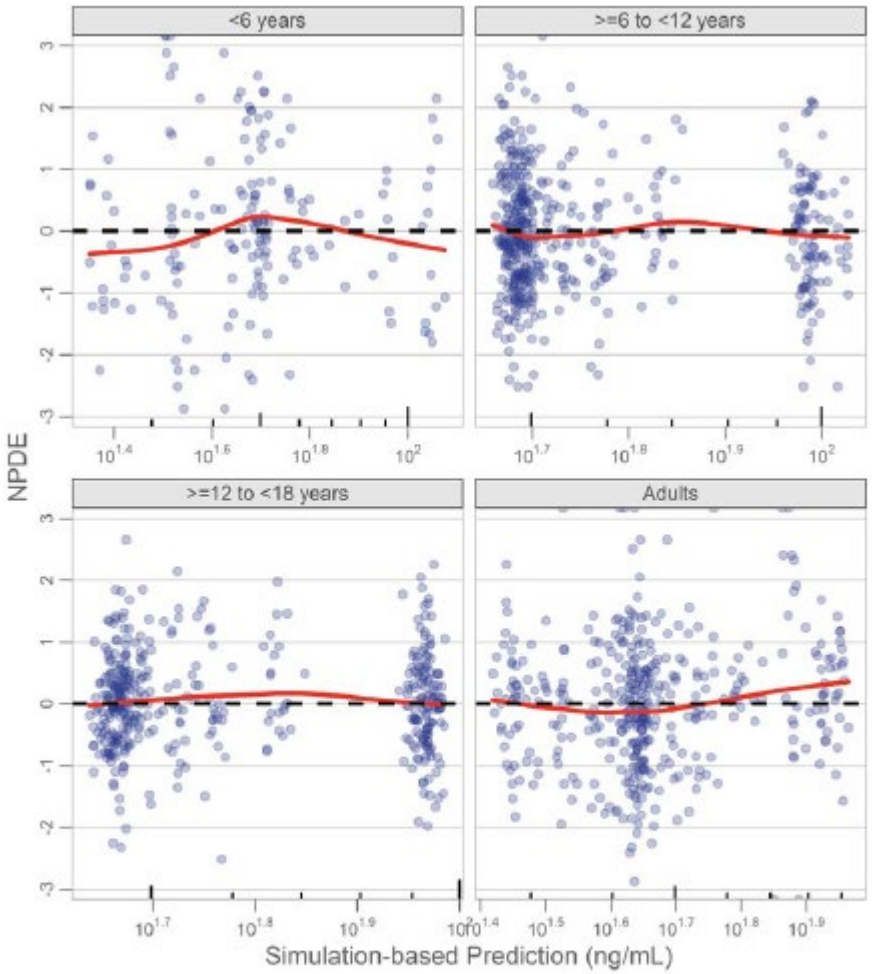
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic; Pred = predicted concentration
Source: Appendix Section 13.1

Figure 32 - NPDE – ALT PK/PD Model – Current Best Model – All Data



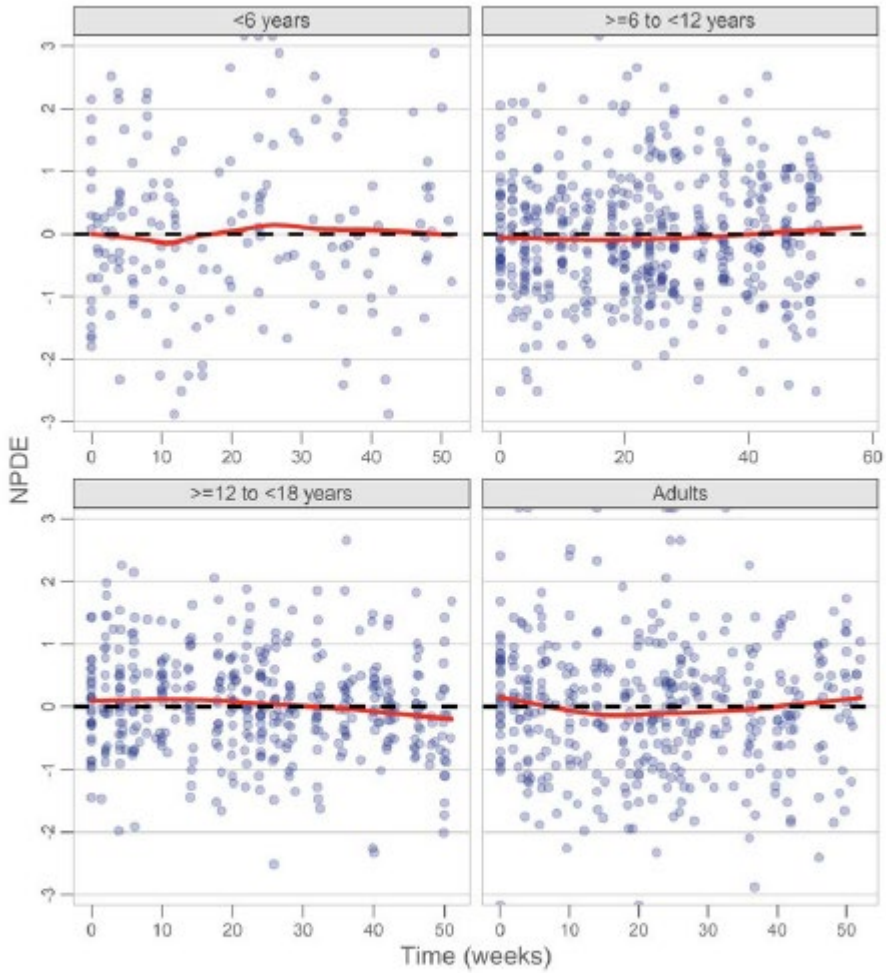
Note: Dashed black line is the line of unity and solid red line is the LOESS.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.2

Figure 33 – NDPE by Age Group With Ages Less Than 6 Years Combined – ALT PK/PD Model – Current Best Model



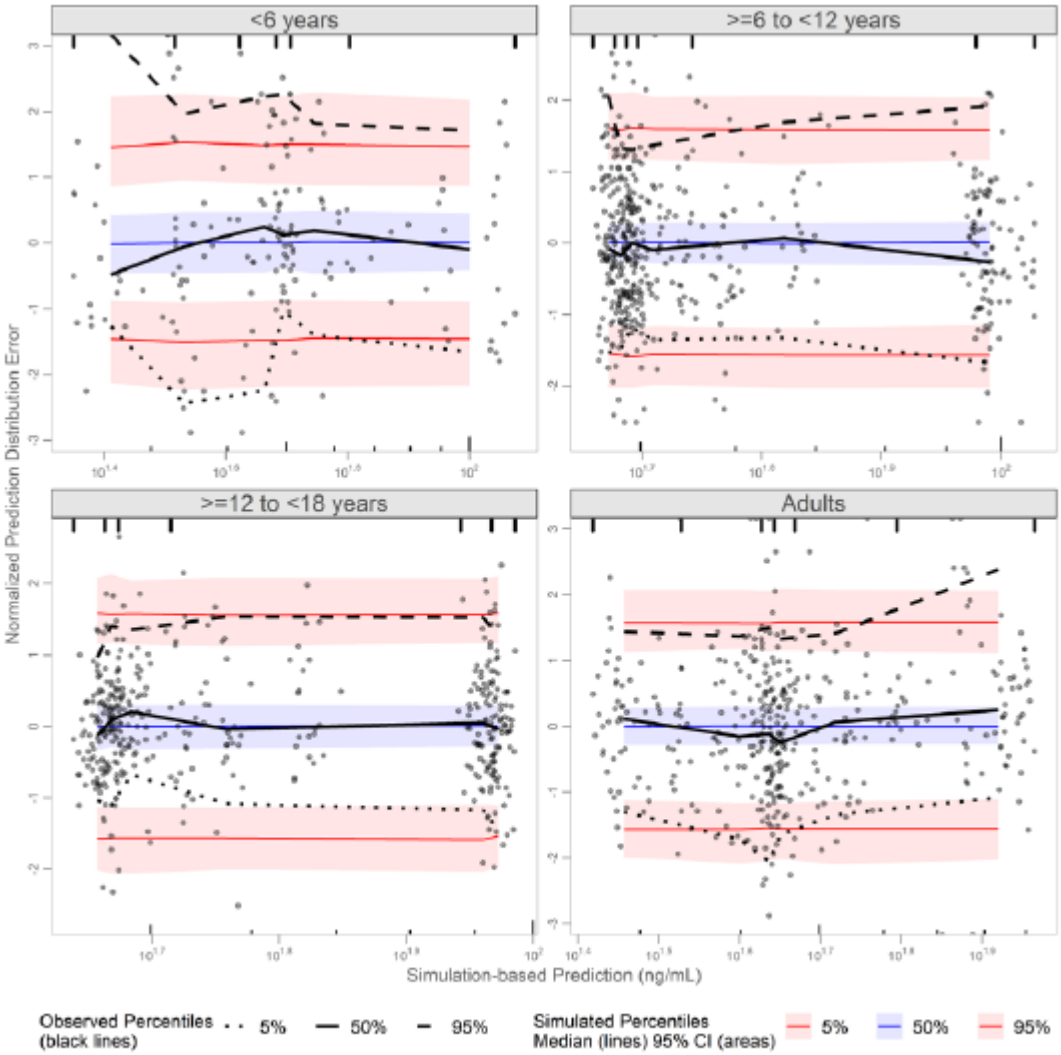
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.3

Figure 34 - NDPE Versus Predicted Concentration by Age Group With Ages Less Than 6 Years Combined – ALT PK/PD Model – Current Best Model



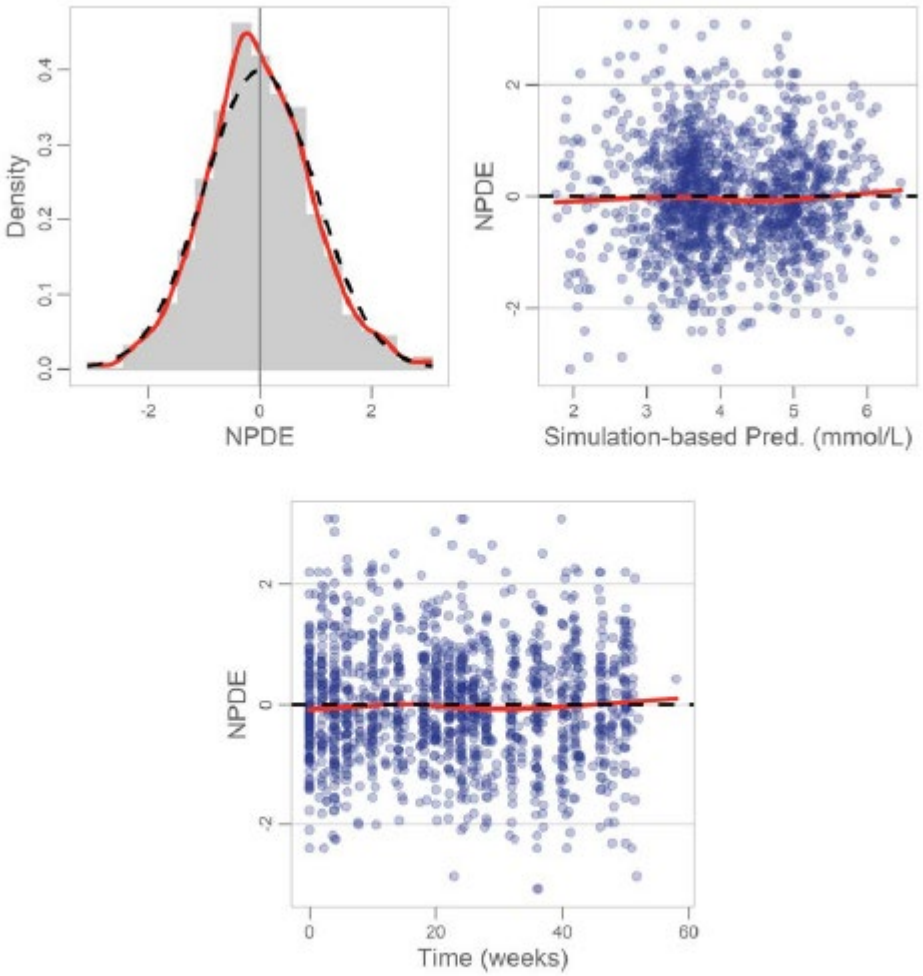
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: ALT = alanine aminotransferase; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.4

Figure 35 - NDPE Versus Time on Treatment by Age Group With Ages Less Than 6 Years Combined – ALT PK/PD Model – Current Best Model



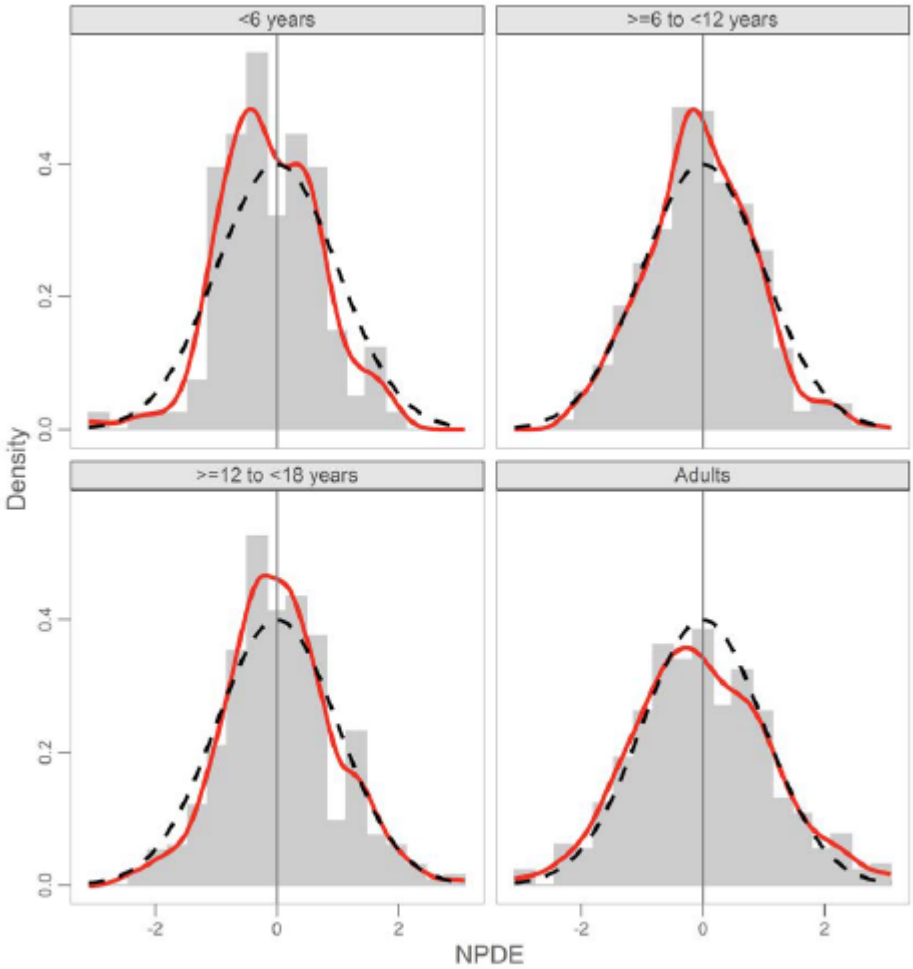
Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.5

Figure 36 - NDPE Versus Predicted Concentration by Age Group With Ages Less Than 6 Years Combined – ALT PK/PD Model – Current Best Model



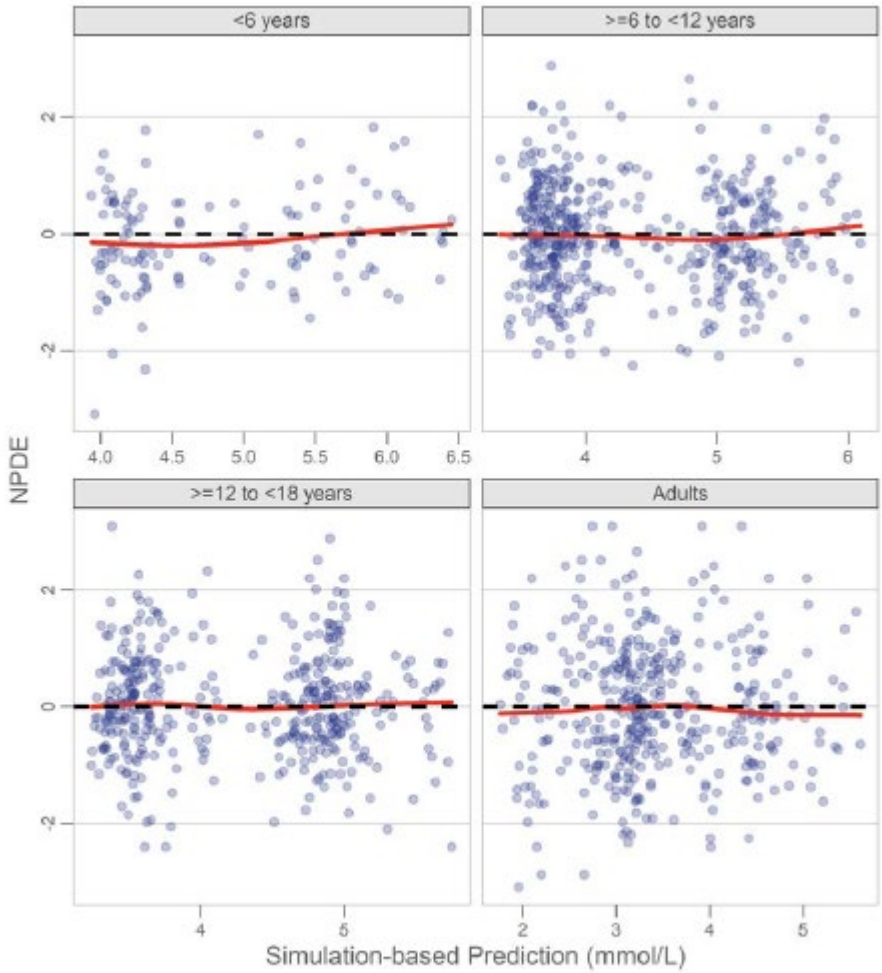
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic; Pred = predicted concentration
Source: Appendix Section 13.6

Figure 37 - NPDE – LDL-C PK/PD Model – Current Best Model – All Data



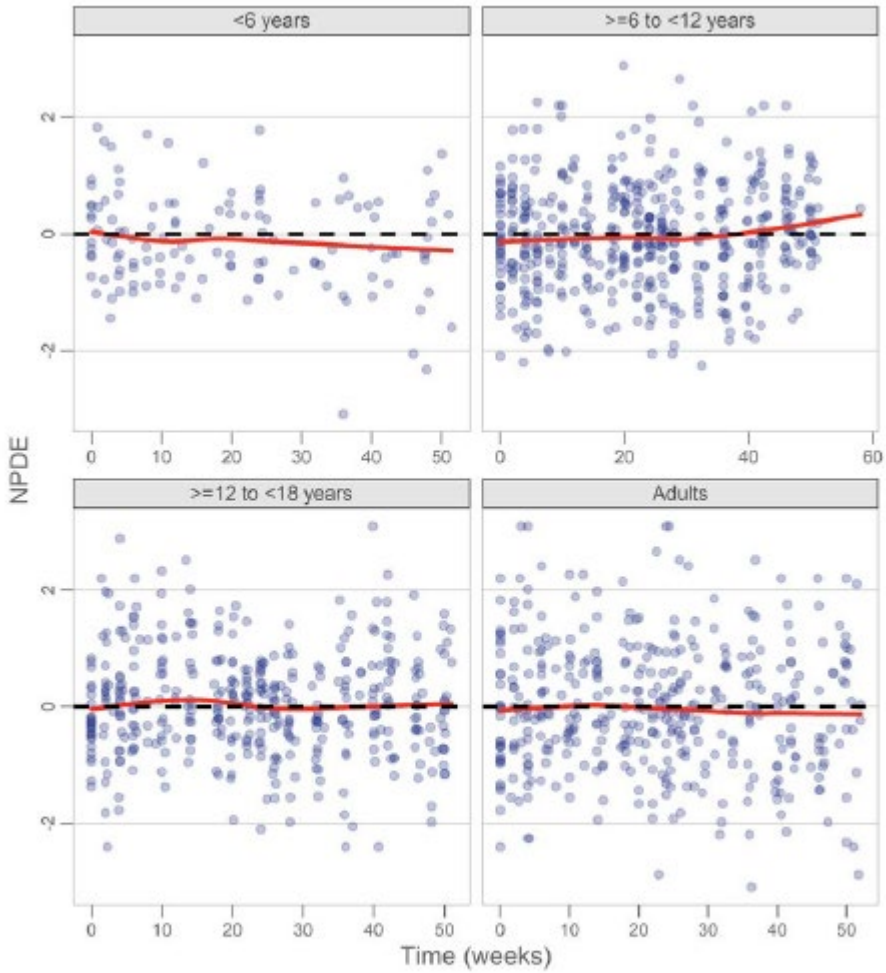
Note: Dashed black line is the line of unity and solid red line is the LOESS.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.7

Figure 38 - NDPE by Age Group With Ages Less Than 6 Years Combined – LDL-C PK/PD Model – Current Best Model



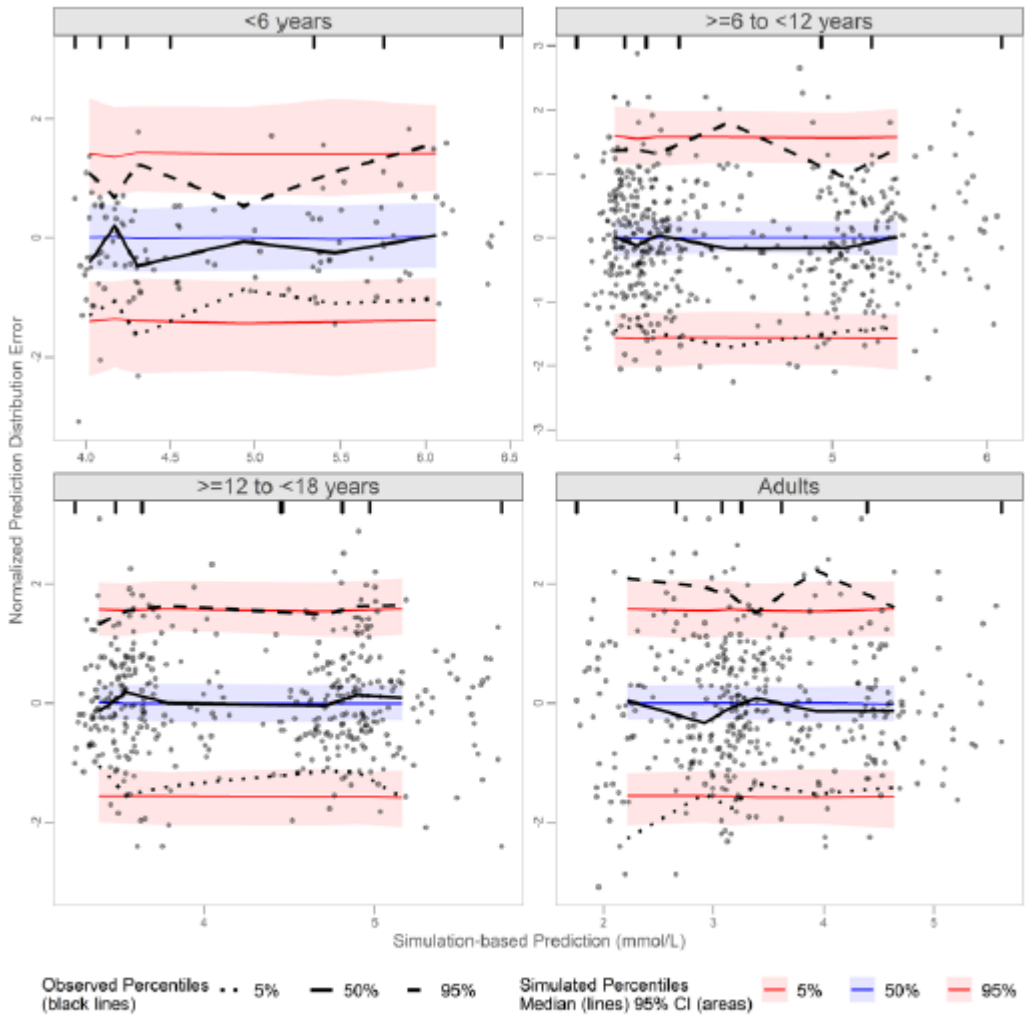
Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.8

Figure 39 - NDPE Versus Predicted Concentration by Age Group With Ages Less Than 6 Years Combined – LDL-C PK/PD Model – Current Best Model



Note: Dashed black line is the line of unity; solid red line is the LOESS; and blue circles are individual data.
Abbreviations: LDL-C = low-density lipoprotein cholesterol; LOESS = locally weighted scatter-plot smoothing; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.9

Figure 40 - NDPE Versus Time on Treatment by Age Group With Ages Less Than 6 Years Combined – LDL-C PK/PD Model – Current Best Model



Abbreviations: CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; NPDE = normalized prediction distribution errors; PD = pharmacodynamic; PK = pharmacokinetic
Source: Appendix Section 13.10

Figure 41 - NDPE Versus Predicted Concentration by Age Group With Ages Less Than 6 Years Combined – LDL-C PK/PD Model – Current Best Model

Assessment of the MAH's response

Endorsed.

Conclusion

Issue closed.

Clinical Efficacy

Question 18

The Applicant's proposed increase of the maximum dosage in infants to 5mg/kg qw does not have sufficient data to unequivocally support this change. However, given the clinical knowledge on the aggressiveness of early-onset LAL-D and the overall trend that seems to emerge from the limited data that there are indeed patients that benefit from higher doses, a higher maximal dose in case of insufficient response could be accepted if the MAH provides a guidance in the SmPC on how and when to escalate or de-escalate the dose, and what to do in case an infant's situation does not become controlled even at the higher maximal dose. Details on the format and content of this guidance is left to the MAH to devise and propose.

Summary of the MAH's response

Across the sebelipase alfa clinical studies, dose modifications were based on clinical response assessment by the Investigators. Per protocol, dose increases were permitted for patients who exhibited a suboptimal clinical response, as determined based on protocol-specified criteria reflecting the key disease manifestations. Dose reductions were also permitted in the event of poor tolerability.

Clinically, infants with rapidly progressive LAL-D frequently present with elevated transaminases, low platelet count, hypoalbuminemia, hyperbilirubinemia, elevated serum ferritin, and coagulopathy (Grabowski, 2012; Jones, 2016). Due to the severity of the disease, infants in the clinical studies received more frequent doses (qw) and underwent more frequent protocol-allowed dose escalations in order to achieve maximum clinical benefit. Fifteen of the 19 patients received a dose escalation to a dose of 3 mg/kg qw and 9 patients received a dose escalation to 5 mg/kg qw. Long-term data are available at both doses, with a median duration of exposure of 15.409 months (and maximum exposure of 54.540 months) at a dose of 3 mg/kg qw and a median duration of exposure of 15.901 months (and maximum exposure of 39.330 months) at a dose of 5 mg/kg qw.

Dose escalation to 5 mg/kg qw was generally associated with stabilization of the clinical course in those infants who had previously had a suboptimal response at a dose of 3 mg/kg qw (Module 2.7.3.3.2.6.2.2). In most patients, dose escalation to 5 mg/kg qw was associated with a clear improvement in growth, as evidenced by increases in weight-for-age (WFA) percentile. Serum transaminases and serum lipids also generally improved after dose escalation to 5 mg/kg qw. All 3 patients with dual whole gene deletion (WGD) had clinical courses that were complicated by high ADA/NAb titers, and all 3 patients required a dose escalation to 5 mg/kg qw. Two of the 3 patients had changes consistent with improvement in their clinical course following dose escalation; 1 patient required a further dose escalation to the protocol-defined maximum of 7.5 mg/kg qw.

No new safety concerns were identified among infants receiving the higher dose of 5 mg/kg qw, and no patient receiving this higher dose had a dose reduction due to poor tolerability. An overview of treatment-emergent adverse events (TEAEs) by dosage regimen is presented in Module 2.7.4 Table 18. Overall, the safety profile was similar in patients treated in the different dosage regimens. At least 1 TEAE was reported for all (100%) patients receiving the following doses: 3 mg/kg qow, 3 mg/kg qw, 5 mg/kg qw, and 7.5 mg/kg qw. A similar proportion of patients who received 3 mg/kg qw and 5 mg/kg qw experienced at least 1 treatment-emergent serious adverse event (TESAE) (14/15 patients [93%] and 9/9 patients [100%], respectively) and at least 1 treatment-related TESAE (4/15 patients [27%] and 2/9 patients [22%], respectively).

In addition, use of a 5 mg/kg qw dose in infants with rapidly progressive LAL-D has support within the medical community. A consortium of physicians with experience treating infants with rapidly progressive LAL-D, including those associated with clinical sites involved in sebelipase alfa clinical studies, has recently developed guidelines for the management of patients with rapidly progressive LAL-D. These guidelines include a recommendation for dose escalation to 5 mg/kg qw based on clinical response (Jones, 2018).

Taking into account EMA's feedback, Alexion proposes the following updates to the EU SmPC to provide further guidance on the dosing recommendations for infant patients (presented in bold underlined):

Section 4.2 Posology and method of administration

Infants (< 6 months of age)

*The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous infusion once weekly. Dose escalation**s*** ~~*to 3 mg/kg once weekly*~~ *should be considered based on* ~~*clinical*~~ *response* ***to clinical and biochemical criteria; e.g., poor growth (especially mid-upper arm circumference, MUAC), deteriorating biochemical markers (e.g., liver transaminases, ferritin, C-reactive Protein, and coagulation parameters), persistent or worsening organomegaly, increased frequency of intercurrent infections, and persistent worsening of other symptoms (e.g., gastrointestinal symptoms):***

- a dose escalation to 3 mg/kg should be considered in case of suboptimal clinical response after a minimum of 4 infusions;

- a further dose escalation up to 5 mg/kg should be considered in case of suboptimal clinical response after a minimum of additional 4 infusions.

Further dose adjustments, as a reduction of the dose or an extension of the dose interval, can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies evaluated doses ranging from 1 to 5 mg/kg once weekly, with one patient receiving a higher dose of 7.5 mg/kg once weekly (see Section 5.1). Doses higher than 7.5 mg/kg have not been studied.

Assessment of the MAH's response

As noted in the initial assessment, it is acknowledged that the dose escalations past the 3 mg/kg limit in infants during the clinical programme did not result in worrisome observations in regards to safety or immunogenicity responses. Nonetheless, the number of case with escalations to such levels were few, which is entirely reasonable given that the condition of LAL-D is ultra-rare in itself, which calls for caution and proper addressment in the SmPC.

As requested the MAH updated the dosing guidance, though a firm guidance for dose de-escalation is not provided and a more general statement that dosing adaptation should be considered based on an patient's response. Given that treatment responses in replacement therapies are usually very individually bound to a particular patient's physical and medical parameters, and that treatment with Kanuma is done by qualified experts in metabolic diseases, this approach is acceptable.

The updates to the dosing guidance have not been reprised in the PIL, but given that this document is aimed at the patient and not at the healthcare professional who will administrate the treatment this can be accepted.

Conclusion

Issue resolved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

SmPC

Question 19

The Applicant should update the ADR tables in section 4.8 of the SmPC as to provide frequency information for each preferred term instead of for the MeDRa SOC as a whole. Additionally, **all** causally related or reasonably considered as potentially causally related events should be listed by preferred term.

Summary of the MAH's response

Alexion confirms that the adverse drug reaction (ADR) tables in section 4.8 of the SmPC currently display frequency information by Preferred Term. All Preferred Terms within each system organ class (SOC) that correspond to a given frequency are listed together (ISS Table 14.3.1.23.2.1.2, Table 14.3.1.23.1.1.1). For instance, in EU SmPC Table 2 (adverse reactions reported in children and adults), within the gastrointestinal SOC, the Preferred Terms of abdominal pain and diarrhoea each occur very commonly, while the Preferred Term of abdominal distension occurs commonly. Nevertheless, to provide additional clarity, the format of the ADR tables in section 4.8 of the SmPC (Table 1 for ADR reported in infants and Table 2 for ADR reported in children and adults) have been updated to list the Preferred Terms vertically (see updated EU SmPC).

Alexion also confirms that all reported adverse events, regardless of Investigator causality assessment at time of report of each individual event, were medically assessed by the Sponsor in aggregate. As such, all Preferred Terms that were considered causally related or potentially causally related to sebelipase alfa treatment were included in the ADR tables.

Assessment of the MAH's response

Though the additional explanation of the MAH has clarified how the table should be read, with the frequency terms relating of the aggregated preferred terms on the right, this is not the usual way of presenting such information. For clarity's sake each individual preferred term should be matched with a singular frequency term, in a respective left to right reading; eg. Anaphylactic reaction: common, eyelid oedema: common.

In itself an aggregated display could be acceptable if the column with frequencies is moved to the right side of the column listing the preferred terms. This will prevent the issue that the current presentation may be misinterpreted as being SOC | overall frequency of adverse events in SOC | preferred terms (of adverse events noted in SOC).

Additionally, the Applicant claims that all preferred terms considered, in aggregate, causally related or potentially causally related to sebelipase alfa treatment have been included in the table. However, between the SmPC as presented in the latest renewal procedure and the version presented in this type-II application certain preferred terms have disappeared from the table (for example menorrhagia). In itself this could be perhaps be due to the aggregate analysis finding certain AEs no longer fulfil the requirements for being labelled (potentially) related to IMP. However, the decision-process in that case is not clear.

As an example, in the SmPC as presented in the renewal dossier the preferred term 'menorrhagia' was seen as a (potentially) related AE in non-infants with a a frequency classification of 'common'. However, in the SmPC as currently proposed for the type II variation under consideration, this preferred term has been removed from the frequency listing. In the provided ISS listings this event is indeed not listed in the Table 14.3.1.22.1.2.1 (*Related Treatment Emergent Adverse Events (TEAE) by Onset >4 and <=24 Hours After End of Infusion, Study and Pooled Safety Set 1*), but the listing of patient 2112-063 from the LAL-CL02 study does however show the event of menorrhagia as being assessed with a 'possibly related' relationship to the IMP.It is thus not clear how these reclassifications were decided upon, especially for events that were previously part of the SmPC AE frequency table and have now been dropped. The Applicant is asked to further clarify how this decision process was undertaken.

Conclusion

The proposed changes to the AE frequency table are a step in the right direction regarding legibility, but it is strongly advised to move the column with frequency terms to the utmost right side of the table (SOC | Preferred Term | Frequency) as to exclude any chance of misinterpretation.

Secondly, though the Applicant notes that the table does contain all (potentially) treatment related adverse events noted during the clinical development and post-approval studies, it is not clear why between the SmPC version as presented at the last renewal and the currently proposed version certain events have been removed from the table, especially given that these events, such as menorrhagia in a LAL-CL02 subject, are still present in the ISS data listings with a causality assessment of 'possibly related'. Presumably this is because Preferred Terms that were reported in 1 patient only in the aggregated data set were not included for further review during ADR identification. The MAH is asked to clarify whether this interpretation is indeed correct.

Finally, as requested in Q4, the following line should be added to the 'immunogenicity' part of the selected adverse events:

Among 125 patients with LAL Deficiency enrolled in the clinical studies, 19/125 (15.0%) patients tested positive for anti-drug antibodies (ADAs) at some timepoint after starting treatment with sebelipase alfa (9 children and adult patients and 10 infants). For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported. Persistence of ADA positivity was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants. Among those 19 patients, 11 (58%) also showed the presence of inhibitory antibody activity (NAbs) at some postbaseline timepoint.

Overall, no conclusion on the relationship between development of ADA/NAbs and associated hypersensitivity reactions or suboptimal clinical response can be made. In clinical studies, 3 patients homozygous for a deletion affecting both alleles of genes Lipase A, lysosomal acid [LIPA] and Cholesterol 25-Hydroxylase developed inhibitory antibody activity associated with a suboptimal clinical response (see section 4.4). These patients underwent either immunomodulatory therapy alone or in combination with hematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT), resulting in improved clinical response to sebelipase alfa.

Issue not yet resolved.

Question 20

Regarding the modifications in the section 5.2, some updates are already proposed :

a) It should be clarified in the title of the table 5 that the parameters were simulated after multiple dose.
b) The table 5 is not in line with the table 8 of the PK/PD simulation report. As an example, the total number N for overall subjects is discrepant (N=72 vs N=4).

c) The conclusions on the linearity of sebelipase alpha PK and accumulation over time are drawn based on the non-compartmental analysis in study LAL-CL04 and in study LAL-CL04 and LAL-CL06, respectively. But the number of patients in each category of age was limited and should be reflected in the SmPC. In addition, the lack of sign of accumulation for the 3 mg/kg qow dosing is not reported in the SmPC. Instead, lack of accumulation at 3 mg/kg once weekly is mentioned. It should be clarified if the source of this information is the study LAL-CL01 while all the PK samples from this study were disqualified. The SmPC should be updated accordingly.

Summary of the MAH's response

a) EU SmPC Tables 4 and 5 that were proposed in the EU SmPC submitted in Dec 2019 (eCTD sequence 0066) have been merged in the proposed EU SmPC, and numbers were updated with the current data as presented in the response to Question 20 b). As such, the title of now Table 4 has been updated accordingly. However, Alexion has acknowledged EMA's request and the title of the EU SmPC Table 4 now reads "Mean (SD) Predicted Pharmacokinetic and Exposure Parameters Following Repeated Administrations of 1 mg/kg Sebelipase Alfa in Patients With LAL Deficiency by Age Group".

b) Alexion confirms that Table 5 in the EU SmPC submitted in Dec 2019 (eCTD sequence 0066) contained a typo, and that the correct number (N) of overall subjects was N = 72, as presented in Table 8 of the PK/PD simulation report. However, EU SmPC Table 4 was updated with the current data as presented below (source: Appendix Section 14.1), and therefore the correction of the number of overall subjects from N = 4 to N = 72 is no longer applicable:

EU SmPC Table 4: Mean (SD) Predicted Pharmacokinetic and Exposure Parameters Following Repeated Administrations of 1 mg/kg Sebelipase Alfa in Patients With LAL Deficiency by Age Group

Parameter	Age < 4 years (N = 5)	Age 4 to < 12 years (N = 32)	Age 12 to < 18 years (N=34)	≥ 18 years (N = 31)
CL (L/h)	17.2 (7.07)	22.8 (11.2)	32.7 (10.8)	37.6 (13.8)
Q (L/h)	1.96 (0.963)	1.41 (0.633)	1.61 (0.551)	1.54 (0.594)
Vc (L)	2.06 (1.22)	2.72 (1.43)	4.06 (2.01)	6.01 (5.43)
Vss (L)	6.13 (1.22)	6.79 (1.43)	8.13 (2.01)	10.1 (5.43)
$t_{½\beta}$ (h)	1.88 (0.69)	2.71 (1.63)	2.18 (1.28)	2.24 (1.05)
AUC_{ss} (ng × h/mL)	521 (174)	1410 (774)	1610 (658)	2060 (793)
$C_{max,ss}$ (ng/mL)	247 (80.6)	679 (370)	786 (315)	997 (367)

Note: Estimates are derived from data from Studies LAL-CL02, LAL-CL03, LAL-CL04, and LAL-CL06.

AUC_{ss} = area under the serum concentration-time curve at steady state; CL = clearance; $C_{max,ss}$ = maximum observed serum concentration under steady state conditions; PK = pharmacokinetic(s); Q = peripheral clearance; $t_{½\beta}$ = terminal elimination half-life; Vc = central volume of distribution; volume of distribution at steady state

c) The nonlinearity of sebelipase alfa is based on noncompartmental analysis (NCA) results in a limited number of adult patients with LAL-D (Module 2.7.2 Table 6). With only 3 patients receiving the 3 mg/kg dosing for this evaluation, the amount of data supporting this finding is limited. The conclusion of no accumulation following multiple dosing is based on both the NCA results from Study LAL-CL04 and the results from the Pop-PK modeling effort, where a mean terminal elimination half-life of approximately 3 hours is predicted. No accumulation is expected considering the maintenance dosing is administered once every 1 to 2 weeks. The disqualification of the Study LAL-CL01 PK data does not impact these conclusions. Therefore, Alexion proposes the following updates to the EU SmPC (presented in strikeout and bold underlined):

Section 5.2 Pharmacokinetic properties

Linearity/non-linearity

~~Based on these data, the pharmacokinetics of sebelipase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure observed between the 1 and 3 mg/kg dose.~~ **No conclusion on the linearity of sebelipase alfa pharmacokinetics can be made due to limited data at higher exposures. However, no accumulation is observed at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly, nor is it expected following less frequent dosing.**

Assessment of the MAH's response

a. Accepted.

b. The updated table 4 is accepted. However, it is not clear why only 75 patients are reported to be included in the POPPPK analysis in the section 5.2 while the mean predicted PK and exposure parameters for 102 patients are reported in table 4.**(OC)** In addition, the subsection "children and adult" and "infants" are now merged. These subtitles should be deleted from the section 5.2.**(OC)** Finally, there are discrepancies between the numbers of patients reported in the different age subgroups in the table provided in AtQ6 and numbers of patients reported in the table 4 provided in the SmPC. They should be clarified.**(OC; see also question 20)**

c. The PK data supporting the statement on the lack of accumulation at 1mg/kg once weekly and 3mg/kg once weekly should be provided.**(OC)**

Regarding the 3mg/kg qow dosing, overall the number of patients were limited and this should be reflected in the SmPC. In addition, it appears that the observations done for the drug accumulation at 3mg/kg qow are based on a limited number of patients. This should be reflected in the SmPC.**(OC)**

The other updates are accepted.

Conclusion **Partly resolved**

Question 21
The MAH should consider providing revised Product Information based on all the comments included in attachment to this Request for Supplementary Information.

Summary of the MAH's response

[The MAH provided an updated SmPC, taking into account the previous comments received]

Assessment of the MAH's response

The provided PIL was updated according to the comments received in the previous round. Note that the PIL should be further aligned, if so affected, with any changes to the SmPC resulting from the latest evaluation round.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

RMP aspects

Question 22
The elements for a public summary of the RMP should be slightly revised to include an explanation to the term "patients with dual WGD", e.g. "patients who lack the enzyme completely".

Summary of the MAH's response
In agreement with the scope of the recommendation, the elements for a public summary of the RMP will be updated with the explanation that "patients with dual WGD" indicate "patients who completely lack the ability to produce both enzymes" to reflect that not only one enzyme is affected by this extensive deletion. Updated EU-RMP version 4.1 is submitted in the present sequence.

Assessment of the MAH's response
The elements for a public summary have been updated as requested.

Conclusion

Issue resolved

10. 2nd request for supplementary information

Other Concerns

PK

1. As part of the corrective actions taken to address data integrity issues detected in a Health Authority inspection carried out in 2016 at the CRO, the Applicant has explained that all samples impacted by these events were identified and reanalyzed when possible or the data were disqualified. Based on the information provided in the original dossier submitted for this variation, it was understood that at the time of data disqualification these samples were beyond the validated long-term storage stability for the study results for KANUMA and could not be reanalysed. These samples were, therefore, unreportable. The Applicant should clarify if PK samples collected in the KANUMA studies were included in the 86% of total number of samples reanalysed and reported as meeting the criteria recommended by EMA in the incurred sample reanalysis.

2. The MAH is requested to provide the inspection report issued after the inspection carried out in 2016 at the CRO . It should be provided in order to see the initial findings and issues. In addition the MAH should give a list of GCP/GCLP inspections performed by European or other authorities outside EU during the same periods as the KANUMA studies periods in this CRO. The inspection results and the corresponding outcome should be discussed.

3. The Applicant is requested to provide the statistical comparison of the validation cut-point (healthy subjects) and the newly established cut points in the target population. The observed false positive error rate of the clinical study baseline samples, after excluding the samples with pre-existing ADA, using the validation cut point should also be taken into account in the discussion on the reliability of the validation cut point in the study population.

4. To avoid redundant statement, the detailed information on the ADA incidence should only be provided in the section 4.8 with a cross-reference to the section 4.8 in the section 5.2 : "As with all therapeutic proteins, there is the potential for the development of immunogenicity. Nineteen of 125 (15%) patients with LAL Deficiency had at least 1◦postbaseline antidrug antibody (ADA) positive result, 9 of which were children and adult patients. For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported". In addition, to give a full overview of all patient populations to the healthcare provider, the following statement on the ADA incidence in infants provided in the document 2.7.2 should be reported in the section 4.8: "On the other hand, persistence of ADA positivity was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants."

5. The following issues should be addressed for the section 5.2 of the SmPC:
    a. it is not clear why only 75 patients are reported to be included in the POPPPK analysis while the mean predicted PK and exposure parameters for 102 patients are reported in the table 4.
    b. The subsection "children and adult" and "infants" are now merged. These subtitles should be deleted from the section 5.2.
    c. There are discrepancies between the numbers of patients reported in the different age subgroups provided in AtQ6 (table entitled 'distribution of PK samples by age group') and the numbers of patients reported in the table 4 provided in the SmPC. They should be clarified.
    d. The PK data supporting the statement on the lack of accumulation at 1mg/kg once weekly and 3mg/kg once weekly should be provided. In addition, it appears that the observations done for the drug accumulation at 3mg/kg qow are based on a limited number of patients. This should be reflected in the SmPC.

SmPC

6. The term 'anaphylactic reactions' as used in the *Hypersensitivity reactions including anaphylactic reactions or anaphylaxis* in section 4.4 is redundant in combination with the term 'anaphylaxis'. Please update the start of the section as follows:

   Hypersensitivity reactions including ***~~anaphylactic reactions or~~*** *anaphylaxis*

   Hypersensitivity reactions, including ***~~anaphylactic reactions or~~*** *anaphylaxis, have been reported in patients treated with sebelipase alfa; see section 4.8.*

7. The readability of treatment durations/exposure times in sections 4.8 and 5.1 should be enhanced for better understanding without conversion effort, e.g. avoid the use of decimals other than '.5' and provide a (rounded) more easily readable years – months – days representation of the durations.

8. The MAH is requested to move the column with frequency terms to the utmost right side of the adverse event frequency table (SOC | Preferred Term | Frequency) in section 4.8 as to exclude any chance of misinterpretation whether the frequency refers to the SOC or the preferred terms.

9. ISS tables 14.3.1.23.2.1.2 and 14.3.1.23.1.1.1 are the basis for the SmPC's ADR frequency tables, but certain individual data listings make reference of events that were considered possibly related to treatment but which were not included in the aforementioned tables (and in some cases have been actively removed from the SmPC frequency table in the timeframe between the last renewal procedure and the current type II dossier). The Applicant is asked to confirm whether this is due to the fact that during the ADR identification in the aggregated safety data Preferred Terms were not included for further review if they were reported in 1 patient only.

11. Assessment of the responses to the 2nd request for supplementary information

PK

1. As part of the corrective actions taken to address data integrity issues detected in a Health Authority inspection carried out in 2016 at the CRO, the Applicant has explained that all samples impacted by these events were identified and reanalyzed when possible or the data were disqualified. Based on the information provided in the original dossier submitted for this variation, it was understood that at the time of data disqualification these samples were beyond the validated long-term storage stability for the study results for KANUMA and could not be reanalysed. These samples were, therefore, unreportable. The Applicant should clarify if PK samples collected in the KANUMA studies were included in the 86% of total number of samples reanalysed and reported as meeting the criteria recommended by EMA in the incurred sample reanalysis.

Summary of the MAH's response

All pharmacokinetic data reported for the KANUMA studies were from analytical runs that met the acceptance criteria for the method, and that were free from the data integrity issue. This is also true for all samples included in the evaluation of incurred sample reanalysis (ISR). In the instance of an ISR result having originated from an analytical run disqualified due to the data integrity issue the sample was analyzed again, or if the sample was beyond long-term stability another sample was chosen for the

purpose of ISR. Thus, all ISR results are considered valid, and meet the criteria recommended by the EMA for ISR.

Assessment of the MAH's response

The MAH's clarification is accepted.

Conclusion
Resolved

2. The MAH is requested to provide the inspection report issued after the inspection carried out in 2016 at the CRO. It should be provided in order to see the initial findings and issues. In addition the MAH should give a list of GCP/GCLP inspections performed by European or other authorities outside EU during the same periods as the KANUMA studies periods in this CRO. The inspection results and the corresponding outcome should be discussed.

Summary of the MAH's response

As requested, the inspection report and CRO responses are provided .

No other Health Authority inspections were conducted during the same time periods as the KANUMA studies. None of these studies inspected were sponsored by Alexion.

The MAH has provided the requested inspection report.

All issues raised during the inspection carried out during the same periods as KANUMA studies were addressed by theCRO.

Conclusion
Resolved

3. The Applicant is requested to provide the statistical comparison of the validation cut-point (healthy subjects) and the newly established cut points in the target population. The observed false positive error rate of the clinical study baseline samples, after excluding the samples with pre-existing ADA, using the validation cut point should also be taken into account in the discussion on the reliability of the validation cut point in the study population.

Summary of the MAH's response

Specific population based cut-points for children (< 18 years) and adults (18 years+) have been determined using data from studies LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06, and LAL-CL08 and then compared to the validation cut-point as described in Study MEMO 8285711 (Annex 2).

Each population was individually analyzed for outliers following which an Analysis of Variance (ANOVA)

was performed to test for a difference in mean response between the populations. This gave no evidence of a difference in mean response between the populations ($p > 0.05$). In addition, t-tests were performed to test for pairwise differences in mean response between the populations, with 95% confidence intervals constructed for each difference. These comparisons gave no evidence of a difference in mean response between any pair of populations ($p > 0.05$, with zero, ie, no difference, contained within each confidence interval). Data is presented in Figure 1 and Table 2.

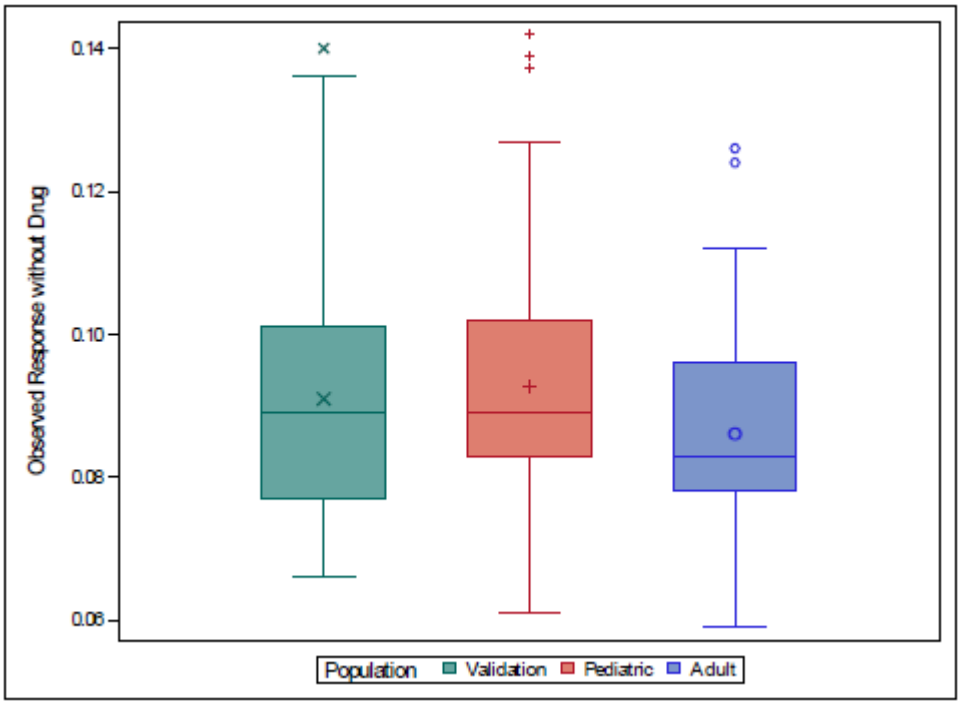


Figure 42 - Observed Population Responses for Validation, Adult and Pediatric Populations

Table 72 - ANOVA Results of Validation, Adult and Pediatric Populations

ANOVA p-value	Difference	Difference (95% CI)	T-test p-value	Significance
0.1853	Adult - Pediatric	-0.00659 (-0.01364, 0.00047)	0.0671	NS
	Adult - Validation	-0.00489 (-0.01127, 0.00149)	0.1325	NS
	Pediatric - Validation	0.00170 (-0.00281, 0.00620)	0.4589	NS

Abbreviations: ANOVA = analysis of variance; CI = confidence interval; NS = not significant (p-value>0.05)

The validation cut-point was calculated to result in a 5% false positive rate for treatment naïve individuals. Table 3 presents the actual false positive rate for the baseline pretreatment samples from each study. Although multiple studies do not have enough baseline samples to accurately compute the false positive rate within the study, overall the false positive rate for all the studies is 4.2%, in agreement with the cut-point design.

Table 73 - Baseline Sample False Positive Rate

	LAL-CL02	LAL-CL03	LAL-CL04	LAL-CL06	LAL-CL08	Total
Baseline False Positive Samples	4	0	0	1	0	5
Total Baseline Samples	66	6	8	30	8	118
% False positive	6.1	0.0	0.0	3.3	0.0	4.2

Therefore, based on the absence of statistically significant differences between the patient populations and the validation cut-point data, along with in-study false positive rates performing as designed, the cut-point used in the KANUMA program for antidrug antibody (ADA) analysis is considered reliable and fit for its intended use.

Assessment of the MAH's response

The MHA has provided a statistical comparison of the cut points calculated for the different populations and the actual false positive rate for the baseline pre-treatment samples. The cut point used in the KANUMA program for ADA analysis seems reasonable.

Conclusion

Resolved

4. To avoid redundant statement, the detailed information on the ADA incidence should only be provided in the section 4.8 with a cross-reference to the section 4.8 in the section 5.2 : "As with all therapeutic proteins, there is the potential for the development of immunogenicity. Nineteen of 125 (15%) patients with LAL Deficiency had at least 1◦postbaseline antidrug antibody (ADA) positive result, 9 of which were children and adult patients. For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported". In addition, to give a full overview of all patient populations to the healthcare provider, the following statement on the ADA incidence in infants provided in the document 2.7.2 should be reported in the section 4.8: "On the other hand, persistence of ADA positivity was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants."

Summary of the MAH's response

Alexion acknowledges the Agency's feedback and has updated the European Union (EU) summary of product characteristics (SmPC) accordingly, as presented below. For ease of review, the added text is captured as **bold underline**, whereas the deleted text is captured as ~~strikethrough~~.

Section 4.8 Undesirable effects

Immunogenicity

[…]

Among 125 patients with LAL Deficiency enrolled in the clinical studies, 19/125 (15.0%) patients tested positive for anti-drug antibodies (ADAs) at some timepoint after starting treatment with sebelipase alfa

(9 children and adult patients and 10 infants). For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported. Persistence of ADA positivity was observed for all 10 infants and persistence of high titer ADAs was observed for 3 of the 10 infants. *Among those 19 patients, 11 (58%) also showed the presence of inhibitory antibody activity (NAbs) at some postbaseline timepoint.*

Overall, no conclusion on the relationship between development of ADA/NAbs and associated hypersensitivity reactions or suboptimal clinical response can be made. In clinical studies, 3 patients homozygous for a deletion affecting both alleles of genes Lipase A, lysosomal acid [LIPA] and Cholesterol 25-Hydroxylase developed inhibitory antibody activity associated with a suboptimal clinical response (see section 4.4). These patients underwent either immunomodulatory therapy alone or in combination with haematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT), resulting in improved clinical response to sebelipase alfa.

Section 5.2 Pharmacokinetic properties

Immunogenicity

As with all therapeutic proteins, there is the potential for the development of immunogenicity ***(see section 4.8)****.* ~~*Nineteen of 125 (15%) patients with LAL Deficiency had at least 1 postbaseline antidrug antibody (ADA) positive result, 9 of which were children and adult patients. For children and adult patients with LAL Deficiency, ADA positivity was transient with generally low titers of ADAs reported. No conclusion on the impact of immunogenicity on sebelipase alfa exposure can be made.*~~

Assessment of the MAH's response

The MAH has updated the SmPC as requested.

Conclusion **Resolved**

5. The following issues should be addressed for the section 5.2 of the SmPC:
    a. it is not clear why only 75 patients are reported to be included in the POPPPK analysis while the mean predicted PK and exposure parameters for 102 patients are reported in the table 4.
    b. The subsection "children and adult" and "infants" are now merged. These subtitles should be deleted from the section 5.2.
    c. There are discrepancies between the numbers of patients reported in the different age subgroups provided in AtQ6 (table entitled 'distribution of PK samples by age group') and the numbers of patients reported in the table 4 provided in the SmPC. They should be clarified.
    d. The PK data supporting the statement on the lack of accumulation at 1mg/kg once weekly and 3mg/kg once weekly should be provided. In addition, it appears that the observations done for the drug accumulation at 3mg/kg qow are based on a limited number of patients. This should be reflected in the SmPC.

Summary of the MAH's response

a.) The original population pharmacokinetic (Pop-PK) analysis that was completed in support of the post-marketing commitment included data from 75 patients from Studies LAL-CL02, LALCL03, LAL-CL04, and LAL-CL06. The subsequent model, per suggestion from the Committee for Medicinal Products for Human Use (CHMP) received in the list of Requests for Supplementary Information (RSI) adopted by the CHMP on 26 Mar 2020 (EMA/7910/2020), included 30 additional patients who were originally randomized to placebo but then subsequently received sebelipase alfa, leading to a total of 105 patients treated with sebelipase alfa overall. Following a Pop-PK sensitivity analysis exploring the effect of dose on clearance (CL) (2019 PK/PD Modeling and Simulation report, Section 6.2.3), it was determined that 3 adult patients weighing > 50 kg and receiving the high dose of 3 mg/kg sebelipase alfa (in Study LAL-CL04) should be removed from the Pop-PK final analysis to reduce the uncertainty in the estimated CL and central volume of distribution (Vc) parameters. Given this exclusion, the total patient count was reduced from 105 to 102 in the SmPC Table 4.

For clarification purpose, the EU SmPC has been updated as presented below. For ease of review, the added text is captured as bold underline, whereas the deleted text is captured as strikethrough.

Section 5.2 Pharmacokinetic properties

*The pharmacokinetics of sebelipase alfa in children and adults were determined using a population pharmacokinetic analysis of ~~75~~**102** patients with LAL deficiency who received intravenous infusions of sebelipase alfa across 4 clinical studies LAL-CL02, LAL-CL03, LAL-CL04 and LAL-CL06 (Table 4).*

Predicted pharmacokinetic and exposure parameters of sebelipase alfa from clinical trials are presented by age group in Table 4. […]

b.) Alexion acknowledges the Agency's comment and confirms the subtitle *"Children and adults"* has been deleted from Section 5.2.

c.) There are differences in both the total and subgroup number of patients between the 2 tables (response to 26 Mar 2020 Request for Supplementary Information, Question [Q]6 and Table 4 of the SmPC). The difference in total number of patients (N) between the 2 tables (N = 102 in the SmPC vs N = 105 in Q6) results from exclusion of data for 3 adult patients who received high dose of 3 mg/kg sebelipase alfa (see response to Q5a), while the data for these 3 patients were included in the summary of all available pharmacokinetic (PK) samples (response to Q6). The differences in number of patients between the assorted age subgroups are the result of different rules being applied. The age categories in the table presented in the response to Q6 were based on patient age at baseline, while values in the SmPC Table 4 were based on the age at the time of the last dose (because steady-state exposure parameters are presented). This resulted in small differences in number of patients per age subgroup between the 2 tables.

d.) Limited sebelipase alfa PK data following once weekly dosing is available, with PK sampling not collected following consecutive doses to provide empiric confirmation of no accumulation. However, based on the relatively fast clearance of sebelipase alfa (mean terminal elimination half-life ~ 3 hours), drug accumulation is not expected following once weekly dosing of sebelipase alfa.

The EU SmPC **Section 5.2 Pharmacokinetic properties** has been updated as presented below. For ease of review, the added text is captured as **bold underline**, whereas the deleted text is captured as ~~strikethrough~~.

Linearity/non-linearity

No conclusion on the linearity of sebelipase alfa pharmacokinetics can be made due to limited data at higher exposures. ~~However, no accumulation is observed at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly, nor is it expected following less frequent dosing.~~ ***No drug accumulation is observed following 1 mg/kg or 3 mg/kg once every other week dosing, although observations for the drug accumulation at 3mg/kg every other week are based on a limited number of patients. Accumulation following once weekly dosing is not expected based on relatively rapid drug clearance.***

Assessment of the MAH's response

a) The MAH has clarified and updated the SmPC text with the total number of patients used to determine the PK parameters from the POPPK analysis.

b) The MAH has deleted the subsection title requested.

c) The MAH has clarified the discrepancies observed between the different data reported. This is related to the patient age considered (at baseline vs at the time of the last dose).

d) The current knowledge is deemed better reflected in the SmPC with the proposed wording.

Conclusion **Resolved**

SmPC

6. The term 'anaphylactic reactions' as used in the *Hypersensitivity reactions including anaphylactic reactions or anaphylaxis* in section 4.4 is redundant in combination with the term 'anaphylaxis'. Please update the start of the section as follows:

   Hypersensitivity reactions including ***~~anaphylactic reactions or~~*** *anaphylaxis*

   Hypersensitivity reactions, including ***~~anaphylactic reactions or~~*** *anaphylaxis, have been reported in patients treated with sebelipase alfa; see section 4.8.*

Summary of the MAH's response

Alexion agrees to the requested update and has edited the outlined text in **Section 4.4 Special warnings and precautions** for use accordingly.

Conclusion **Issue resolved.**

7. The readability of treatment durations/exposure times in sections 4.8 and 5.1 should be enhanced for better understanding without conversion effort, e.g. avoid the use of decimals other than '.5' and provide a (rounded) more easily readable years – months – days representation of the durations.

Summary of the MAH's response

Alexion acknowledges the Agency's feedback and has updated **Sections 4.8 Undesirable effects** and **5.1 Pharmacodynamic properties** of the EU SmPC as recommended by the EMA.

Assessment of the MAH's response

Overall the MAH has now provided more rounded numbers as requested.

Conclusion

Issue Resolved.

8. The MAH is requested to move the column with frequency terms to the utmost right side of the adverse event frequency table (SOC | Preferred Term | Frequency) in section 4.8 as to exclude any chance of misinterpretation whether the frequency refers to the SOC or the preferred terms.

Summary of the MAH's response

Alexion agrees to the requested format change and has updated the adverse drug reaction (ADR) tables in **Section 4.8 Undesirable effects** accordingly.

Conclusion

Issue resolved

9. ISS tables 14.3.1.23.2.1.2 and 14.3.1.23.1.1.1 are the basis for the SmPC's ADR frequency tables, but certain individual data listings make reference of events that were considered possibly related to treatment but which were not included in the aforementioned tables (and in some cases have been actively removed from the SmPC frequency table in the timeframe between the last renewal procedure and the current type II dossier). The Applicant is asked to confirm whether this is due to the fact that during the ADR identification in the aggregated safety data Preferred Terms were not included for further review if they were reported in 1 patient only.

Summary of the MAH's response

A review of all the aggregated safety data was conducted for identification of adverse drug reactions (ADRs) and the Applicant confirms that Preferred Terms that were only reported in 1 patient were not included in the ADR tables.

During the identification of ADRs, the Applicant assessed relatedness at the Applicant-level based on the aggregate review of data, taking into account the population treated and underlying disease, rather than

relying solely on the individual patient investigator assessment at the time of each adverse event. Following medical assessment, some terms were considered as not related to KANUMA and most likely related to underlying disease, comorbid conditions or expected within the treated population demographic. The Investigator's causality assessment, as included in the integrated summary of safety (ISS) listings displaying related (or possibly related) terms, was considered as one aspect of the Applicant's assessment for ADR identification. Therefore, Preferred Terms reported in more than 1 patient that did not meet the definition of an ADR based on Sponsor's medical judgement were not included or removed from the ADR tables.

Assessment of the MAH's response

The Applicant confirmed the underlying reasoning for the 1-patient cut-off rule.

Conclusion **Issue resolved**