Summary Report of Benefit-Risk Assessment

KANUMA CONCENTRATE FOR SOLUTION FOR INFUSION 2 MG/ML

NEW DRUG APPLICATION

Active Ingredient	Sebelipase alfa
Product Registrant	AstraZeneca Singapore Pte Ltd
Product Registration Number	SIN17346P
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A INTRODUCTION

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

The active substance, sebelipase alfa, is a recombinant human lysosomal acid lipase that catalyses the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids, thereby restoring lipid metabolism and reducing substrate accumulation in lysosomes.

Kanuma is available as a concentrate for solution for infusion containing 2 mg/mL of sebelipase alfa. Other ingredients in the vial are trisodium citrate dihydrate, citric acid monohydrate, human serum albumin and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

Both the drug substance, sebelipase alfa, and the drug product, Kanuma concentrate for solution for infusion 2 mg/ml, are manufactured at Alexion Pharma International Operations Limited (Alexion Athlone Manufacturing Facility), Monksland, Ireland. The manufacturer is compliant with Good Manufacturing Practice (GMP) standard.

Drug substance:

The drug substance is expressed in transgenic chicken and purified from the egg whites of transgenic hens. The eggs are defined as the starting material, and adequate controls are in place for adventitious agents and viral safety. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 2 - 8°C with a shelf life of 12 months. The packaging is either 5 L or 10 L single use, disposable gamma-irradiated polyethylene storage containers.

Drug product:

The manufacturing process involves pooling and mixing of the formulated bulk drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

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Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored between 2 - 8°C. The container closure system is a 10R type I glass vial with 20 mm grey bromobutyl fluoropolymer coated rubber stopper, sealed with a 20 mm aluminium seal with plastic flip-off cap. Chemical and physical in-use stability after dilution has been demonstrated for up to 24 hours at 2 - 8°C, or up to 12 hours below 25°C.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of sebelipase alfa in the treatment of LAL deficiency in children and adults was based on the pivotal Phase III study LAL-CL02 and supportive studies LAL-CL01/LAL-CL04 and LAL-CL06, while its efficacy in the treatment of infants with LAL deficiency was supported by studies LAL-CL03 and LAL-CL08.

Efficacy in children and adults with LAL deficiency

Study LAL-CL02 was a Phase III, multicentre, randomised, double-blind, placebo-controlled study in patients aged 4 to 58 years with LAL deficiency. The study consisted of a screening period of up to 6 weeks, a 20-week double-blind treatment period, and an open-label period of up to 234 weeks. Patients in the placebo group could crossover to receive sebelipase alfa in the open-label period.

The study included patients with a confirmed diagnosis of LDL deficiency by dried blood spot testing at screening and elevated alanine aminotransferase (ALT) levels (≥1.5× ULN on 2 consecutive screening measurements obtained at least 1 week apart). The study excluded patients with severe hepatic dysfunction (Child-Pugh Class C), previous haematopoietic or liver transplant and patients who received high-dose corticosteroids (acute or chronic) within 26 weeks prior to randomisation.

Patients were randomised in a 1:1 ratio to receive sebelipase alfa 1 mg/kg or placebo via intravenous infusion every other week (qow) for 20 weeks. Dose modifications were not permitted during the double-blind treatment period. Patients with clinical progression were transitioned to open-label treatment.

In the open-label extension phase, all patients received sebelipase alfa 1 mg/kg qow, with dose escalation to 3 mg/kg qow allowed for inadequate response and dose reduction to 0.35 mg/kg qow permitted for tolerability issues.

The primary endpoint was the proportion of patients who achieved ALT normalisation at Week 20. Secondary endpoints included changes from baseline to Week 20 in LDL-C (low-density lipoprotein cholesterol), non-HDL-C (high-density lipoprotein cholesterol), aspartate

aminotransferase (AST) normalisation, triglycerides, HDL-C, liver fat content, liver histopathology, and liver volume.

Of the 66 patients randomised (36 patients in the sebelipase alfa group and 30 patients in the placebo group), the mean age was 16.6 years (range 4.7 to 58.8 years). A total of 36% were patients aged <12 years, 35% were adolescents aged 12 to <18 years, and 29% were adults aged 18 years and over. Genetic testing showed that 85% of patients carried at least one copy of the c.894G>A exon 8 splice junction mutation (32% homozygotes, 53% compound heterozygotes). The median age at onset of LAL-related abnormalities was 5.0 years. All patients had ALT >1.5× ULN. The majority of patients (58%) had LDL-C >4.9 mmol/L at study entry, and 24% of these patients (with LDL-C >4.9 mmol/L) were on lipid-lowering medicines. Among the 32 patients who underwent liver biopsy, 100% had fibrosis and 31% had cirrhosis.

ALT normalisation at Week 20 was achieved in 31% of patients in the sebelipase alfa group as compared with 7% in the placebo group (p=0.0271), which was statistically significant and clinically relevant. Secondary endpoints demonstrated statistically significant improvements in AST normalisation (42% vs 3%, p=0.0003), LDL-C reduction (−28.42% vs −6.25%, p<0.0001), non-HDL-C reduction (−27.97% vs −6.94%, p<0.0001), triglyceride reduction (−25.45% vs −11.14%, p=0.0375), HDL-C increase (+19.57% vs −0.29%, p<0.0001), and liver fat content reduction (−31.98% vs −4.21%, p<0.0001). Improvements in liver histology and liver volume were observed but did not reach statistical significance.

Summary of efficacy results at Week 20 in Study LAL-CL02

Efficacy endpoint	**Sebelipase alfa (N=36)**	**Placebo (N=30)**	**p value**
Primary Endpoint			
Normalisation of ALT, n (%)	11 (31)	2 (7)	0.0271
Secondary Endpoints			
Normalisation of AST, n (%)	15 (42)	1 (3)	0.0003
LDL-cholesterol, mean % change from baseline	-28.42	-6.25	<0.0001
Non-HDL-cholesterol, mean % change from baseline	-27.97	-6.94	<0.0001
Triglycerides, mean % change from baseline	-25.45	-11.14	=0.0375
HDL-cholesterol, mean % change from baseline	19.57	-0.29	<0.0001
Liver fat content, mean % change from baseline	(n=32) -31.98	(n=25) -4.21	<0.0001

During the open-label extension phase, sustained improvements in liver enzymes, lipid parameters, liver volume, and liver fat content were observed with continued sebelipase alfa treatment. Among patients who received sebelipase alfa from study initiation, the proportion achieving normalisation of ALT and AST increased from 41% and 58% at Week 22 to 56% and 69%, respectively, at the last open-label assessment. Patients who switched from placebo to sebelipase alfa demonstrated comparable improvements, with ALT and AST normalisation observed in 37% and 62%, respectively. Beneficial effects on dyslipidaemia were similarly sustained, with substantial proportions of patients in both groups achieving normalisation of LDL-C, triglyceride, and HDL-C levels.
Reductions in liver volume were maintained over time, with median reduction from baseline of 27.2% and 20.1% in patients who continued sebelipase alfa and those who switched from placebo, respectively, at the last open-label assessment. Improvements in liver fat content were preserved, with median reductions from baseline of 19.1% and 7.8%, respectively.

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Overall, the findings indicate that long-term sebelipase alfa treatment provides durable improvements in biochemical, lipid, and hepatic disease parameters.

Supportive studies

Study LAL-CL01 was a Phase I/II, open-label, dose-escalation study in adult patients with liver dysfunction due to LAL deficiency. Upon completing the 4-dose schedule (0.35 mg/kg once a week (qw), 1 mg/kg qw, or 3 mg/kg qw) in LAL-CL01, patients had a treatment-free period (which ranged from 9 to 28 weeks) before they entered Study LAL-CL04, which is a Phase II, open-label, extension study designed to assess the long-term safety, tolerability, and efficacy of sebelipase alfa at 2 dose levels (1 and 3 mg/kg qow) for up to 5 years.

A total of 9 adult patients enrolled in LAL-CL01, and 8 of these also enrolled in the LAL-CL04 extension study. A total of 5 patients received 1 mg/kg qow and 3 patients received 3 mg/kg qow.

Early reductions in serum transaminases were observed and sustained throughout treatment, with median ALT and AST decreases of −43.0 U/L and −16.0 U/L, respectively, at Week 260. Improvements in lipid parameters were also evident, including sustained reductions in LDL-C, triglycerides, and total cholesterol, and increases in HDL-C. Imaging data demonstrated consistent reductions in liver volume and liver fat content across both dose cohorts. These findings support the long-term efficacy of sebelipase alfa in improving hepatic and lipid biomarkers in adults with LAL deficiency.

Study LAL-CL06 was a Phase II, multicentre, open-label study evaluating sebelipase alfa in 31 patients aged 3 to 55 years with LAL deficiency. The study was designed to include patients with advanced disease or prior interventions (e.g., haematopoietic stem cell or liver transplantation) who were ineligible for previous placebo-controlled trials. The study comprised a screening period of up to 45 days, a 96-week treatment phase, and a 48-week extension, with a median treatment duration of 33.15 months (range 14 to 33.5 months).

A total of 28 patients completed the 96-week treatment period (1 patient discontinued treatment at Week 61 due to withdrawal of consent, 1 patient at Week 64 due to pregnancy and 1 patient at Week 76 due to transition to commercial therapy). Twenty-five of the 28 patients who completed the 96-week treatment period continued to receive treatment with sebelipase alfa during the extended treatment period.

All 31 patients received sebelipase alfa at a starting dose of 1 mg/kg qow. Thirteen of the 31 patients received dose escalations as allowed by the study protocol. A total of 11 of these 13 patients had an initial dose escalation from 1 mg/kg qow to 3 mg/kg qow, and 4 of these patients had a further dose escalation to 3 mg/kg qw.

Baseline hepatic dysfunction was characterised by elevated transaminases, hepatosplenomegaly, and abnormal liver histopathology. ALT and AST levels exceeded 1.5× ULN in 58% and 48% of patients, respectively, with higher transaminase levels observed in younger age groups. Dyslipidaemia was prevalent, with elevated triglycerides (58%), LDL-C (63%), and reduced HDL-C (71%).

Treatment with sebelipase alfa resulted in sustained reductions in ALT (−40.3 U/L; −32.0%) and AST (−42.2 U/L; −34.2%) by Week 144. Improvements in lipid parameters were also observed, including reductions in LDL-C (−54.2 mg/dL; −31.2%), triglycerides (−47.5 mg/dL;

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−19.1%), and non-HDL-C (-63.7 mg/dL; −30.3%), alongside an increase in HDL-C (+10.2 mg/dL; +39.7%) at Week 144.

Magnetic resonance imaging (MRI) assessments demonstrated reductions in liver volume and fat content, with mean liver fat content decreasing by −0.940% at Week 96 and −0.842% at Week 144. Spleen volume also decreased, although spleen fat content remained unchanged. Histopathological analysis revealed stabilisation or improvement in liver fibrosis and steatosis, with 75% of patients showing no progression or improvement in Ishak scores by Week 48. Quantitative morphometry indicated reductions in collagen and macrophage infiltration, while portal and lobular inflammation remained largely unchanged.

Overall, Study LAL-CL06 demonstrated that sebelipase alfa resulted in clinically meaningful improvements in multiple LAL deficiency-related abnormalities, including decreases in serum transaminases, improvements in serum lipid profiles and liver volume, fat content and histopathology, including those with advanced disease.

Efficacy in infants with LAL deficiency

Study LAL-CL03 was a Phase II/III, open-label, dose-escalation study in 9 children aged 1 to 6 months with LAL deficiency-related growth failure before 6 months of age. Patients also had rapidly progressive liver disease and severe hepatosplenomegaly. The study consisted of a screening period of up to 3 weeks, a treatment period of up to 5 years, and a follow-up visit 30 days after the last dose of sebelipase alfa.

The starting dose was 0.35 mg/kg weekly, which could be escalated to 1 mg/kg and then to 3 mg/kg based on clinical response.

Efficacy was assessed by comparing the survival rate of sebelipase alfa-treated patients beyond 12 months of age with a historical cohort of untreated infants presenting with LAL deficiency with similar clinical characteristics. Secondary endpoints included growth parameters and hepatic enzyme changes.

Sebelipase alfa treatment demonstrated significant survival benefit in infants with LAL deficiency, with 67% (95% CI: 29.9, 92.5) of treated patients (6/9) surviving beyond 12 months compared to 0% (95% CI: 0, 16.1) survival in the historical cohort of 21 untreated patients who died by 8 months of age. Of the 6 survivors, 5 remained alive at study conclusion at ages ranging from 58.1 to 67.0 months, whilst one patient died at 15.0 months. The three patients who did not reach the 12-months survival endpoint died between 2.8 and 4.3 months of age and had received between 1 to 4 sebelipase alfa infusions.

Growth parameters showed marked improvement in all 6 patients surviving beyond Week 4. Weight-for-age percentiles improved substantially from a baseline mean of 12.74% to 43.17% at Week 240. The prevalence of malnutrition decreased considerably, with baseline rates of underweight (2/9; 22%), stunting (4/8; 50%), and wasting (2/8; 25%) improving such that by Week 48, only one patient met stunting criteria and none met criteria for underweight or wasting.

Hepatic function demonstrated rapid and sustained improvement. Mean ALT and AST levels decreased by 43.50 U/L and 45.25 U/L, respectively, from baseline to Week 240. Serum albumin levels increased from 26.90 g/L to 31.98 g/L over the same period. Dose escalation to 3 mg/kg weekly was associated with additional improvements in weight gain, lymphadenopathy, and serum albumin levels.

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Serum ferritin levels normalised rapidly in all 6 surviving patients with elevated baseline values, with median reductions of 122.0 µg/L by Week 1 and 269.3 µg/L by Week 6. Time to normalisation ranged from 1 to 13 weeks, correlating with baseline ferritin levels.

Haematological parameters improved significantly, with 100% (6 out of 6) of patients who met the 12-months survival endpoint achieving transfusion-free haemoglobin normalisation, including all 3 patients with baseline anaemia. Two patients maintained sustained transfusion-free haemoglobin normalisation from Week 6 through final assessment.

These findings demonstrated that sebelipase alfa produces clinically meaningful improvements across the multi-systemic manifestations of infantile LAL deficiency, including enhanced survival, growth normalisation, hepatic function restoration, and correction of haematological abnormalities.

Supportive study

Study LAL-CL08 was a Phase II, multicentre, open-label, supportive study evaluating sebelipase alfa in 10 infants aged 8 months and below with confirmed rapidly progressive LAL deficiency requiring urgent intervention. The median patient age was 2.83 months (range 0.5 to 4.1 months), with 80% completing the study and a median treatment duration of 33.9 months (range 0.76 to 36.80 months).

Survival outcomes demonstrated substantial benefit, with 90% of patients surviving to 12 months, 80% to 18 to 24 months, and 75% to 36 months of age. Two patients died at age 4.9 and 13.8 months from causes deemed unrelated to treatment, specifically pericardial effusion and sepsis, respectively. The remaining 8 patients survived through study completion with final ages ranging from 27.76 to 40.57 months.

Treatment commenced with sebelipase alfa 1 mg/kg weekly in all patients. Nine patients surviving beyond Week 4 received dose escalation to 3 mg/kg weekly, with 7 subsequently escalated to 5 mg/kg weekly per protocol. One patient required further escalation to 7.5 mg/kg weekly. Two patients underwent successful transplantation procedures (bone marrow transplant and haematopoietic stem cell transplant) with subsequent dose reductions.

Growth parameters showed marked improvement, with weight-for-age percentile increases evident by Week 24. All 8 patients with low baseline weight-for-age percentiles who survived through study completion demonstrated sustained improvement. Height and weight increased gradually, with consistent improvements in weight-for-height Z-scores from Week 24 onwards, reaching a median change of 3.07 at Week 144, representing a clinically meaningful improvement in nutritional status and catch-up growth.

Hepatic function parameters improved substantially across the study population. Median changes from baseline to final assessment included AST reduction of 34.5 U/L, gamma-glutamyl transferase (GGT) reduction of 66.67 IU/L, total bilirubin reduction of 63.64 µmol/L, and serum albumin increase of 33.33 g/L. Normalisation rates among patients with abnormal baseline values were 50% for AST, 83% for GGT, 100% for total bilirubin, and 50% for albumin.

Haematological parameters demonstrated significant improvement. Seven of 10 patients achieved short-term transfusion-free haemoglobin normalisation with an estimated median time of 5.5 months. Platelet counts increased with a median change of 156.0 × 10^9/L from baseline, with normalisation occurring in 3 of 4 patients presenting with baseline

thrombocytopenia. Serum ferritin levels, available for 2 patients, showed rapid reductions of 96.8 and 95.4 µg/L, respectively.

Three patients with whole-gene deletions involving *LIPA* developed persistent high-titre neutralising antibodies that were associated with attenuation of treatment response. While all three patients survived beyond 12 months of age, diminished efficacy was reflected by impaired growth trajectories and variable responses in selected hepatic parameters, necessitating dose escalation and additional interventions, including immunomodulatory therapy and/or hematopoietic stem cell transplantation or bone marrow transplant.

Overall, the supportive study corroborated the efficacy and safety profile established in the pivotal trial, demonstrating consistent improvements across multiple disease manifestations in this critically ill infant population.

Dose optimisation

In studies LAL-CL02 and LAL-CL06 in children and adults with LAL deficiency, 23 patients underwent dose escalation, primarily in response to worsening serum transaminases, deterioration in lipid parameters, or reduced weight gain in paediatric patients. Most dose escalations to 3 mg/kg qow were followed by improvements in serum transaminases and lipid parameters that were maintained through the end of study. A total of 4 patients subsequently underwent further escalation to 3 mg/kg qw to optimise disease control.

In studies LAL-CL03 and LAL-CL08 in infants with LAL deficiency, 15 infants with rapidly progressive disease required dose escalation due to suboptimal clinical response. Dose escalation, including increases to 5 mg/kg qw, was generally associated with clinically meaningful improvements in growth, as reflected by increases in weight-for-age percentile, as well as improvements in serum transaminases and lipid parameters.

Taken together, these findings support dose individualisation in optimising treatment response in patients with LAL deficiency.

Integrated analysis of efficacy

The integrated analysis of efficacy results observed across the submitted trials were consistent with the individual studies, with significant improvements in survival for infants, and in key parameters of LAL deficiency such as serum transaminases, lipid profiles, growth and liver size across the paediatric and adult populations.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of sebelipase alfa was based on the integrated safety analysis from a total of 125 patients (19 infants, 69 children and 37 adults) with LAL deficiency enrolled across 6 clinical studies (LAL-CL01, LCL-CL02, LCL-CL03, LAL-CL04, LAL-CL06, and LAL-CL08).

Safety in children and adults with LAL deficiency

Among children and adults, 85% of patients received sebelipase alfa for at least 130 weeks, with a cumulative exposure of 348.09 patient-years (PYs) and maximum individual exposure duration of 60.48 months (5.04 years).

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Across all studies conducted in children and adults, 102 patients received sebelipase alfa 1 mg/kg qow at a median (min, max) duration of exposure of 33.199 months (range 5.98 to 59.14 months), with 292.55 PYs of exposure. Further, 26 patients received 3 mg/kg qow at a median (min, max) duration of exposure of 18.628 months (range 2.83 to 58.51 months), with 49.09 PYs of exposure.

Overall, the safety profile in terms of frequencies of any adverse event (AE) was similar in patients treated at 1 mg/kg qow and at 3 mg/kg qow.

Overview of safety profile in children and adults – Pooled Safety Set 1

AE	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 AE	9 (100)	65 (98)	31 (100)	105 (99)
Treatment-related AE	5 (56)	22 (33)	10 (32)	37 (35)
Serious AE (SAE)	1 (11)	13 (20)	10 (32)	24 (23)
Treatment-related SAE	0	2 (3)	1 (3)	3 (3)
Discontinuations due to AE	0	0	0	0
Deaths due to AE	0	0	0	0

Across the clinical studies in children and adults, 105 of 106 patients (99%) experienced at least one AE, with the majority (95/106; 90%) experiencing events within the System Organ Class (SOC) of Infections and Infestations. The most frequently reported AEs were nasopharyngitis (49%), headache (44%), and pyrexia (42%), with most events being mild to moderate in severity. Severe AEs occurred in 13% of patients, the most frequent of which were abdominal pain, gastrointestinal haemorrhage, and hyperaemia, each reported in 2 patients (2%). Treatment-related AEs occurred in 35% of patients, with urticaria (7%), abdominal pain (6%), and fatigue (5%) being most common. The overall safety profile of sebelipase alfa was generally comparable between children (n=69) and adult (n=37) patients.

During or within 4 hours post-infusion, 54% of patients experienced AEs, with urticaria (6%) being the most frequent event occurring in ≥5% of patients, followed by pyrexia, abdominal pain, nausea, and vitamin D deficiency (5% each). Between 4 and 24 hours after infusion, 70% of patients experienced at least one AE, with headache (12%), nasopharyngitis (11%), and diarrhoea (10%) being most common.

SAEs were reported in 23% of patients, with no single event affecting more than 3 individuals. Treatment-related SAEs occurred in 3% of patients, including one case of anaphylactic reaction. All treatment-related SAEs resolved without sequelae, with no fatal events or study discontinuations reported. Nine patients tested positive for anti-drug antibodies (ADA), with two developing neutralising antibodies, though no clear relationship was observed between antibody development and hypersensitivity reactions or suboptimal clinical response.

Infusion-associated reactions occurred in 18% of patients, the most frequent of which was urticaria occurring in 7 patients (7%). Two patients experienced serious signs and symptoms consistent with anaphylaxis during infusion, and serious hypersensitivity reactions were reported in 2% of patients. No infusion-associated reactions occurred during ADA-positive periods.

Safety in infants with LAL deficiency

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The safety database of sebelipase alfa in infants comprised 19 patients, with 68% receiving sebelipase alfa for at least 52 weeks and 47% for at least 156 weeks. The median exposure duration was 35.61 months (range 0.03 to 60.19 months) with a cumulative exposure of 47.73 PYs. Seventeen patients received 1 mg/kg weekly (qw) with a median exposure of 2.267 months (range 0.23 to 19.84 months; 6.08 PYs), of which 15 patients also received 3 mg/kg weekly with a median exposure of 15.409 months (range 0.92 to 54.54 months; 25.83 PYs).

Overview of safety profile in infants – Pooled Safety Set 2

AE	LAL-CL03 (N=9) n (%)	LAL-CL08 (N=10) n (%)	Pooled Safety Set 2 (N=19) n (%)
Any AE	9 (100)	10 (100)	19 (100)
Treatment-related AE	6 (67)	8 (80)	14 (74)
SAE	9 (100)	10 (100)	19 (100)
Treatment-related SAE	1 (11)	5 (50)	6 (32)
Discontinuations due to AE	0	0	0
Deaths due to AE	4 (44)	2 (20)	6 (32)

No apparent dose-dependent safety signal was identified across the various dosage regimens. The incidence and pattern of AEs, SAEs, treatment-related SAEs, and infusion-associated reactions were generally comparable across dose groups, and no patient required dose reduction due to poor tolerability. However, conclusions regarding dose-response relationships were limited by the small sample sizes and the inclusion of patients in multiple dose categories following dose escalation.

Overview of AEs 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 AE	7 (88)	15 (88)	15 (100)	3 (100)	9 (100)	1 (100)	19 (100)
Treatment-related AE	1 (13)	9 (53)	12 (80)	2 (67)	7 (78)	1 (100)	14 (74)
SAE	2 (25)	14 (82)	14 (93)	2 (67)	9 (100)	1 (100)	19 (100)
Treatment-related SAE	0	3 (18)	4 (27)	0	2 (22)	1 (100)	6 (32)
Discontinuations due to AE	0	0	0	0	0	0	0
Deaths due to AE	2 (25)	2 (12)	1 (7)	0	1 (11)	0	6 (32)

All infant patients (19/19; 100%) experienced AEs, primarily in the Gastrointestinal disorders and Investigations SOCs (each in 18/19 patients; 95%). The most common events were diarrhoea, vomiting, and pyrexia (79% each), followed by gastroenteritis and cough (58% each), rhinitis, diaper dermatitis, and tachycardia (53% each).

During infusion and within 4 hours post-infusion, 79% of patients experienced AEs, most frequently pyrexia (63%), vomiting and tachycardia (47% each), and urticaria (32%). Between 4 and 24 hours post-infusion, 95% experienced at least one event, though no clear pattern emerged in relation to the type of AEs observed. Severe AEs affected 84% of patients, most commonly tachycardia (21%), anaemia (16%), and respiratory distress (16%), which were considered primarily attributable to the underlying disease burden or procedure-related complications commonly observed in this critically ill infant population.

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Treatment-related AEs occurred in 74% of patients, most commonly pyrexia (58%), tachycardia (47%), urticaria (37%), and vomiting (32%). During or within 4 hours of infusion, 63% experienced treatment-related events, whilst 47% experienced such events between 4 and 24 hours post-infusion, with pyrexia being most frequent (21%).

All patients experienced at least one SAE, with 74% of patients reporting a SAE in the SOC infections and infestations, which were generally not treatment-related. SAEs reported in >25% of patients included pyrexia (47%), gastroenteritis and vomiting (42% each), diarrhoea (37%), and tachycardia (32%). Treatment-related SAEs occurred in 32% of patients, most commonly tachycardia (26%), pyrexia, respiratory distress, and urticaria (16% each). Six patients (32%) died during the studies, with no deaths considered treatment-related.

Infusion-associated reactions occurred in 68% of patients (13/19), predominantly pyrexia and tachycardia (47% each), urticaria (37%), and vomiting (32%). Serious hypersensitivity reactions, such as anaphylactic reaction and suspected anaphylaxis, were reported in 3 of the 19 infants (16%) treated in the clinical studies.

Anti-drug antibodies developed in 10 patients, with ADA-positive patients experiencing higher AE rates than ADA-negative patients. Treatment-related events affected 80% of ADA-positive patients, most commonly pyrexia (70%), tachycardia (60%), urticaria, and agitation (40% each), though no anaphylactic reactions occurred in this subset.

Three patients with homozygous *LIPA* gene deletions developed inhibitory antibodies and demonstrated suboptimal clinical responses to sebelipase alfa. This observation is biologically plausible, as a dual whole-gene deletion involving both the *LIPA* and *Cholesterol 25-Hydroxylase* genes may alter the underlying disease phenotype and increase the risk of clinically relevant immunogenic responses that adversely affect treatment efficacy.

Overall, the clinical development programme of sebelipase alfa remains limited by the small sample size, reflecting the rarity of the disease. The high incidence of adverse events observed across the clinical programme was attributed to the underlying disease and its associated complications. In contrast, treatment-related adverse events were primarily hypersensitivity and infusion-associated reactions, consistent with the known safety profile of enzyme replacement therapies.

Appropriate risk mitigation strategies, including preventive measures and systematic monitoring protocols for hypersensitivity reactions, have been incorporated into the product labelling. There was no apparent impact of dose escalation on the safety profile based on the data presented.

E ASSESSMENT OF BENEFIT-RISK PROFILE

LAL deficiency is a rare and life-threatening autosomal recessive monogenic disorder characterised by a marked decrease in LAL activity. Historically, treatment options across all age groups were limited to supportive care and management of disease complications. Current treatment options for infants are limited to a variety of supportive therapies, including nutritional support, blood transfusions, and albumin. In children and adults, dietary modification, lipid-lowering therapies, and management of hepatic complications may mitigate disease manifestations, but do not address the underlying enzyme deficiency and targeted therapies

remain lacking. Sebelipase alfa replaces the missing or deficient enzyme, thereby resulting in reduction of the accumulated substrates and restoration of normal lipid metabolism.

The efficacy of sebelipase alfa in LAL deficiency was demonstrated in the pivotal placebo-controlled Study LAL-CL02 conducted in children and adults, which showed clinically meaningful improvements in serum transaminases (ALT normalisation 31% vs 7%, p=0.0271; AST normalisation 42% vs 3%, p=0.0003), lipid profiles (LDL-C reduction −28.42% vs −6.25%, p<0.0001; non-HDL-C reduction −27.97% vs −6.94%, p<0.0001; triglyceride reduction −25.45% vs −11.14%, p=0.0375; HDL-C increase +19.57% vs −0.29%, p<0.0001) and liver fat content (−31.98% vs −4.21%, p<0.0001) as compared to placebo at Week 20. In the open-label phase where patients from the placebo arm were switched to active treatment, efficacy results seen in these patients were similar to those observed in patients receiving the active treatment arm during the double-blind phase.

The supportive Studies LAL-CL01/04 and LAL-CL06 demonstrated efficacy outcomes consistent with those observed in the pivotal study LAL-CL02 and provided support for the maintenance of treatment effects during longer-term follow-up.

Infants with LAL deficiency enrolled in LAL-CL03 and LAL-CL08 demonstrated significant improvements in survival, with 67% living to or beyond 12 months of age. Growth indicators also improved in the majority of patients, which was clinically relevant as LAL deficiency is associated with stunted growth and failure to thrive. The clinical importance of these findings was further corroborated by the results of the natural history study, in which untreated patients did not survive beyond 6 months of age.

While the clinical dataset supporting the stepwise up-titration was limited, given the small sample sizes of the clinical studies due to the rarity of the disease, this was nonetheless considered acceptable given that the dosing is individualised and guided by each patient's clinical response, with close monitoring by the treating physician.

The safety exposure of sebelipase alfa was overall limited by the small sample size, reflecting the rarity of the disease. The safety profile of sebelipase alfa was mainly characterised by hypersensitivity reactions such as infusion-related reactions and hypersensitivity events. Five out of 125 (4%) patients treated with sebelipase alfa, including 3 of 19 (16%) infants and 2 of 106 (2%) children and adults, experienced serious signs and symptoms consistent with anaphylaxis to sebelipase alfa. The package insert has included guidance on the monitoring and management of hypersensitivity reactions. A total of 19/125 (15.0%) patients tested positive for anti-drug antibodies (ADA), with 11 (58%) patients also detected positive for neutralising antibodies. For children and adult patients, ADA positivity was transient with generally low titres of ADAs reported. Persistence of ADA positivity was observed for all 10 infants and persistence of high titre ADAs was observed for 3 of the 10 infants. Overall, there was no clear relationship between development of ADAs or neutralising antibodies and associated hypersensitivity reactions or suboptimal clinical response.

Dose optimisation in patients with a suboptimal treatment response at the initial starting dose demonstrated that higher doses of sebelipase alfa were generally well-tolerated and associated with improved clinical outcomes in both paediatric and adult patients.

The totality of clinical evidence demonstrated that sebelipase alfa improved clinical outcomes for patients with LAL deficiency. The benefit-risk balance was considered favourable when weighed against the risk, which were primarily infusion-related, taking into account the

significant clinical benefits observed across all age groups and its place in therapy for this rare and life-threatening condition.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Kanuma for long-term enzyme replacement therapy in patients with LAL deficiency was deemed favourable and approval of the product registration was granted on 30 September 2025.

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KANUMA®
(sebelipase alfa)

1. NAME OF THE MEDICINAL PRODUCT

KANUMA concentrate for solution for infusion 2 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 2 mg sebelipase alfa. One vial of 10 mL contains 20 mg sebelipase alfa.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear to slightly opalescent, colorless to slightly colored solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KANUMA is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.

4.2 Posology and method of administration

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).

Patients with rapidly progressive LAL Deficiency presenting within the first 6 months of life

The recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL Deficiency is 1 mg/kg or 3 mg/kg administered as an intravenous (IV) infusion once weekly (qw), depending on the clinical status of the patient. Dose escalations should be considered based on suboptimal response to clinical and biochemical criteria, including, 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.
- a further dose escalation up to 5 mg/kg should be considered in case of persistent suboptimal clinical response.

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. Doses higher than 7.5 mg/kg have not been studied.

Pediatric and adult patients with LAL Deficiency

The recommended dose in children and adults presenting with LAL Deficiency is 1 mg/kg administered as an IV infusion once every other week (qow). Dose escalation to 3 mg/kg once every other week should be considered based on suboptimal response to clinical and biochemical criteria, including, e.g., poor growth persistent or deteriorating biochemical markers (e.g., parameters of liver injury (ALT, AST), parameters of lipid metabolism (TC, LDL-c, HDL-c, TG), persistent or worsening organomegaly, and persistent worsening of other symptoms (e.g., gastrointestinal symptoms).

Special populations

Elderly population (≥ 65 years old)

The safety and efficacy of KANUMA in patients older than 65 years have not been evaluated and no alternative dosage regimens can be recommended for these patients.

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 5.1 and Section 5.2.

Paediatric population

Eighty-eight of 125 patients (70%) who received KANUMA during clinical studies were in the paediatric and adolescent age range (1 month up to 18 years) at the time of first dose. Currently available data are described in Section 4.8 and Section 5.1.

Method of administration

KANUMA is for intravenous (IV) use only.

The total volume of the infusion should be administered over approximately 2 hours. A 1-hour infusion may be considered for those patients receiving the 1 mg/kg dose after patient tolerability is established. The infusion period may be extended in the event of dose escalation. KANUMA should be administered through a 0.2 μm filter.

For instructions on the preventive measures and monitoring of hypersensitivity reactions, see Section 4.4.

For instructions on dilution of the medicinal product before administration, see Section 6.5.

4.3 Contraindications

Life-threatening hypersensitivity (anaphylactic reaction) to the active substance when attempts to rechallenge are unsuccessful, or to egg or any of the excipients listed in section 6.1, (see section 4.4).

4.4 Special warnings and special precautions for use

Hypersensitivity reactions including anaphylactic reactions or anaphylaxis

Hypersensitivity reactions, including anaphylactic reactions or anaphylaxis, have been reported in KANUMA-treated patients (see Section 4.8). Therefore, appropriate medical support must be readily available when sebelipase alfa is administered. If these reactions occur, immediately stop the KANUMA infusion and initiate appropriate medical treatment. The current medical standards for emergency treatment are to be followed.

The risks and benefits of re-administering KANUMA following a severe reaction should be considered. For patients who have experienced allergic reactions during infusion, caution should be exercised upon re-administration.

The management of hypersensitivity reactions may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. If interrupted, the infusion may be resumed at a slower rate with increases as tolerated. Pretreatment with antipyretics and/or antihistamines may prevent subsequent reactions in those cases where symptomatic treatment was required.

The medicinal product may contain traces of egg proteins. Patients with known egg allergies were excluded from clinical studies. Consider the risks and benefits of treatment with KANUMA for patients with known egg allergies.

Following the first sebelipase alfa infusion, including the first infusion after a dose escalation, patients should be observed for 1 hour in order to monitor for any signs or symptoms of anaphylaxis or a severe hypersensitivity reaction.

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 antibody 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.

During clinical trials, 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).

4.5 Interaction with other medicinal products and forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data from the use of sebelipase alfa in pregnant women to determine if sebelipase alfa exposure during pregnancy poses any risk to the mother or foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3). As a precautionary measure, it is preferable to avoid use of KANUMA during pregnancy.

Breast-feeding

There are no data from studies in breast-feeding women. It is not known whether sebelipase alfa is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from KANUMA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of sebelipase alfa on fertility. Animal studies show no evidence of impaired fertility (see Section 5.3).

4.7 Effect on ability to drive and use machines

No specific studies have been conducted to assess the direct effect of sebelipase alfa on the ability to drive and use machines. However, adverse effects of sebelipase alfa include dizziness which could affect the ability to drive or use machines (see Section 4.8).

4.8 Undesirable effects

Summary of safety profile

The data described below reflect exposure to KANUMA in 125 patients who received KANUMA at doses ranging from 0.35 mg/kg once every other week (qow) to 7.5 mg/kg once weekly (qw) in clinical studies (see Section 5.1), with a treatment duration range from 0.03 to 60.48 months (5.04 years). Patients were between 0.5 month and 59 years old (70% were < 18 years old) at the time of first treatment with KANUMA, and included 68 males and 57 females. In infants, the safety of KANUMA was evaluated in an open-label, single-arm, Phase 2/3 study (Study LAL CL03; doses of 0.35, 1, 3 and 5 mg/kg qw) and in an open-label, Phase 2 study (Study LAL-CL08; starting dose of 1 mg/kg qw with potential sequential dose escalations to 3 mg/kg qw, 5 mg/kg qw, and 7.5 mg/kg qw). In children and adults, the safety of KANUMA was evaluated in a randomised placebo-controlled Phase 3 study (Study LAL CL02; doses of 1 and 3 mg/kg qow);an open-label, single-arm, Phase 2 study in adults (LAL-CL01/LAL-CL04; dosage of 0.35, 1, and 3 mg/kg qw for 4 weeks followed by a period when patients were off treatment with KANUMA before entering an extension period during which patients resumed the previous dosage for another 4 weeks and then switched to a regimen of 1 or 3 mg/kg qow) and an open- label, single-arm, Phase 2 study in children and adults (≥8 months) (LAL-CL06; dose 1 mg/kg qow with potential dose escalation up to 3 mg/kg qw for clinical progression).

Overall, 102/106 (96.2%) children and adult patients have received sebelipase alfa at a dosage regimen of 1 mg/kg qow, with a median duration of exposure of 33.199 months (5.98, 59.14 months). The majority of these 102 patients were from Study LAL-CL02 (66/102, 64.7%). The median duration of exposure for the 19 infants enrolled in clinical trials was 35.614 months (0.03, 60.19 months). A majority (17/19, 89.5%) of infants received sebelipase alfa at a dosage regimen of 1 mg/kg qw.

The most serious adverse reactions experienced by 4% of patients in clinical trials were signs and symptoms consistent with anaphylaxis. Signs and symptoms included chest discomfort, conjunctival hyperaemia, dyspnoea, hyperaemia, eyelid oedema, severe respiratory distress, tachycardia, tachypnoea, irritability, flushing, pruritus, urticaria, rhinorrhoea, stridor, hypoxia, pallor, and diarrhoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via their national reporting system.

Tabulated list of adverse reactions

The data in Table 1 describe adverse reactions reported in infants who received KANUMA in clinical studies. The data in Table 2 describe adverse reactions reported in children and adults who received KANUMA in clinical studies.

Adverse reactions with KANUMA are listed by system organ class and preferred term using MedDRA frequency convention very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Due to the small patient population, an adverse reaction reported in 2 or more patients is classified as common (children and adults) or very common (infants).

Table 1 Adverse Reactions Reported in Infants Receiving KANUMA (N=19 patients)

MedDRA System Order Class	Very Common (≥ 1/10)	Common (≥1/100 to <10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not Known**
Immune system disorders	Hypersensitivity[a] Anaphylactic reaction[b]					
Eye Disorders	Eyelid oedema					
Cardiac disorders	Tachycardia					
Respiratory, thoracic and mediastinal disorders	Respiratory distress					
Gastrointestinal disorders	Diarrhoea, vomiting					
Skin and subcutaneous tissue disorders	Rash, rash maculo-papular					
General disorders and administration site conditions	Hyperthermia, pyrexia					
Investigations	Body temperature increased, oxygen saturation decreased, blood pressure increased, heart rate increased, respiratory rate increased, drug specific antibody present					

[a] May include: irritability, agitation, vomiting, urticaria, eczema, pruritus, pallor, and drug hypersensitivity.

[b] Occurred in 3 infant patients treated in clinical trials. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis.

** Cannot be estimated from the available data.

Table 2 Adverse Reactions Reported in Children and Adults Receiving KANUMA (N=106 patients)

MedDRA System Order Class	Very Common (≥ 1/10)	Common (≥1/100 to <10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not Known **
Immune system disorders	Hypersensitivity[a]	Anaphylactic reaction[b]				
Nervous system disorders	Dizziness					
Cardiac Disorders		Tachycardia				
Vascular disorders		Hyperaemia, hypotension				
Respiratory, thoracic and mediastinal disorders		Dyspnoea				
Gastrointestinal disorders	Abdominal pain, diarrhoea	Abdominal distension				
Skin and subcutaneous tissue disorders		Rash, rash papular				
General disorders and administration site conditions	Fatigue, pyrexia	Chest discomfort, infusion site reaction[c]				
Investigations		Body temperature increased				

[a] May include: chills, eczema, laryngeal oedema, nausea, pruritus, urticaria.
[b] Occurred in 2 patients treated in clinical trials. Based on Preferred Term 'anaphylactic reaction' and application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis.
[c] Includes: Infusion site extravasation, infusion site pain and infusion site urticaria.
** Cannot be estimated from the available data.

Description of selected adverse reactions

Hypersensitivity

Five of 125 (4%) patients treated with KANUMA in clinical studies experienced serious signs and symptoms consistent with anaphylaxis to KANUMA. Anaphylaxis occurred during the infusion as late as 1 year after treatment initiation.

In clinical studies, 59 of 125 (47%) KANUMA-treated patients, including 13 of 19 (68%) infants and 46 of 106 (43%) children and adults, experienced at least 1 hypersensitivity reaction (selected using a validated, pre-determined set of terms grouped together to identify potential hypersensitivity reactions).

Signs and symptoms either consistent with or that may be related to a hypersensitivity reaction occurring in two or more patients included but were not limited to abdominal pain, agitation, bronchospasm, chills, diarrhoea, eyelid oedema, eczema, face oedema, hypertension, irritability, laryngeal oedema, lip swelling, nausea, oedema, pallor, pruritus, pyrexia/body temperature increased, rash, tachycardia, urticaria, and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion.

Transient hyperlipidaemia

Consistent with its known mechanism of action, asymptomatic increases in circulating cholesterol and triglycerides have been observed following initiation of KANUMA. These increases have generally occurred within the first 2 to 4 weeks and improved within a further 8 weeks of KANUMA treatment. See Section 5.1.

Immunogenicity

There is potential for immunogenicity (see Section 4.4). 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. 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.

4.9 Overdose

There is no experience with overdose of KANUMA.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes.
ATC code: A16AB14

General description

KANUMA for intravenous (IV) infusion is a recombinant human lysosomal acid lipase (rhLAL). Lysosomal acid lipase (LAL, EC 3.1.1.13) is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids.

KANUMA is produced by recombinant DNA (rDNA) technology and purified from the egg white of transgenic Gallus. Purified sebelipase alfa is a monomeric glycoprotein containing 6 N-linked glycosylation sites (MW = 55,000). The deduced amino acid sequence for sebelipase alfa is identical to the Genbank® reference sequence (NM_000235.2) for human LAL.
KANUMA is supplied as a sterile, nonpyrogenic aqueous solution comprised of 20 mg sebelipase alfa (2 mg/mL), formulated in 13.7 mg/mL trisodium citrate dihydrate, 1.57 mg/mL citric acid monohydrate, 10 mg/mL Human Serum Albumin, pH 5.9 in a single-use vial. Each vial contains 10.5 mL solution and a

total extractable volume of 10 mL at 2 mg/mL. The specific activity of KANUMA is 195-345 units/mg. One unit is the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate, 4-methylumbelliferyl oleate, per minute at 37°C under the assay conditions. KANUMA does not contain preservatives. Each vial is for single use only.

5.1 Pharmacodynamic properties

Lysosomal Acid Lipase (LAL) Deficiency

LAL Deficiency is a rare disease associated with significant morbidity and mortality, which affects individuals from infancy through adulthood. LAL Deficiency presenting in infants is a medical emergency with rapid disease progression over a period of weeks that is typically fatal within the first 6 months of life. LAL Deficiency is an autosomal recessive lysosomal storage disorder characterised by a genetic defect resulting in a marked decrease or loss in activity of the lysosomal acid lipase (LAL) enzyme.

Deficient LAL enzyme activity results in the lysosomal accumulation of cholesteryl esters and triglycerides in a variety of cell populations, organs and organ systems, among them hepatocytes and macrophages. In the liver, this accumulation leads to hepatomegaly, increased hepatic fat content, transaminase elevation signaling chronic liver injury, and progression to fibrosis, cirrhosis, and complications of end-stage liver disease. In the spleen, LAL Deficiency results in splenomegaly, anaemia, and thrombocytopenia. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. Dyslipidaemia is common, with elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides and low high-density lipoprotein cholesterol (HDL-C), associated with increase liver fat content and transaminase elevations. In addition to liver disease, patients with LAL Deficiency experience increased risk for cardiovascular disease and accelerated atherosclerosis. The enzyme deficiency also leads to reduced generation of free cholesterol, which results in increased production of apoB-containing lipoproteins and reduced HDL-C particle formation.

Lipid-modifying agents such as HMG-CoA reductase inhibitors or PCSK9 inhibitors may lead to reductions in LDL-C in patients with LAL Deficiency but do not impact the associated liver disease progression as these agents do not address the underlying enzyme deficiency.

Mechanism of action

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL).

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

In a rat disease model of LAL Deficiency that recapitulates many aspects of the human disease, improvements in serum transaminases and reduction in hepatomegaly, improvement in liver pathology including reduction in liver fibrosis, restoration of normal growth, and prolonged survival were observed following treatment with sebelipase alfa.

Pharmacodynamic effect

Deficient LAL activity results in lysosomal accumulation of cholesteryl ester and triglycerides and disruption of normal lipid metabolism. KANUMA is an enzyme replacement therapy that has been shown to reduce substrate accumulation and improve lipid metabolism.

In clinical studies, after initiation of dosing with KANUMA, breakdown of accumulated lysosomal lipid led to initial increases in circulating cholesterol and triglycerides within the first 2 to 4 weeks of treatment. Improvements in dyslipidaemia related to LAL Deficiency were seen within a further 8 weeks of treatment with KANUMA and were accompanied by improvements in ALT by Week 4 that were maintained through Week 20 in all patients treated with KANUMA. These improvements were maintained until Week 260 for infants and Week 256 for children and adults treated with KANUMA.

5.2 Pharmacokinetic properties

The pharmacokinetics of KANUMA 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 3). 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 doses. No accumulation is seen at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly.

Table 3 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)
Vc (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; Vc = 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 4.

Table 4 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.

Characteristics in specific groups of patients

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 Vc (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.

Renal elimination of sebelipase alfa is considered a minor pathway for clearance.

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.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity in rats and monkeys, or fertility, embryo-foetal and peri- and postnatal development in rats and rabbits. Chronic toxicity studies in juvenile cynomolgous monkeys showed no toxicity at doses up to 3 times the recommended dose in infants and 10 times the recommended dose in adults/children. No adverse findings were observed in rat and rabbit embryofoetal development studies at doses up to at least 10 times the adult/children recommended dose and in rat fertility and peri-postnatal development studies at doses up to 10 times the adult/children recommended dose.

Studies to evaluate the mutagenic and carcinogenic potential of sebelipase alfa have not been performed.

5.4 Clinical efficacy and safety

Infants presenting with LAL Deficiency

Study LAL-CL03

LAL-CL03 was a multi-center, open-label, single-arm study of KANUMA in 9 patients under 24 months of age with a confirmed diagnosis of LAL Deficiency and growth failure with onset before 6 months of age. Patients also had rapidly progressive liver disease and severe hepatosplenomegaly. The median age of patients at the time of initiation of dosing was 3.0 months (range = 1.1 to 5.8 months). The median duration of exposure to sebelipase alfa was 55.589 months per patient (range = 0.03 to 60.19 months). Patients received KANUMA at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. Based on clinical response, dose escalation to 3 mg/kg once weekly occurred as early as 1 month and up to 20 months after starting treatment at 1 mg/kg qw for 6 patients. Two of these 6 patients were subsequently dose escalated to 5 mg/kg once weekly, as allowed by the study protocol.

Efficacy was assessed by comparing the survival experience of KANUMA-treated patients who survived past 12 months of age in Study LAL-CL03 with a historical cohort of untreated infants presenting with LAL Deficiency with similar clinical characteristics. In LAL-CL03, 6 of 9 KANUMA-treated infants survived beyond 12 months (67% 12-month survival, 95% CI: 30% to 93%). With continued treatment until 48 months of age, 1 additional patient died at age 15 months. In the historical cohort, 0 of 21 patients survived beyond 8 months of age (0% 12-month survival, 95% CI: 0% to 16%).

KANUMA resulted in improvements in alanine aminotransferase (ALT) / aspartate aminotransferase (AST) levels (indicating a decrease in liver injury) and in weight gain; improvements were noted within the first several weeks of treatment and were maintained through the end of the study. From baseline to Week 240 (Month 60), the mean reductions for ALT and AST were -43.5 U/L and -45.25U/L, respectively. From baseline to Week 240, mean weight-for-age percentile improved from 12.74% to 43.17% and mean serum albumin levels increased from 26.9 g/L to 31.98g/L. Dose escalation to 3 mg/kg once weekly was associated with additional improvements in weight gain, lymphadenopathy and serum albumin.

Study LAL-CL08

Study LAL-CL08 was a multi-center, open-label study of KANUMA in 10 infants ≤ 8 months of age with confirmed diagnosis of rapidly progressive LAL Deficiency requiring urgent intervention, including but not restricted to marked abdominal distension and hepatomegaly, failure to thrive, disturbance of coagulation, severe anemia, and/or a sibling with a rapidly progressive course of LAL Deficiency.

The median age of the study patients on the date of their first infusion of sebelipase alfa was 2.83 months (range: 0.5 to 4.1 months). Eight (80%) patients completed the study. The median duration of exposure was 33.9 months (range: 0.76 to 36.80 months). Two (20%) patients were considered early terminated due to death. All 10 patients received a starting dose of 1 mg/kg qw. The 9 patients who survived beyond Week 4 each received a dose escalation to 3 mg/kg qw, and 7 of these patients received a subsequent dose escalation to 5 mg/kg qw, as allowed per study protocol. One patient received a further dose escalation to 7.5 mg/kg qw. Two patients had a subsequent dose reduction, which occurred after successful transplant procedures; one patient received a BMT, and the other patient received a HSCT. The percentages (95% confidence intervals [CIs]) of patients surviving to 12, 18, 24, and 36 months of age were 90% (55.5%, 99.7%), 80% (44.4%, 97.5%), 80% (44.4%, 97.5%), and 75% (34.9%, 96.8%), respectively. Two patients

were <36 months of age at the time of study completion and were excluded from the analysis for survival to 36 months. Reductions in AST, gamma glutamyltransferase (GGT), and total bilirubin and increases in serum albumin were observed in the overall study population, with median changes from baseline to last assessment of -34.5 U/L, -66.67 IU/L, -63.64 μmol/L, and 33.33 g/L, respectively.

Height and weight increased gradually. Median changes from baseline in Z-scores for weight for height (WFH) were decreases through Week 4. Starting from Week 24, there were consistent improvements. At Week 144, the median change (range) in Z-scores for WFH was 3.07 (-1.0, 5.3) from baseline.

Children and adults with LAL Deficiency

Study LAL-CL02

Study LAL-CL02 was a multi-center, double-blind, placebo-controlled study in 66 children and adults with LAL Deficiency. Patients were randomized to receive KANUMA at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week (qow) for 20 weeks in the double-blind period. The mean age at randomization was 16.62 years, range 4-58 years (36% were <12 years old and 71% were <18 years old). For study entry, patients were required to have ALT levels of ≥1.5 X upper limit of normal (ULN). The majority of patients (58%) had LDL-cholesterol >190 mg/dL at study entry, and 24% of patients with LDL-cholesterol >190 mg/dL were on lipid lowering medications. Of the 32 patients who had a liver biopsy at study entry, 100% had fibrosis and 31% had cirrhosis. The age range of patients with biopsy evidence of cirrhosis was 4-21 years.

Randomization was stratified by: 1) age at randomization (<12 years old, ≥12 years old); 2) ALT level at screening (<3 X ULN, ≥3 X ULN); and 3) use of lipid-lowering medications (yes, no). The following endpoints were assessed: normalization of ALT, normalization of AST, decrease in LDL-cholesterol, decrease in non-HDL-cholesterol, decrease in triglycerides, increase in HDL-cholesterol, decrease in liver fat content assessed by multi-echo gradient echo (MEGE) MRI, decrease in liver volume assessed by MRI, and improvement in hepatic steatosis measured by morphometry.

At the completion of the 20-week double-blind period of the study, a statistically significant improvement in multiple efficacy endpoints was observed in the KANUMA-treated group as compared to the placebo group, as shown in Tables 5 & 6. Normalization of ALT was achieved in 31% (11/36) of KANUMA-treated patients and 7% (2/30) placebo patients. LDL-cholesterol normalization (<130 mg/dL) was achieved in 40.6% (13/32) among KANUMA-treated patients who have abnormal LAL-cholesterol at the baseline and 6.7% (2/30) of placebo patients with abnormal baseline LDL-cholesterol (≥130 mg/dL) at the end of the 20-week double-blind period.

Table 5 Efficacy Endpoints in Study LAL-CL02

Efficacy Endpoint	Baseline		Week 20		Normalization at Week 20 n (%)		p-value
	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	
ALT (U/L)					11 (31)	2 (7)	0.0271
Mean (SD)	105.1	99.0 (42.23)	45.5	92.4 (43.42)			

Efficacy Endpoint	Baseline		Week 20		Normalization at Week 20 n (%)		p-value
	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	
	(45.31)		(18.87)				
Median	90.0	86.5	44.5	85.5			
Range	52, 212	50, 237	17, 107	33, 232			
AST (U/L)					15 (42)	1 (3)	0.0003
Mean (SD)	86.6 (33.49)	78.2 (34.93)	45.0 (17.89)	71.9 (42.49)			
Median	74.5	71.0	41.0	61.5			
Range	41, 173	39, 220	19, 98	34, 261			

Table 6 Efficacy Endpoints in Study LAL-CL02

Efficacy Endpoint	Baseline		Week 20		% Change from Baseline at Week 20		p-value
	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	
LDL-C (mg/dL)							
n	36	30	35	29	36	30	
Mean (SD)	189.9 (57.16)	229.5 (69.95)	136.8 (66.30)	209.8 (64.13)	-28.42 (22.30)	-6.25 (13.01)	p<.0001
non-HDL-C (mg/dL)							
n	36	30	35	29	36	30	
Mean (SD)	220.5 (61.48)	263.8 (75.48)	160.1 (69.76)	239.6 (65.60)	-27.97 (18.61)	-6.94 (10.92)	p<.0001
Triglyceride (mg/dL)							
n	36	30	35	30	36	30	
Mean (SD)	152.8 (54.43)	174.4 (65.90)	115.8 (54.90)	148.4 (58.62)	-25.45 (29.41)	-11.14 (28.83)	p=0.0375
HDL-C (mg/dL)							

Efficacy Endpoint	Baseline		Week 20		% Change from Baseline at Week 20		p-value
	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	KANUMA (n=36)	Placebo (n=30)	
n	36	30	35	29	36	30	
Mean (SD)	32.4 (7.09)	33.4 (7.46)	38.2 (9.65)	33.1 (8.67)	19.57 (16.83)	-0.29 (12.36)	p<.0001
Liver fat content (%)							
n	35	26	32	26	32	25	
Mean (SD)	8.7 (3.95)	8.2 (2.80)	5.2 (1.70)	8.1 (3.20)	-31.98 (26.76)	-4.21 (15.56)	p<.0001

Paired liver biopsies at Baseline and Week 20 were available in a subset of patients (n = 26). Of patients with paired liver biopsies, 63% (10/16) of KANUMA-treated patients had improvement in hepatic steatosis (at least ≥ 5% reduction) as measured by morphometry compared to 40% (4/10) of placebo patients. This difference was not statistically significant.

Open-label period

Patients who participated in Study LAL-CL02 were eligible to continue treatment in an open-label periods of the study. 66 patients entered the first open-label period during which all patients received KANUMA at a dosage regimen of 1 mg/kg once every other week. Twelve (12) of 66 patients in the open label period were dose escalated to 3 mg/kg once every other week based on clinical response. In patients who had received KANUMA during the double-blind period, reductions in ALT levels during the first 20 weeks of treatment were maintained (Figure 1) and further improvements were seen in lipid parameters including LDL-cholesterol and HDL-cholesterol levels (Figure 2).

Placebo patients had persistently elevated serum transaminase and abnormal serum lipid levels during the double-blind period of the study. Consistent with what was observed in KANUMA-treated patients during the double-blind period, initiation of treatment with KANUMA during the open-label period produced improvements in ALT levels (Figure 1) and in lipid parameters including LDL-cholesterol and HDL-cholesterol levels (Figure 2).

Figure 1 Mean Change From Baseline in ALT Values Over Time in Study LAL-CL02

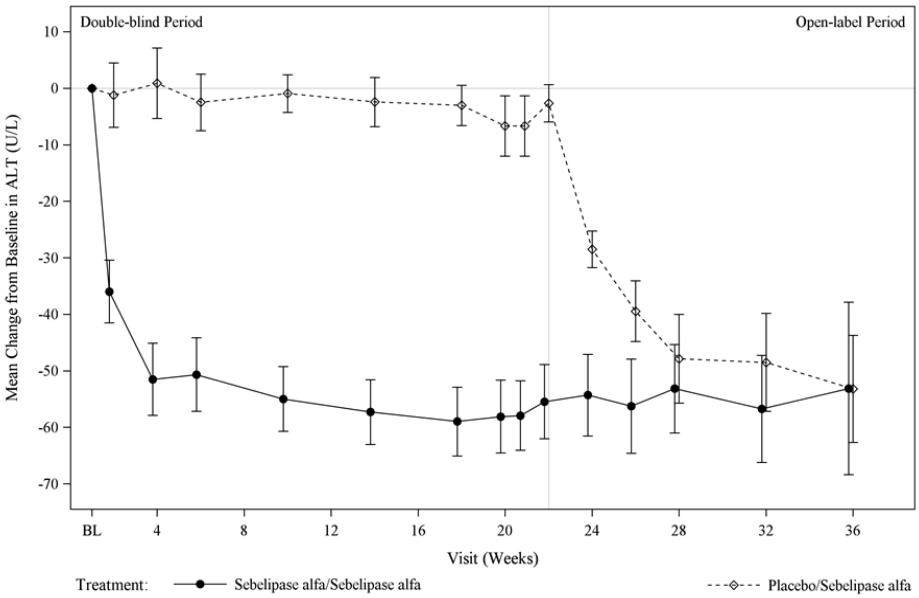
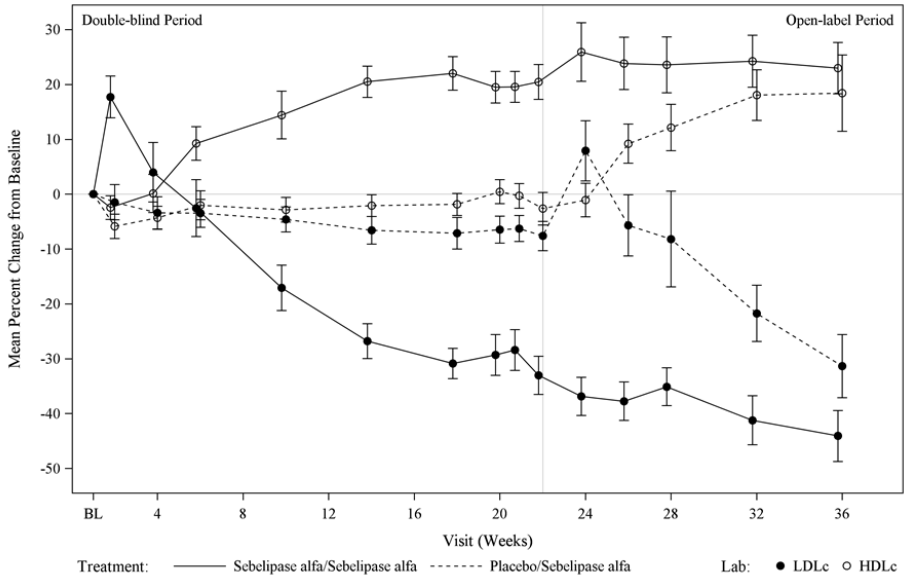


Figure 2 Mean Percent Change in Lipid Levels Over Time in Study LAL CL02



Improvements in ALT levels and in lipid parameters (LDL-cholesterol and HDL-cholesterol levels) were maintained during the open-label expanded treatment period for up to 256 weeks (5 years), with overall mean treatment duration of 42.45 months.

Study LAL-CL01/LAL-CL04

In a separate open-label study (LAL-CL01/LAL-CL04) in adult patients with LAL Deficiency, improvements in serum transaminase and lipid levels were sustained through the 260-week treatment period. Eight of nine patients transitioned from Study LAL-CL01 after 4 weeks of treatment (0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw) to Study LAL-CL04 (1 mg/kg qow or 3 mg/kg qow), with 5 patients receiving a dose of 1 mg/kg qow and 3 patients receiving a dose of 3 mg/kg qow. Increases in serum

transaminases and LDL-cholesterol and decreases in HDL-cholesterol were observed during the period in which patients were off treatment with KANUMA.

Study LAL-CL06

LAL-CL06 was a multicenter, open-label study in 31 children and adults with LAL Deficiency and was designed to include patients who may have been ineligible for previous clinical studies due to age, disease progression, previous treatment by hematopoietic stem cell or liver transplantation, less common disease manifestations, or disease characteristics that precluded participation in a placebo-controlled study. At least 4 patients in the study were to be between the age of 2 and 4 years. The study consisted of a screening period of up to 45 days, a treatment period of up to 96 weeks and an expanded treatment period of up to 48 weeks (for a total of up to 144 weeks of treatment). The median duration of exposure to sebelipase alfa was 33.15 months (range: 14.03 to 33.35 months).

Twenty-eight of the 31 patients completed the 96-week treatment period (1 patient discontinued treatment at Week 61 due to withdrawal of consent, 1 patient at Week 64 due to pregnancy and 1 patient at Week 76 due to transition to commercial therapy). Twenty-five of the 28 patients who completed the 96-week treatment period continued to receive treatment with sebelipase alfa during the extended treatment period. All 31 patients received sebelipase alfa at a starting dose of 1 mg/kg qow. Thirteen of the 31 patients received dose escalations as allowed by the study protocol. Eleven of these 13 patients had an initial dose escalation from 1 mg/kg qow to 3 mg/kg qow, and 4 of these patients had a further dose escalation to 3 mg/kg qw.

Serum transaminases (ALT/AST) were elevated at Baseline in approximately 75% of patients, and approximately half of the patients had levels > 1.5 x ULN. Reductions in ALT and AST were evident by Week 4 and were sustained during long-term treatment with sebelipase alfa, with mean changes from Baseline to Week 144 of -40.3 U/L (-32.0%) and -42.2 U/L (34.2%), respectively.

Transient increases in total cholesterol, non-HDL-C, and LDL-C were observed shortly after initiation of treatment (Week 4), and then levels dropped to below baseline by the next assessment at Week 8. This observation is consistent with mobilization of accumulated lipid substrates from the affected tissues and has been observed in previous clinical studies of sebelipase alfa. Continued long-term therapy with sebelipase alfa produced an improvement in the serum lipid profile, with mean changes from Baseline to Week 144 in LDL-C, triglycerides, and non-HDL-C of -54.2 mg/dL, -47.5 mg/dL, and -63.7 mg/dL, respectively, and mean percent changes of -31.2%, -19.1%, and -30.3%, respectively. An increase in HDL-C levels was observed, with a mean increase from Baseline to Week 144 of 10.2 mg/dL and a mean percent increase of 39.7%.

Liver Biopsy Data in Children and Adults Population

Liver biopsy is the accepted standard for histologic assessment of liver disease activity and fibrosis, despite such limitations as sampling variability, potential complications of an invasive technique, and subjective scoring.

Liver biopsies from 59 patients enrolled in Studies LAL-CL02 and LAL CL06 were assessed by an independent pathologist at a central facility, who was blinded to assessment timepoint and treatment assignment. All biopsies were evaluated semi-quantitatively for histologic features such as Ishak Fibrosis Score, portal inflammation, lobular inflammation, macrovesicular steatosis, and microvesicular steatosis.

Computer-assisted morphometry was used to quantify percent steatosis, fibrogenic cells, collagen, and macrophages.

Liver biopsies were evaluable for Ishak Fibrosis Scores for 59 patients at baseline and 38 patients at Month 12 (meaning after 12 months of exposure to sebelipase alfa). There were 36 patients who had Ishak scores at both baseline and Month 12.

At baseline, 3 of 59 patients (5%) had Ishak scores of 0 (no fibrosis) and 15 (25%) patients had Ishak scores of 6, indicating established or advanced cirrhosis. Ishak scores improved by Month 12, when 9 of 38 patients (24%) had Ishak scores of 0 and 7 patients (18%) had Ishak scores of 6. Overall, 31 of 36 patients (86.1%) had Ishak scores that had improved or did not progress at Month 12. There were 10 patients (28%) with a ≥ 2-point reduction in Ishak scores from baseline to Month 12, including changes from stage 2 to stage 0, from stage 3 to stages 1 and 0, from stage 5 to stage 0 (> 3-point reduction), and from stage 6 to stages 4 and 3. Globally, these 10 patients with a ≥ 2-point reduction in Ishak stage scores had also substantial improvements in other study-related assessments, such as reduction in ALT, LDL-C, HDL-C, and non-HDL-C over the same time period.

Based on eligibility criteria, patients in Study LAL CL06 generally were expected to have more cirrhosis and intractable disease than patients in Study LAL CL02, due to more advanced liver disease at baseline. The liver biopsy findings in Studies LAL-CL02 and LAL CL06 were consistent with each other. At baseline, in both studies, the majority of patients had microvesicular steatosis (57 of 59, 97%), including 45 of 59 patients (76%) with a score 4 (scale of 0 4, with severe is defined as 4 and equivalent to > 66% hepatocyte involvement/replacement), as expected with the underlying disease. At Month 12, the percentage of patients with severe microvesicular steatosis were decreased, with 17 of 38 patients (45%) having > 66% hepatocyte involvement/replacement (score 4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate dihydrate
Citric acid monohydrate
Human serum albumin
Water for injections

6.2 Shelf life

Unopened vials: 2 years.

After dilution: Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2°C to 8°C (36°F to 46°F), or up to 12 hours below 25°C (77°F).

From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (36°F to 46°F), or up to 12 hours below 25°C (77°F) unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.3 Special precautions for storage

Store in a refrigerator (2°C to 8°C; 36°F to 46°F).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see Section 6.2.

6.4 Nature and contents of container

KANUMA is supplied as a sterile, nonpyrogenic aqueous solution comprised of 20 mg sebelipase alfa (2 mg/mL) in a single use vial.

Clear glass vial (Type I) with a siliconized butyl rubber stopper, and an aluminium seal with a plastic flip-off cap, containing 20 mg sebelipase alfa in 10 mL of solution (2 mg/mL).

Pack size: 1 vial

6.5 Instructions for use and handling of disposal

Each vial of KANUMA is intended for single use only. KANUMA has to be diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion using aseptic technique.

The diluted solution should be administered to patients using a low-protein binding infusion set equipped with an in-line, low-protein binding 0.2 μm filter, with a surface area of greater than 4.5 cm^2 as available in order to avoid filter occlusion.

Preparation of the sebelipase alfa infusion

KANUMA should be prepared and used according to the following steps.
Aseptic technique should be used.

a) The number of vials to be diluted for infusion should be determined based on the patient's weight and prescribed dose.
b) It is recommended to allow KANUMA vials to reach a temperature between 15°C (59°F) and 25°C (77°F) prior to reconstitution to minimize the potential for the formation of sebelipase alfa protein particles in solution. The vials should not be left outside the refrigerator longer than 24 hours prior to dilution for infusion. The vials should not be frozen, heated or microwaved and should be protected from light.
c) The vials should not be shaken. Prior to dilution, the solution in the vials should be inspected visually; the solution should be clear to slightly opalescent, colourless to slightly coloured (yellow). Due to the proteinaceous nature of the product, slight flocculation (e.g., thin translucent fibres) may be present in the vials or diluted solution and is acceptable for use.
d) Do not use if the solution is cloudy, or if foreign particulate matter is present.
e) Up to 10 mL of solution should be slowly withdrawn from each vial and diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion. See Table 7 for recommended total infusion volumes by weight range. The solution should be mixed gently by inversion, and not be shaken.

Table 7 Recommended Infusion Volumes*

Weight range (kg)	1 mg/kg dose	3 mg/kg dose**	5 mg/kg dose***
	Total Infusion Volume (mL)	Total Infusion Volume (mL)	Total Infusion Volume (mL)
1-2.9	4	8	12
3-5.9	6	12	20
6-10.9	10	25	50
11-24.9	25	50	150
25-49.9	50	100	250
50-99.9	100	250	500
100-120.9	250	500	600

* The infusion volume should be based on the prescribed dose and should be prepared to a final KANUMA concentration of 0.1 - 1.5 mg/mL.
** For patients who do not achieve an optimal clinical response with a dose of 1 mg/kg.
*** For patients with LAL Deficiency presenting within the first 6 months of life who do not achieve an optimal clinical response with a dose of 3 mg/kg.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner

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