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DILI, Autoimmune, Cholestatic and Genetic Diseases

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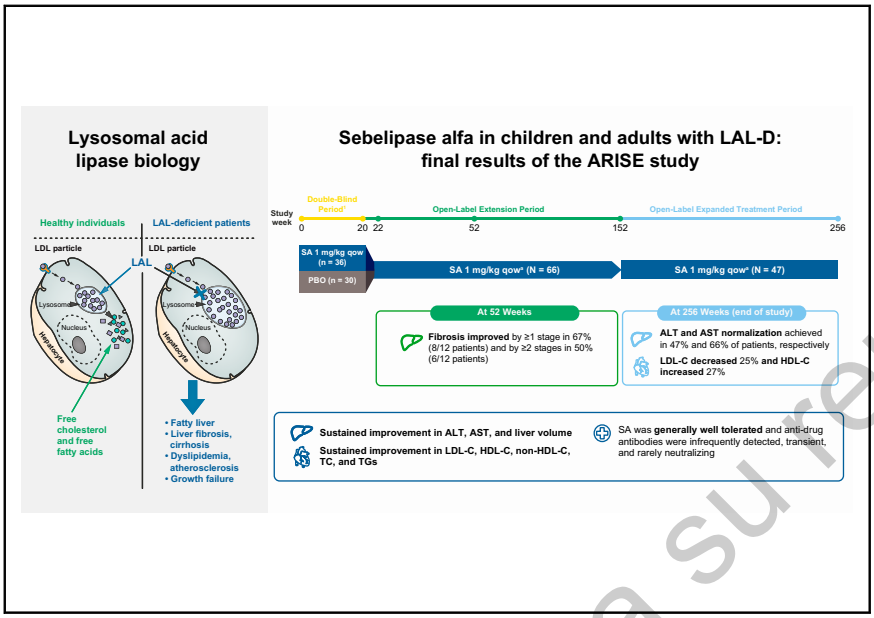
Sebelipase alfa in children and adults with lysosomal acid lipase deficiency: Final results of the ARISE study

Graphical abstract



Highlights

- Long-term sebelipase alfa treatment provided multiple benefits for patients with LAL-D.
- Improvements in liver and lipid parameters with sebelipase alfa were sustained.
- Liver histology was mostly stable or improved from baseline with sebelipase alfa.
- Improvements were noted in all age groups and irrespective of lipid medication use.
- Sebelipase alfa therapy for up to 5 years was generally well tolerated.

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Lay summary

Sebelipase alfa is used to treat lysosomal acid lipase deficiency (LAL-D), a rare, inherited disease of lipid metabolism. We report the final results of the phase III ARISE clinical study, which show that replacement of the defective LAL enzyme with sebelipase alfa for up to 5 years allows adults and children 4 years of age and older to maintain their initial improvements in liver and cholesterol parameters over the long term, without worsening of liver disease.

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Sebelipase alfa in children and adults with lysosomal acid lipase deficiency: Final results of the ARISE study

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See Editorial, pages 501–502

Background & Aims: Children and adults with lysosomal acid lipase deficiency (LAL-D) experience cirrhosis and dyslipidemia from lysosomal accumulation of cholesteryl esters and triglycerides. Sebelipase alfa enzyme replacement therapy is indicated for individuals with LAL-D. We report final results from the phase III randomized ARISE study of sebelipase alfa in children aged ≥4 years and adults with LAL-D.

Methods: The study included a 20-week, double-blind, placebo-controlled period; a 130-week, open-label, extension period; and a 104-week, open-label, expanded treatment period. In the open-label periods, all patients received intravenous sebelipase alfa every other week. The primary outcome was alanine aminotransferase (ALT) level normalization; aspartate aminotransferase (AST) levels, lipid parameters, liver histology, liver and spleen volume and fat content, and safety were also assessed.

Results: Of 66 patients enrolled, 59 completed the study. Median (range) age at randomization was 13 (4.7–59) years. At the last open-label visit, ALT and AST levels had normalized in 47% and 66% of patients, respectively. Patients who switched from placebo to sebelipase alfa experienced sustained improvements in ALT and AST during the open-label periods that mirrored those observed in the sebelipase alfa group during the double-blind period. Median (IQR) percent changes in lipid levels included a 25% (39%, 6.5%) reduction in low-density lipoprotein cholesterol and a 27% (19%, 44%) increase in high-density lipoprotein cholesterol. Most adverse events during the open-label periods were mild to moderate in severity; 13 patients had infusion-associated reactions (serious in 1 patient). Six patients (9%) developed anti-drug antibodies.

Conclusions: Early and rapid improvements in markers of liver injury and lipid abnormalities with sebelipase alfa were sustained, with no progression of liver disease, for up to 5 years.

Clinical Trial Number: NCT01757184; EudraCT Number: 2011-002750-31

Lay summary: Sebelipase alfa is used to treat lysosomal acid lipase deficiency (LAL-D), a rare, inherited disease of lipid metabolism. We report the final results of the phase III ARISE clinical study, which show that replacement of the defective LAL enzyme with sebelipase alfa for up to 5 years allows adults and children 4 years of age and older to maintain their initial improvements in liver and cholesterol parameters over the long term, without worsening of liver disease.

Introduction

Lysosomal acid lipase deficiency (LAL-D) is a rare, autosomal recessive lysosomal storage disorder associated with functional mutations in the LAL gene (*LIPA*) that cause a deficiency or absence of LAL activity.[1] It is characterized by intracellular accumulation of cholesteryl esters and triglycerides (TGs) and multisystem involvement.[2–4] Rapidly progressive LAL-D with clinical signs and symptoms (Wolman disease) occurs in infants, and is usually fatal within the first 6 months of life.[1] If the initial presentation occurs later in life (cholesteryl ester storage disease in children and adults), disease progression typically results in liver fibrosis or cirrhosis, severe dyslipidemia, and early-onset atherosclerosis.[1]

Sebelipase alfa (Alexion, AstraZeneca Rare Disease, Boston, MA), a recombinant human LAL enzyme replacement therapy, was approved by the European Medicines Agency and the United States Food and Drug Administration in 2015 to treat LAL-D patients.[5,6] The phase III Acid Lipase Replacement Investigating Safety and Efficacy (ARISE) study (NCT01757184; EudraCT Number: 2011-002750-31) was the pivotal clinical study of sebelipase alfa in children and adults with LAL-D.[7] At the end of the 20-week double-blind phase, 31% of sebelipase alfa recipients *vs.* 7% of placebo recipients achieved the primary outcome of normalized alanine aminotransferase (ALT) levels. Normalization of aspartate aminotransferase (AST) levels was achieved by 42% *vs.* 3% of patients.

In the open-label extension period, normalized ALT and AST levels were maintained over time.[8–10] After 52, 76, and 100 weeks, among all patients, 47%, 51%, and 45%, respectively,

Keywords: liver; lysosomal storage disease; transaminases; enzyme replacement therapy; dyslipidemia.
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had normalized ALT levels, and 58%, 65%, and 68% had normalized AST levels. Sebelipase alfa treatment also improved lipid parameters and liver fat content during the 20-week double-blind period; these improvements were maintained in the open-label extension.[8–10]

The objective of this analysis was to determine the efficacy and safety of long-term sebelipase alfa treatment of patients with LAL-D based on the final results of the ARISE study.

Patients and methods

The methods of the multicenter ARISE study have been published elsewhere[7]; a brief summary is provided here.

Study design

The ARISE study comprised a 20-week, double-blind, placebo-controlled treatment period followed by a 130-week, open-label extension period and a 104-week, open-label expanded treatment period. Patients were randomly assigned (1:1) to receive intravenous infusions of sebelipase alfa 1 mg/kg body weight or placebo every other week (qow) during the double-blind period; randomization was stratified by age (<12 *vs.* ≥12 years), average screening ALT level (<3 *vs.* ≥3x upper limit of normal [ULN]; ULN was defined as 34 U/L for all females and males aged 4–10 years and 43 U/L for males aged ≥10 years), and use of lipid-lowering medication (LLM) at baseline (yes *vs.* no).

Each site's institutional review board/independent ethics committee approved the protocol, and procedures complied with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. The patient or the patient's parent/legal guardian provided written informed consent, and age-appropriate assent was obtained from patients of minor age, per local regulations.

Patients

Eligible patients were ≥4 years of age with a confirmed enzyme activity–based diagnosis of LAL-D and a baseline ALT level ≥1.5x the ULN on 2 consecutive screening measurements ≥1 week apart. Patients taking LLM were required to be on a stable dose for ≥6 weeks before screening and ≥32 weeks after treatment began. Patients were excluded if they had severe hepatic dysfunction (Child-Pugh class C), or had undergone hematopoietic stem cell transplantation or liver transplantation.

Dosing

In the open-label extension period, all patients received sebelipase alfa 1 mg/kg body weight qow. A dose increase to 3 mg/kg qow was permitted in this period and the expanded open-label period for any of the following: i) ALT, AST, low-density lipoprotein cholesterol (LDL-C), or TG levels remained abnormal and did not improve from baseline over the preceding 8 infusions; ii) a patient <18 years old at assessment for inadequate clinical response had a weight-for-age *z* score 2 standard deviations below the mean and did not improve during the preceding 6 months despite not missing >20% of infusions. Doses could be reduced to 0.35 mg/kg qow in this period and the expanded open-label period in case of poor tolerability.

Assessments

Efficacy assessments were based on blood sample analyses for serum transaminases and serum lipids. ALT normalization was defined as an abnormal value that becomes normal (per ULN defined above). AST normalization was defined using these ULN values: females: 48 U/L (ages 4–7 years), 40 U/L (7–18 years), and 34 U/L (≥18 years); males: 59 U/L (ages 4–7 years), 40 U/L (7–18 years), and 36 U/L (≥18 years) – information provided by the central laboratory included overlapping age ranges. Relative changes in ALT, AST, total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and TG levels were determined. Prespecified subgroup analyses were conducted based on age at randomization and LLM use at baseline.

Abdominal multi–echo gradient echo magnetic resonance imaging assessed relative reductions in liver volume (normal volume = 2.5% of body weight) and fat content, and relative reductions in spleen volume (normal = 0.2% of body weight) and fat content. A central reader blinded to treatment assignment and timepoint of image acquisition read the images. Liver biopsies were obtained at screening and week 20[7] (and optionally at week 52 and/or weeks 104–152) from patients ≥18 years of age, and were optional at screening for younger patients with parental/guardian consent. All biopsies were evaluated semi-quantitatively for histologic features (*e.g.*, Ishak stage [0: no fibrosis/normal; 1: portal fibrosis/mild; 2: portal fibrosis/moderate to severe; 3: bridging fibrosis/few bridges; 4: bridging fibrosis/many bridges; 5: early cirrhosis; 6: established or advanced cirrhosis]) by an independent pathologist at a central facility, blinded to assessment timepoint and treatment assignment. Computer-assisted morphometry quantified the percentage of steatosis.

For patients aged ≤18 years at informed consent, weight and height were measured at various intervals. Weight, height, and body mass index (BMI) percentiles were determined based on age- and sex-standardized norms.[11]

Safety assessments

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that first occurred or worsened following the first sebelipase alfa infusion. They were obtained through spontaneous reporting or by questioning the patient or the patient's parent/legal guardian from the date of informed consent through the follow-up phone call approximately 4 weeks after the last sebelipase alfa dose; graded by investigators as mild, moderate, or severe; assessed as not related, unlikely related, possibly related, or related to study drug; and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. Infusion-associated reactions (IARs) were defined as any TEAE during or within 4 hours after infusion and investigator-assessed as at least possibly related to the study drug.

Immunogenicity was evaluated by the proportion of patients who tested positive for anti-drug antibodies (ADAs) and the proportion of those who developed neutralizing antibodies to sebelipase alfa.

Statistical analyses

The study was designed to ensure that ≥50 patients received ≥1 infusion of sebelipase alfa. Results were summarized using descriptive statistics; missing data were not imputed using statistical or manual methods. Efficacy and safety data were analyzed in all patients who received ≥1 sebelipase alfa infusion in the open-label periods. Patients were compared by time since the first dose of sebelipase alfa (week 0 in the sebelipase alfa/sebelipase alfa group and week 22 in the placebo/sebelipase alfa group), unless otherwise indicated. No formal inferential

statistical testing was planned or performed. All analyses used SAS® Life Science Analytics Framework version 4.7.2 or later.

Results

Patient disposition

From January to December 2013, 66 patients were enrolled in 15 countries (Argentina, Australia, Croatia, Czech Republic, France, Germany, Italy, Japan, Mexico, Poland, Russia, Spain, Turkey, the United Kingdom, and the USA) and received sebelipase alfa (n = 36) or placebo (n = 30). Of the 66 patients, 65 completed the 20-week double-blind period and entered the open-label extension period (Fig. 1); 1 patient in the sebelipase alfa group discontinued treatment during the double-blind period after experiencing a serious atypical IAR and re-entered the study under a desensitization protocol during the open-label extension period.

Of the 63 patients who completed the 130-week open-label extension period, 47 entered the 104-week expanded open-label treatment period; 43 patients completed the expanded period, and 59 completed the study (11 patients who transitioned to the commercial product and 5 who enrolled at a site that did not participate in the 104-week expanded open-label period were counted as having completed the study). The last patient completed the study in December 2018. Table 1 summarizes the patients' baseline demographics and disease characteristics.

Liver parameters

ALT normalization was achieved by 47% of patients at the last open-label assessment. The rate of ALT normalization was 49% among patients with baseline ALT <3x ULN and 41% among patients with baseline ALT ≥3x ULN. Fig. S1A shows median ALT levels over time. Marked and sustained improvements in ALT levels during the open-label periods in patients who had received placebo and switched to sebelipase alfa mirrored those in patients who received sebelipase alfa during the double-blind period.

Four of the 5 patients in the placebo/sebelipase alfa group at treatment week 232 (study week 256) had high ALT readings (49, 66, 83, and 119 U/L). Also at treatment week 232, the patient with ALT 49 U/L had an AE of mild left arm ecchymosis; the patient with ALT 83 U/L had mild abdominal pain and mild fever; and the patient with ALT 119 U/L had a high TG level (214 mg/dl) and an AE of mild urticaria, an IAR that led to dose interruption. The patients with treatment week 232 ALT levels of 66, 83, and 119 U/L were ADA-positive on screening but ADA-negative on confirmatory assay at weeks 172, 244, and 256, respectively.

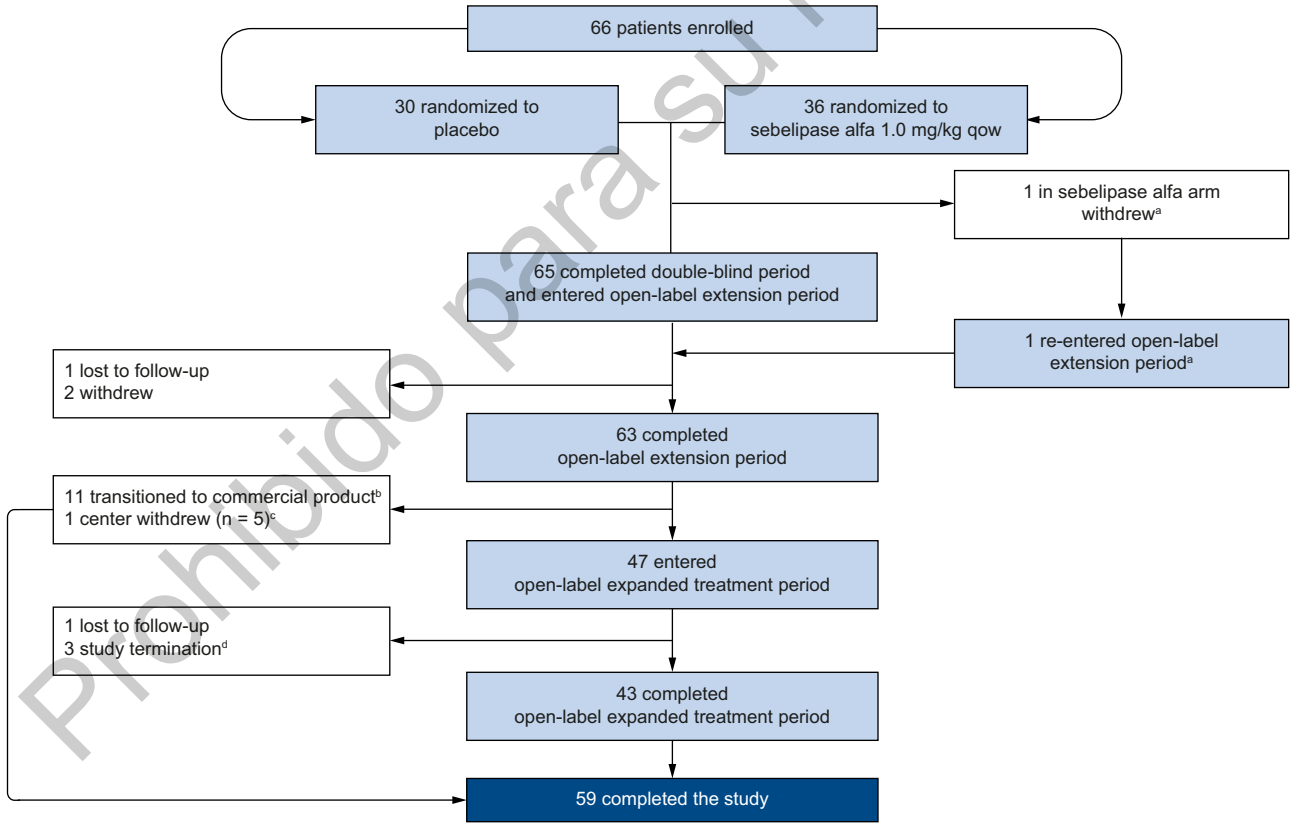

Fig. 1. Patient disposition. [a]1 patient withdrew from the double-blind period after experiencing a serious atypical infusion-related reaction during the second infusion of sebelipase alfa; the patient was later successfully rechallenged with sebelipase alfa during the open-label extension period. [b]Patients transitioned to the commercial product were counted as having completed the study. [c]These 5 patients were enrolled at a site in France that did not participate in Amendment 5, which is the protocol amendment that added the 104-week open-label expanded treatment period in regions where sebelipase alfa was not yet registered and available; these patients were counted as having completed the study. [d]These patients 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. qow, every other week.

Table 1. Baseline demographics and disease characteristics.[a]

Variable	Total (N = 66)
Age, median (min, max), years	13.4 (4.7, 58.8)
Age category, n (%)	
<12 years	24 (36)
12 to <18 years	23 (35)
≥18 years	19 (29)
Sex, n (%)	
Male	33 (50)
Female	33 (50)
Race, n (%)	
White	55 (83)
Asian	3 (5)
Black	1 (2)
Other[b]	7 (11)
ALT, median (IQR), U/L[c]	87 (72, 119)
ALT category, n (%)	
<3x ULN[d]	49 (74)
≥3x ULN	17 (26)
AST, median (IQR), U/L[c]	70 (58, 101)
AST category, n (%)	
<3× ULN[e]	57 (86)
≥3× ULN	9 (14)
GGT, median (IQR), U/L[c]	33 (24, 51)
Albumin, median (IQR), g/dl[f]	4.2 (4.1, 4.4)
Direct bilirubin, median (IQR), mg/dl[g]	0.14 (0.12, 0.22)
Ishak stage, n (%)	n = 32
Stage 0: no fibrosis (normal)	0
Stage 1: Portal fibrosis (mild)	2 (6)
Stage 2: Portal fibrosis (moderate to severe)	5 (16)
Stage 3: Bridging fibrosis (few bridges)	13 (41)
Stage 4: Bridging fibrosis (many bridges)	2 (6)
Stage 5: Early cirrhosis	2 (6)
Stage 6: Established or advanced cirrhosis	8 (25)
Percentage of steatosis, median (range)	25 (5.4–81)
Hemoglobin, median (IQR), g/dl[f]	13 (13, 14), n = 63

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; ULN, upper limit of normal.
[a]Baseline = prior to first dose of sebelipase alfa (week 0 in the sebelipase alfa/sebelipase alfa group and week 22 in the placebo/sebelipase alfa group, reset to a baseline of week 0).
[b]Included mixed race (n = 4), Hispanic (n = 2), and Middle Eastern (n = 1).
[c]To convert values to SI units (μkat/L), multiply by 0.0167.
[d]ULN = 34 U/L for all females and for males aged 4–10 years and 43 U/L for males aged 10 years and older. Information provided by the central laboratory included overlapping age ranges.
[e]ULN = females: 48 U/L (aged 4–7 years), 40 U/L (7–18 years), and 34 U/L (18 years and older); males 59 U/L (aged 4–7 years), 40 U/L (7–18 years), and 36 U/L (18 years and older). Information provided by the central laboratory included overlapping age ranges.
[f]To convert values to SI units (g/L), multiply by 10.
[g]To convert values to SI units (μmol/L), multiply by 17.104.

AST normalization was achieved by 66% of all patients at the last open-label assessment. The rate was 67% among patients with baseline ALT <3x ULN and 65% among patients with baseline ALT ≥3x ULN. Fig. S1B shows median AST levels over time. Marked and sustained improvements during the open-label periods among patients who had received placebo and switched to sebelipase alfa mirrored those observed in patients who received sebelipase alfa during the double-blind period.

Median albumin and direct bilirubin levels were within the normal range at baseline (Table 1) and did not change over time (data not shown). Liver assessments are summarized in Table 2; analyses of liver parameters by age at randomization are in Table 3.

Hematologic parameters

The median hemoglobin level was within the normal range at baseline (Table 1) and did not change over time (data not shown). In contrast with patients with rapidly progressive LAL-D in infancy,[12] serum ferritin levels were considered normal at baseline and throughout treatment in all patients, and no trends were apparent over time (Table 2). Levels of serum chitotriosidase, a marker of macrophage activation, decreased from baseline in the open-label periods. No clinically meaningful changes occurred over time in standard hematology parameters, suggesting no safety concern with long-term sebelipase alfa treatment.

Lipid parameters

The median (IQR) percent reduction in LDL-C was 21% (49%, 6.5%) in the sebelipase alfa/sebelipase alfa group and 30% (37%, 1.5%) in the placebo/sebelipase alfa group (24% [39%, 5.1%] overall) at the last open-label assessment; corresponding values at the end of the study were 21% (49%, 8.3%) and 30% (36%, 1.5%), respectively (25% [39%, 6.5%] overall) (Table 2). The median (IQR) percent increase in HDL-C levels was 23% (15%, 42%) in the sebelipase alfa/sebelipase alfa group and 27% (21%, 48%) in the placebo/sebelipase alfa group (26% [18%, 44%] overall) at the last open-label assessment; corresponding values at the end of the study were 23% (18%, 42%) and 28% (22%, 48%), respectively (27% [19%, 44%] overall). The median LDL-C level (Fig. 2A) increased and the median HDL-C level (Fig. 2B) decreased in the placebo/sebelipase alfa group at week 256; this may have been skewed by the low number of participants with available data toward the end of the study. Reductions from baseline in median total cholesterol, non-HDL-C, and TG levels were sustained over time.

Subanalysis by LLM use at baseline

Table S1 presents a subanalysis of outcomes by LLM use at baseline. In the sebelipase alfa/sebelipase alfa group, 15 of 36 (42%) patients used LLM at baseline; in the placebo/sebelipase alfa group, 9 of 30 (30%) patients did (24/66 [36%] overall). Two patients started LLM after sebelipase alfa initiation; postbaseline, 16 (44%) patients in the sebelipase alfa/sebelipase alfa group and 10 (33%) patients in the placebo/sebelipase alfa group (26 [39%] overall) were taking concomitant LLM. During the open-label periods only, 6 (17%) patients in the sebelipase alfa/sebelipase alfa group and 7 (23%) patients in the placebo/sebelipase alfa group (13 [20%] overall) were using LLM; of these 13 patients, 11 were taking a statin (1 fluvastatin, 2 simvastatin, 2 rosuvastatin, 6 atorvastatin), and 2 patients were taking a bile acid sequestrant (cholestyramine).

Diet

At screening, 38 (58%) patients were on a low-cholesterol or low-saturated fat diet (21 [58%] patients in the sebelipase alfa/sebelipase alfa group and 17 [57%] patients in the placebo/sebelipase alfa group). For most patients, this consisted of reduced fatty dairy products (37/38 patients) and reduced animal-derived fatty foods (33/38 patients); 22/38 patients increased their consumption of cholesterol-lowering foods.

Dietary changes were reported for 6 patients during the study. In the sebelipase alfa/sebelipase alfa group: increases in fat and cholesterol content at a single timepoint (n = 2; 1 at week

Table 2. Liver, hematologic, and lipid assessments.

Parameter	Median (IQR)		
	Baseline[a]	Last open-label visit[b]	End of study[c]
Liver parameters			
ALT, U/L[d]	87 (72, 119)	39 (30, 53)	38 (28, 51)
AST, U/L[d]	70 (58, 101)	33 (28, 43)	32 (28, 39)
GGT, U/L[d]	33 (24, 51)	20 (15, 36)	20 (15, 36)
Hematologic parameters			
Platelets, × 10^9/L	233 (195, 285), n = 63	227 (184, 269)	228 (190, 269)
Ferritin, ng/ml (μg/L)	41 (25, 76), n = 65	38 (22, 74)	35 (21, 70), n = 56
Chitotriosidase, U/ml (kU/L)	4.7 (3.4, 8.3)	3.0 (2.0, 4.0)	2.1 (1.5, 3.1), n = 7
Lipid parameters			
Total cholesterol, mg/dl[e]	258 (217, 306)	212 (179, 254)	214 (187, 254)
LDL-C, mg/dl[e]	197 (153, 238)	140 (107, 192)	142 (111, 188)
HDL-C, mg/dl[e]	32 (27, 38)	40 (34, 48)	39 (34, 48)
Non-HDL-C, mg/dl[e]	225 (180, 279)	170 (124, 216)	172 (133, 213)
Triglycerides, mg/dl[f]	142 (110, 191)	116 (78, 152)	125 (78, 156)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Baseline = prior to first dose of sebelipase alfa (week 0 in the sebelipase alfa/sebelipase alfa group and week 22 in the placebo/sebelipase alfa group, reset to a baseline of week 0); n = 66 unless otherwise noted.
[b]Last open-label visit = last visit of open-label treatment periods; n = 66 unless otherwise noted.
[c]End of study = last visit on study (end of study or early withdrawal); n = 61 unless otherwise noted.
[d]To convert values to SI units (μkat/L), multiply by 0.0167.
[e]To convert values to SI units (mmol/L), multiply by 0.0259.
[f]To convert values to SI units (mmol/L), multiply by 0.0113.

Table 3. Analysis of liver parameters by age at randomization.

Parameter	<12 years (n = 24)	≥12 to <18 years (n = 23)	≥18 years (n = 19)
ALT normalization, n (%)	10 (42)	12 (52)	9 (47)
AST normalization, n (%)	17 (71)	15 (68), n = 22	11 (58)
Liver fat content, % change from baseline[a]	3.9 (−19, 26), n = 23	−15 (−50, 17), n = 20	−26 (−34, 14), n = 17
Liver volume, % change from baseline[a]	−32 (−38, −25)	−24 (−32, −18), n = 21	−11 (−19, −0.13), n = 18
Liver histopathology improvement, n (%)	2 (33), n = 6	3 (75), n = 4	6 (75), n = 8

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Median (IQR).

12, 1 at week 30) with reductions 2 weeks later; an increase in fat content at a single timepoint (n = 1; week 12); and reductions in fat and cholesterol content (n = 1; week 2). In the placebo/sebelipase alfa group: increases in fat and cholesterol content at a single timepoint (n = 1; week 30) followed by reductions 2 weeks later; and increases in fat and cholesterol content at a single timepoint (n = 1; week 32).

Liver and spleen volume and fat content

Table 4 shows changes in liver and spleen volume and fat content in the overall study population. During the first 20 weeks of open-label treatment, reductions in liver volume and fat content in the placebo/sebelipase alfa group were comparable to those observed in the sebelipase alfa group during the 20-week double-blind period. In both groups, long-term treatment was associated with further reductions in liver volume; however, the effect on liver fat content became less pronounced over time.

Liver biopsy

Baseline biopsy data were available for 32 patients (Table 1). Changes from baseline in Ishak stage showed that after 52 weeks of sebelipase alfa treatment, 11/12 patients (92%) with paired biopsy data had an improved or stable Ishak stage, with 8/12 (67%) having a ≥1-stage improvement and 6/12 (50%) having a ≥2-stage reduction (Fig. 3). Of the 6 patients with a ≥2-point reduction in Ishak stage, 1 had a baseline Ishak stage of 5 and 5 had a baseline Ishak stage of 3. Patients who had the greatest reductions in Ishak stage after 52 weeks of sebelipase alfa treatment also demonstrated improvements in markers of liver injury, hepatic fat content, and lipid parameters (data not shown). In the placebo/sebelipase alfa group, 7/8 (88%) patients had an improved or stable Ishak stage, with 50% having a 1-stage reduction.

Among patients with paired biopsy data at baseline and week 20, a higher proportion of patients in the sebelipase alfa arm had improvement (≥5% decrease) or no change (<5% increase or decrease) from baseline in hepatic steatosis compared with the placebo arm (94% [15/16] *vs.* 50% [5/10]). Patients who received sebelipase alfa showed greater median percentage improvement in steatosis than those who received placebo (−43% *vs.* 12%). In patients who received sebelipase alfa for 52 weeks (n = 12), median percentage of steatosis decreased by 37% from baseline. Too few biopsies were performed after week 52 to permit aggregate analysis.

Growth parameters

Among patients ≤18 years of age, baseline weight was at or below the 50th centile for 29/51 (57%) patients. Baseline height was below the 50th centile in the same proportion of patients (all of whom had baseline height at or below the 40th centile). Twenty-two (43%) patients had a baseline BMI at or below the

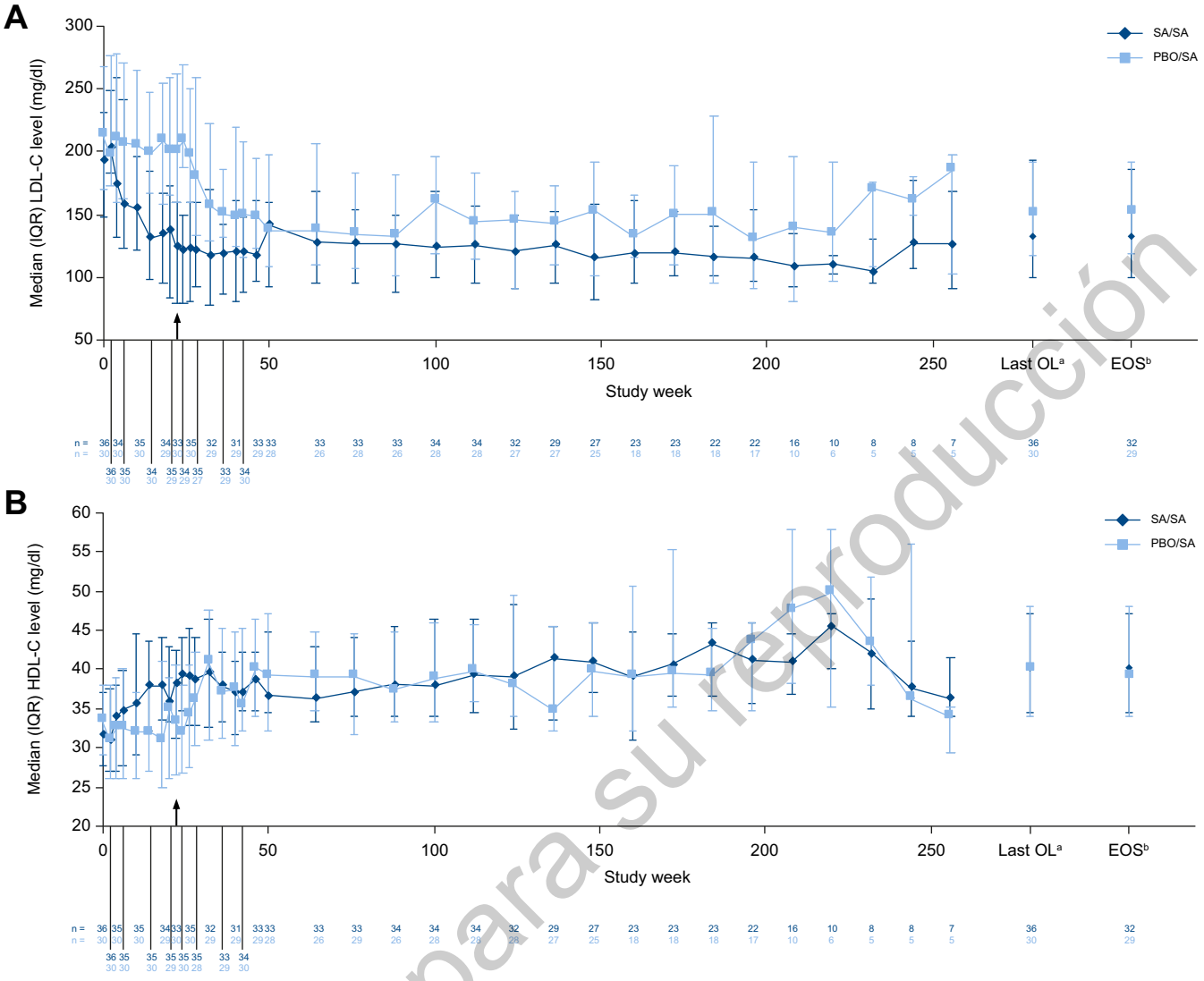

Fig. 2. Change in lipid parameters over time. Median (A) LDL-C and (B) HDL-C levels over time. The arrow indicates when participants in the PBO/SA group started receiving SA (week 22). LDL-C ULN = 129 mg/dl (young males), 140 mg/dl (young females), 185 mg/dl (adult males), 159 mg/dl (adult females). HDL-C LLN = 37 mg/dl (young males), 36 mg/dl (young females), 28 mg/dl (adult males), 33 mg/dl (adult females). To convert values to SI units (mmol/L), multiply by 0.0259. [a]Last OL visit = last visit of OL treatment period. [b]EOS = last visit on study (EOS or early withdrawal). EOS, end of study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; OL, open-label; PBO, placebo; SA, sebelipase alfa; ULN, upper limit of normal.

50th centile. At the last open-label visit, the proportions of patients at or below the 50th centiles were: 21 (48%) of 44 for weight, 26 (59%) for height, and 17 (39%) for BMI.

Safety

Drug exposure

During the open-label periods, 62/66 patients (94%) received ≥50 sebelipase alfa infusions. The maximum number of infusions administered was 110–119 for 12 patients (18%), and dose adjustments were reported for 12 (18%) patients.

The dose was increased to 3 mg/kg qow for 11 patients (n = 4, sebelipase alfa/sebelipase alfa group; n = 7, placebo/sebelipase alfa group); all were prepubertal children or adolescents aged 4.9–14.3 years at randomization. All 11 continued at that dosage for the duration of treatment.

Dose reduction to 0.35 mg/kg qow was carried out for 1 patient in the sebelipase alfa/sebelipase alfa group under a desensitization protocol; upon re-challenge, the patient received 2 infusions (at weeks 88 and 90), with an increase to 1 mg/kg qow (at week 92), which was continued throughout treatment with the exception of 1 infusion of 0.35 mg/kg (week 98).

Adverse events

Sixty-four patients (97%) had ≥1 TEAE during the study. TEAEs were mild to moderate in 58/64 (91%) patients. Table 5 summarizes the most commonly reported TEAEs during the open-label periods. No patient discontinued participation due to TEAEs; however, 2 patients, both of whom were ADA-negative throughout the study, withdrew from treatment after experiencing IARs. Overall, 13 (20%) patients experienced IARs during the open-label periods; in all but 1 patient they were mild or moderate in severity.

Table 4. Liver and spleen assessments.

Parameter	Median (IQR)					
	Baseline[a]	Week 20	Week 52	Week 100	Last open-label visit[b]	End of study[c]
Liver volume, MN	1.4 (1.2, 1.6), n = 63	1.3 (1.1, 1.5), n = 59	1.2 (1.0, 1.4), n = 56	1.1 (1.0, 1.4), n = 54	1.1 (0.9, 1.2), n = 65	1.1 (0.9, 1.2), n = 39
Liver fat content, %	8.1 (6.6, 11), n = 60	4.8 (3.5, 6.5), n = 58	6.2 (4.6, 7.8), n = 56	5.9 (5.2, 8.8), n = 54	6.4 (5.0, 10), n = 65	6.0 (4.8, 9.7), n = 39
Spleen volume, MN	2.8 (2.1, 4.0), n = 63	2.4 (2.0, 3.6), n = 59	2.2 (1.9, 3.2), n = 56	2.4 (1.8, 3.3), n = 53	2.2 (1.7, 3.1), n = 65	2.0 (1.5, 3.1), n = 39
Spleen fat content, %	1.4 (0.8, 1.9), n = 60	1.2 (0.7, 1.8), n = 58	1.3 (1.0, 2.1), n = 56	1.3 (0.6, 2.2), n = 49	1.3 (0.8, 2.7), n = 65	1.5 (1.1, 2.6), n = 38

MN, multiples of normal.
[a]Data are reported from time since first dose of sebelipase alfa (week 0 in the sebelipase alfa/sebelipase alfa group and week 22 in the placebo/sebelipase alfa group, reset to a baseline of week 0).
[b]Last open-label visit = last visit of open-label treatment periods.
[c]End of study = last visit on study (end of study or early withdrawal).

Eleven patients had serious TEAEs during the open-label periods; only 1 had serious TEAEs (IARs) considered related to treatment. This patient, in the placebo/sebelipase alfa group, experienced serious IARs during 2 infusions of sebelipase alfa (infusions 29 and 30) including chest discomfort, pruritus, hyperemia, dyspnea, eyelid edema, and urticaria. Although they resolved within 1 to 2 days following infusion interruption and administration of antihistamine or corticosteroid, the patient withdrew from the study. The patient tested negative for ADAs at all study assessments. Another patient, in the sebelipase alfa/sebelipase alfa group, who had discontinued treatment during the double-blind period due to serious IARs was successfully rechallenged with sebelipase alfa during the open-label extension period under a desensitization protocol. All infusions during open-label treatment were administered without premedication. This patient received open-label treatment for approximately 1 year with no IAR recurrence. The patient tested ADA-negative at all study assessments. Details of the desensitization protocol have been published elsewhere.[13] No TEAE led to death.

The most common vital sign abnormality reported as a TEAE during open-label treatment was pyrexia and/or increased body temperature (MedDRA preferred terms); for 3 patients in the placebo/sebelipase alfa group, these TEAEs were assessed as treatment-related, non-serious, mild IARs. One patient in the sebelipase alfa/sebelipase alfa group who had an electrocardiogram (ECG) reported as abnormal-clinically significant at baseline had normal ECGs at all assessments during treatment. Three patients with abnormal-not clinically significant ECGs at baseline had occasional ECGs reported as abnormal-clinically significant during treatment; 1 patient in the sebelipase alfa/sebelipase alfa group had a TEAE of ECG QT prolongation at week 52, assessed as mild, non-serious, and unlikely related to treatment, with an outcome reported as unknown, and 2 patients in the placebo/sebelipase alfa group who had ECGs reported as abnormal-clinically significant at week 42 (also reported in 1 of these patients at weeks 52 and 100) were diagnosed with a TEAE of arrhythmia at day 140, assessed as mild, non-serious, and unlikely related to treatment. All other patients had ECGs that were normal or abnormal-not clinically significant at baseline and throughout treatment with sebelipase alfa. Lymphadenopathy and skin manifestations of liver disease (tendinous and tuberous xanthomas, xanthelasma, angiomas, gynecomastia, cutaneous evidence of portosystemic channels) were reported for a small number of patients at baseline, with no clear changes observed with long-term treatment.

Immunogenicity

During sebelipase alfa treatment, ADAs were detected in 6 (9%) patients (n = 5, sebelipase alfa/sebelipase alfa group; n = 1, placebo/sebelipase alfa group). Two of these patients developed neutralizing antibodies with cell uptake inhibition, and 1 of the 2 also developed activity-neutralizing antibodies. At the last open-label assessment, 5/6 patients tested ADA-negative; the ADA-positive patient was the one who had developed activity-neutralizing antibodies. Only 1/6 patients with an ADA-positive result during the study also experienced an IAR; this patient was ADA-negative when the IAR occurred. The safety and efficacy profiles for the ADA-positive patients were consistent with those of the overall study population. Neither patient who developed neutralizing antibodies required a dose increase.

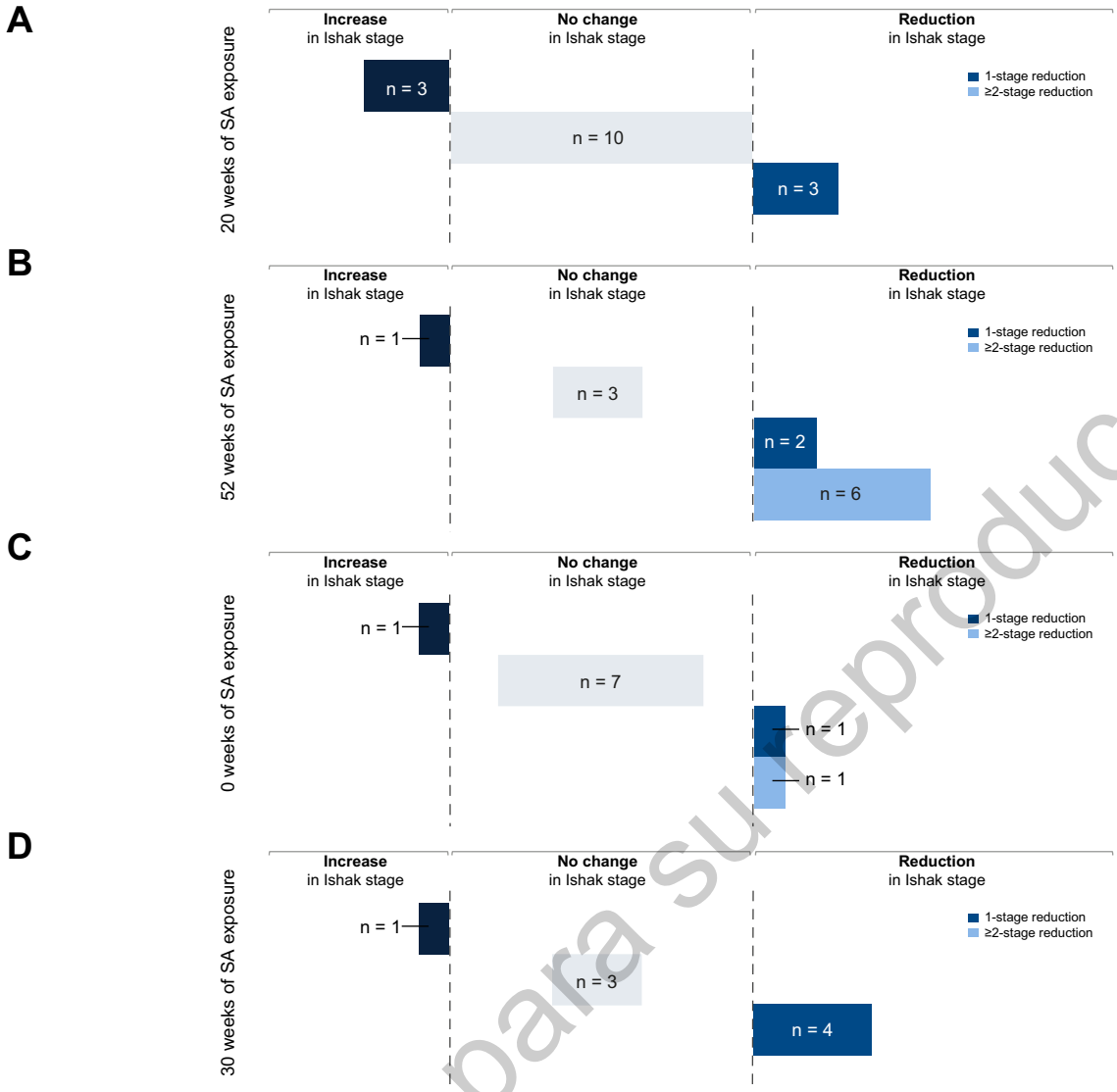

Fig. 3. Changes in Ishak stage from baseline in the double-blind and open-label phases. Changes (A and B) in the sebelipase alfa/sebelipase alfa group and (C and D) the placebo/sebelipase alfa group. [a]10 of these 12 patients also had a biopsy at 20 weeks; 3 had an increase, 5 had no change, and 2 had a 1-stage reduction. SA, sebelipase alfa.

Discussion

We assessed the long-term safety and efficacy of sebelipase alfa administration for up to 5 years in adults and children ≥4 years of age with LAL-D. In both the sebelipase alfa/sebelipase alfa and placebo/sebelipase alfa treatment groups, improvements in liver biochemical parameters, serum lipid parameters, and liver volume observed during initial treatment with sebelipase alfa were sustained over time. After switching to sebelipase alfa in the open-label extension period, patients in the placebo/sebelipase alfa group who had persistent LAL-D–related abnormalities during the double-blind period showed rapid and meaningful improvements that mirrored those in the sebelipase alfa/sebelipase alfa group during the double-blind period. Liver fat content improved with treatment, but the effect was not sustained over time. Hypotheses for the lack of sustained improvement include the potential impact of LAL-D severity, patient growth and development, changes in dietary fat intake, lack of compliance with LLM use, or inadequate imaging; however, a confirmed reason for this loss of effect has not been established. Among patients ≤18 years of age, growth parameters remained stable throughout the study, based on the proportion of patients with weight, height, or BMI at or below the 50th centile over time.

Meaningful reductions in ongoing liver cell injury were reflected by rates of ALT and AST normalization and by clinically relevant reductions in levels of these and other markers of liver injury. Liver histology as reflected by Ishak stage was stable or improved from baseline with sebelipase alfa treatment in the majority of patients in both groups at week 52, with longer treatment duration associated with greater reduction in Ishak stage; assessments were not made beyond week 52. Sebelipase alfa treatment also improved dyslipidemia, generally reducing levels of LDL-C, non-HDL-C, TGs, and total cholesterol and increasing HDL-C levels, and maintaining these changes over

Table 5. Treatment-emergent adverse events reported by ≥20% of patients in the overall population during the open-label periods.

Adverse event	n (%)
Headache	31 (47)
Nasopharyngitis	31 (47)
Pyrexia	24 (36)
Cough	21 (32)
Diarrhea	18 (27)
Abdominal pain	16 (24)
Vomiting	16 (24)
Upper respiratory tract infection	15 (23)
Gastroenteritis	13 (20)
Rhinitis	13 (20)
Rhinorrhea	13 (20)
Upper abdominal pain	13 (20)

time. The increase in the median LDL-C level and decrease in the median HDL-C level observed in the placebo/sebelipase alfa group at week 256 may have been related to the low number of participants with available data toward the end of the study, or the fact that all but 1 of the patients who had ever used statins during the study had discontinued study treatment or statin use before week 256.

The effects of sebelipase alfa on liver and lipid parameters appeared consistent, irrespective of LLM use at baseline, which suggests that benefits are obtained regardless of additional efforts to manage dyslipidemia. The cardiovascular risk of 6 study patients (mean age, 45 years; 50% males) who met the criteria for the 10-year Framingham risk score (30–74 years of age) was compared with that of normal healthy individuals adjusted for age and risk factors at normal levels as defined by the Framingham risk equation.[14] Their baseline Framingham risk score was 7.1%, which represented a 54% greater risk than in the normal population. During the 20-week double-blind period, patients in the placebo arm experienced a 14% reduction and patients in the sebelipase alfa arm experienced a 207% reduction in incremental Framingham CV risk.[14] Supporting this are findings of significant improvements in cholesterol levels and atherogenic biomarkers with sebelipase alfa treatment, regardless of concomitant LLM use, during the 20-week double-blind period, with a sustained effect observed through week 52.[15] Sebelipase alfa treatment reduced LDL particle numbers, LDL-C levels, and apolipoprotein B levels and increased HDL-C and apolipoprotein A1 levels, reducing risk related to atherogenic lipids and lipoproteins in these patients.[15] Changes in diet during sebelipase alfa treatment were reported infrequently, and did not suggest any clear or consistent trend with respect to dietary management of LAL-D.

As with other lysosomal storage disorders, the presentation and severity of LAL-D in children and adults are highly variable.[1] In this study, 12 patients had dose adjustments. Management of LAL-D patients should be individualized, taking into consideration the patient's presentation and disease severity, dietary care, response to enzyme replacement therapy, use of concomitant medications, and tolerability.

Long-term treatment with sebelipase alfa was generally well tolerated, and the long-term safety profile was consistent with that observed during the double-blind treatment period.[7] Most AEs were mild to moderate in severity. Transient ADAs were detected in 9% of patients, but were rarely neutralizing. Safety and efficacy profiles for ADA-positive patients were consistent with those of the overall study population. Changes in clinical laboratory data, ECGs, and vital signs did not show any clinically meaningful trends that would suggest a potential safety concern with long-term sebelipase alfa treatment.

These study results are consistent with findings from a 144-week single-arm, open-label study of sebelipase alfa treatment (LAL-CL06), in which treatment was well tolerated and achieved sustained improvements in markers of liver injury and lipid parameters in a diverse population of patients with LAL-D.[16] They are also consistent with the results of another long-term study in adults with LAL-D (LAL-CL04), in which sebelipase alfa treatment for up to 5 years resulted in sustained improvements in liver and lipid parameters, as well as improvements in liver volume and fat content, and was well tolerated.[17]

Study limitations include the open-label design of the extension and expanded treatment periods, which did not allow for statistical comparisons. Fibrosis/cirrhosis does not occur uniformly in the liver; therefore, sampling can influence assessment of Ishak stage. The biopsy results are limited by the small numbers of patients with paired liver biopsy data and inherent limitations associated with subjective scoring of liver biopsy samples. Patients assigned to the sebelipase alfa/sebelipase alfa group had 52 weeks of sebelipase alfa exposure while those assigned to the placebo/sebelipase alfa group had only 30 weeks of sebelipase alfa exposure; therefore, direct between-group comparisons of biopsy data were not possible. Also, 36% of patients were receiving concomitant LLM at baseline, and 20% were receiving concomitant LLM during the open-label periods, which could have confounded study outcomes. Although the subgroup analysis suggested that outcomes were similar regardless of LLM use at baseline, the study was not designed to allow for statistically meaningful comparisons between subgroups. Finally, because 47 of 66 patients were between 4 and 18 years of age at the first infusion, metabolic and dietary changes during puberty and adolescence may have influenced study outcomes.

In patients with LAL-D, sebelipase alfa treatment led to early and rapid improvements in markers of liver injury and lipid abnormalities that were sustained for up to 5 years, and long-term treatment was generally well tolerated.

Abbreviations

ADA, anti-drug antibody; AE, adverse event; ALT, alanine aminotransferase; ARISE, Acid Lipase Replacement Investigating Safety and Efficacy; AST, aspartate aminotransferase; BMI, body mass index; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; IAR, infusion-associated reaction; LAL-D, lysosomal acid lipase deficiency; LDL-C, low-density lipoprotein cholesterol; LLM, lipid-lowering medication; qow, every other week; TEAE, treatment-emergent adverse event; TG, triglyceride; ULN, upper limit of normal.

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Conflict of interest

B. K. Burton has received funding for the conduct of clinical studies from Alexion, AstraZeneca Rare Disease, BioMarin, Shire (Takeda), Genzyme, Ultragenyx, Homology Medicines, Denali, and Sangamo; funding for independent research from BioMarin and Shire; and consulting fees and honoraria from BioMarin, Shire (Takeda),

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: All authors. Drafting the article or revising it critically for important intellectual content: All authors. Final approval of the version to be published: All authors

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors

Data availability statement

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://alexion.com/our-research/research-and-development.

Link to data request form: https://alexion.com/contact-alexion/medical-information

Role of the sponsor

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Supplementary data

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Author names in bold designate shared co-first authorship

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