ORIGINAL ARTICLE

A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency

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ABSTRACT

BACKGROUND

Lysosomal acid lipase is an essential lipid-metabolizing enzyme that breaks down endocytosed lipid particles and regulates lipid metabolism. We conducted a phase 3 trial of enzyme-replacement therapy in children and adults with lysosomal acid lipase deficiency, an underappreciated cause of cirrhosis and severe dyslipidemia.

METHODS

In this multicenter, randomized, double-blind, placebo-controlled study involving 66 patients, we evaluated the safety and effectiveness of enzyme-replacement therapy with sebelipase alfa (administered intravenously at a dose of 1 mg per kilogram of body weight every other week); the placebo-controlled phase of the study was 20 weeks long and was followed by open-label treatment for all patients. The primary end point was normalization of the alanine aminotransferase level. Secondary end points included additional disease-related efficacy assessments, safety, and side-effect profile.

RESULTS

Substantial disease burden at baseline included a very high level of low-density lipoprotein cholesterol (≥190 mg per deciliter) in 38 of 66 patients (58%) and cirrhosis in 10 of 32 patients (31%) who underwent biopsy. A total of 65 of the 66 patients who underwent randomization completed the double-blind portion of the trial and continued with open-label treatment. At 20 weeks, the alanine aminotransferase level was normal in 11 of 36 patients (31%) in the sebelipase alfa group and in 2 of 30 (7%) in the placebo group ($P=0.03$), with mean changes from baseline of −58 U per liter versus −7 U per liter ($P<0.001$). With respect to prespecified key secondary efficacy end points, we observed improvements in lipid levels and reduction in hepatic fat content ($P<0.001$ for all comparisons, except $P=0.04$ for triglycerides). The number of patients with adverse events was similar in the two groups; most events were mild and were considered by the investigator to be unrelated to treatment.

CONCLUSIONS

Sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with lysosomal acid lipase deficiency. (Funded by Synageva BioPharma and others; ARISE ClinicalTrials.gov number, NCT01757184.)

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This article was updated on January 5, 2016, at NEJM.org.

N Engl J Med 2015;373:1010-20.
DOI: 10.1056/NEJMoa1501365

Lysosomal acid lipase deficiency (Online Mendelian Inheritance in Man number, 278000)[1] is an autosomal recessive storage disease that is caused by mutations in the *LIPA* gene.[2] In infants, progression of the disease (historically known as Wolman's disease) is very rapid, with death typically occurring by 6 months of age.[2] In older patients, progression of the disease (historically known as cholesteryl ester storage disease) leads to cirrhosis and other complications in childhood or later in life.[3] Common features in infants, children, and adults include elevated serum aminotransferase levels, dyslipidemia, hepatomegaly, liver fibrosis, and cirrhosis.[3-5] Awareness of the disease is low, which has led to delayed diagnosis or misdiagnosis, and the severity of disease-related complications is not widely appreciated.[2,5,6]

The clinical manifestations and complications of the disease are due to the lysosomal accumulation of cholesteryl esters and triglycerides.[2,3,5] The enzyme deficiency also leads to reduced generation of free cholesterol, which results in increased production of apolipoprotein B–containing lipoproteins and reduced formation of high-density lipoprotein (HDL) cholesterol particles.[7] There are no safe or effective therapies for lysosomal acid lipase deficiency.[2] Statins and other lipid-lowering medications have been used with limited success in the control of low-density lipoprotein (LDL) cholesterol levels and have had little, if any, effect on liver injury and progression of fibrosis.[3,5] In patients with advanced liver disease, liver transplantation is required because of complications related to portal hypertension and liver failure, and there is limited information on long-term outcomes after transplantation.[3]

Sebelipase alfa (Synageva BioPharma) is an investigational recombinant human enzyme-replacement therapy for lysosomal acid lipase deficiency.[8] A phase 1–2 study and follow-up extension study involving adults with lysosomal acid lipase deficiency showed that sebelipase alfa was associated with rapid decreases in serum aminotransferase levels accompanied by improvements in the serum lipid profile.[8,9] We report results from the phase 3 Acid Lipase Replacement Investigating Safety and Efficacy (ARISE) trial, which was a multicenter, randomized, double-blind, placebo-controlled trial of sebelipase alfa in children and adults with lysosomal acid lipase deficiency.

METHODS

STUDY DESIGN AND PATIENTS

The trial design included a screening period, a 20-week double-blind, placebo-controlled period, and an ongoing open-label period (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Efficacy assessments included evaluations of alanine aminotransferase and aspartate aminotransferase levels (including the proportion of patients with normalized levels) and levels of other biochemical markers of liver function; serum lipid levels (LDL cholesterol, non-HDL cholesterol, triglyceride, and HDL cholesterol levels), hepatic fat content (assessed by means of multi-echo gradient-echo magnetic resonance imaging [MRI]), organ volumes (assessed by means of MRI), and liver histopathological findings in a subgroup of patients (see the Supplementary Appendix). Exploratory assessments included apolipoprotein A1 and apolipoprotein B levels. The safety evaluation included assessment of adverse events, infusion-associated reactions, electrocardiographic results, vital signs, laboratory testing, and testing for antidrug antibodies. This article describes the results of the 20-week double-blind treatment period and preliminary results through an additional 16 weeks of the open-label period.

Eligibility criteria included an age of at least 4 years, confirmed enzyme activity–based diagnosis of the disease[10] with an alanine aminotransferase level that was at least 1.5 times the upper limit of the normal range (the upper limit of the normal range was defined as 34 U per liter for female patients 4 to 69 years of age and male patients 4 to 10 years of age and as 43 U per liter for male patients 10 to 69 years of age). (Information provided by the central laboratory included overlapping age ranges.) Patients who were taking lipid-lowering medications had to have been taking a stable dose for 6 weeks or more before screening and had to continue taking a stable dose throughout the study. Patients who had undergone transplantation or who had severe hepatic dysfunction (Child–Pugh class C) were excluded.

STUDY OVERSIGHT

The study was designed by the sponsor (Synageva BioPharma) with input from all the authors. The study protocol (available at NEJM.org), amend-

ments, and informed-consent forms were approved by an independent institutional ethics review committee before initiation of the study (see the Supplementary Appendix). Safety was monitored by an independent safety review committee. Data were collected at the study sites by the investigators and their staff. Other organizations involved in the collection, management, and analysis of study data are listed in the Supplementary Appendix.

The first draft of the manuscript was written jointly by the first and last authors, and all the authors aided in the revision. Editorial and medical-writing assistance, paid for by the sponsor, was provided by Peloton Advantage. The first author and representatives of the sponsor made the decision to submit the manuscript for publication. All the authors had access to all the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

RANDOMIZATION AND TREATMENT

Randomization was stratified according to age (<12 years vs. ≥12 years), alanine aminotransferase level (<3 times the upper limit of the normal range vs. ≥3 times the upper limit of the normal range), and use or nonuse of lipid-lowering medications at baseline. Patients were randomly assigned in a 1:1 ratio to receive an intravenous infusion of sebelipase alfa (at a dose of 1 mg per kilogram of body weight) or placebo every other week for 20 weeks (11 infusions) before entering the open-label extension period, at which point all the patients were to receive sebelipase alfa.

STATISTICAL ANALYSIS

Efficacy and safety analyses were performed with data from the full analysis set, which included all the patients who underwent randomization and received at least one dose of study drug. The last assessment in the double-blind period was the last measurement before the week 20 infusion. The primary efficacy end point (normalization of the alanine aminotransferase level) was analyzed with the use of Fisher's exact test at a two-sided alpha level of 0.05. Key secondary end points were analyzed with the use of the Wilcoxon rank-sum test, and statistical significance was assessed with the use of a prespecified fixed-sequence hypothesis-testing approach to ensure strong control of the type I error rate at an alpha level of 0.05. Testing for significance was stopped if the P value was greater than 0.05 for an end point, and any remaining end points were not considered to be statistically significant. Descriptive P values were computed for other analyses of differences between the study groups (see the Supplementary Appendix).

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TREATMENT

A total of 66 patients were randomly assigned to receive either sebelipase alfa (36 patients) or placebo (30 patients) (Fig. S1 in the Supplementary Appendix). All but 2 patients (97%) received all 11 planned infusions during the double-blind period; 1 patient in the sebelipase alfa group temporarily discontinued dosing after an atypical infusion-associated reaction, and 1 in the placebo group missed 1 infusion. The characteristics of the study groups were well balanced at baseline (Table 1, and Table S1 in the Supplementary Appendix).

Baseline assessments showed a substantial burden of disease in this young population (Table 1). In addition to elevated aminotransferase levels, LDL cholesterol levels were very high (≥190 mg per deciliter) in 38 of 66 patients (58%). A total of 38% of the patients had an elevated baseline γ-glutamyltransferase level and 8% had an elevated total bilirubin level. Low platelet counts were present at baseline in 11% of the patients. Evidence of disturbed coagulation was also observed in some patients. Hepatomegaly was common, with 67% of the patients having a liver volume that was at least 1.25 times the normal volume, and 21% of patients had a spleen volume that was at least 4 times the normal volume.

All the liver-biopsy samples that were obtained at baseline from 32 patients showed fibrosis (Ishak score, ≥1, on a scale from 0 to 6, with higher scores indicating a greater degree of fibrosis); 15 of these patients (47%) had bridging fibrosis (Ishak score, 3 or 4), and 10 (31%) had cirrhosis (Ishak score, 5 or 6). The mean age of the patients with biopsy-proven cirrhosis was 12 years, and 8 of these 10 patients did not have a medical history of cirrhosis.

Among the 50 patients who were 18 years of age or younger, 12% were below the fifth percentile for height. A total of 65 of the 66 patients completed the double-blind treatment period and entered the open-label period.

EFFICACY

Sebelipase alfa was associated with a significantly higher rate of normalization of the alanine aminotransferase level, (the primary end point) than was placebo (31% vs. 7%, P=0.03). In addition, sebelipase alfa was associated with significant improvement in six consecutive secondary end points, as compared with placebo (Table 2). The decrease from baseline in the mean alanine aminotransferase level was significantly greater in the sebelipase alfa group than in the placebo group (–58 U per liter vs. –7 U per liter, P<0.001) (Fig. 1A). Similar results were seen with respect to normalization of the aspartate aminotransferase level (42% vs. 3%, P<0.001; mean reduction from baseline, –42 U per liter vs. –6 U per liter; P<0.001) (Fig. S2A in the Supplementary Appendix). An additional analysis of reduction in the alanine aminotransferase level with the use of recently applied criteria in studies of nonalcoholic fatty liver disease[11] showed a response rate of 67% with sebelipase alfa versus 7% with placebo (Fig. S2B in the Supplementary Appendix).

Decreases in the serum aminotransferase levels were accompanied by significant reductions in hepatic fat content as assessed by means of multi-echo gradient-echo MRI (mean reduction from baseline, –32.0 percentage points in the sebelipase alfa group vs. –4.2 percentage points in the placebo group; P<0.001) (Table 2 and Fig. 2A). Paired morphometric assessments of microvesicular steatosis at baseline and at week 20 were available in 16 patients in the sebelipase alfa group and in 10 in the placebo group. A reduction in steatosis occurred more frequently in the sebelipase alfa group than in the placebo group but the between-group difference did not reach significance (Fig. 2B). Although patients in the sebelipase alfa group had greater reductions in liver volume than did those in the placebo group, the prespecified hierarchical fixed-sequence hypothesis testing nullified the significance of this last secondary end point.

The sebelipase alfa group had significantly greater mean percentage decreases from baseline in the LDL cholesterol level (difference from the change with placebo, –22.2 percentage points; P<0.001), the non-HDL cholesterol level (difference from placebo, –21.1 percentage points; P<0.001), and the triglyceride level (difference from placebo, –14.4 percentage points; P=0.04) and a significantly greater mean percentage increase in the HDL cholesterol level (difference from placebo, 19.9 percentage points; P<0.001) (Table 2 and Fig. 1B and 1C, and Fig. S2C in the Supplementary Appendix). These improvements in the serum lipid levels were accompanied by significant decreases from baseline in mean serum apolipoprotein B level (difference from placebo, –23.1 percentage points; P<0.001) and an increase from baseline in mean serum apolipoprotein A1 level (difference from placebo, 11.7 percentage points; P<0.001).

A significant positive correlation was seen between decreases in the LDL cholesterol level and decreases in the alanine aminotransferase level among patients in the sebelipase alfa group (Fig. S2D in the Supplementary Appendix). Decreases in the LDL cholesterol level with sebelipase alfa were seen regardless of baseline status with regard to use of lipid-lowering medication (mean change from baseline, –36.7 percentage points among patients receiving lipid-lowering medication vs. –22.5 percentage points among those not receiving lipid-lowering medication).

At baseline, 38% of the patients had an elevated level of γ-glutamyltransferase. Among these patients, normalization of the γ-glutamyltransferase level was seen in 62% of those in the sebelipase alfa group, as compared with 8% of those in the placebo group (mean change, –23.4 U per liter vs. –2.4 U per liter). Spleen volumes were also reduced significantly in the sebelipase alfa group, as compared with the placebo group (difference from baseline, –6.8% vs. 5.8%; P<0.001).

SAFETY AND IMMUNOGENICITY

The frequency and overall distribution of adverse events were similar in the two study groups; most events were considered by the site investigator to be unrelated to the study drug and were mild in intensity (Table 3). Infusion-associated reactions were uncommon. Three serious adverse events were reported during the 20-week

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Sebelipase Alfa (N=36)	Placebo (N=30)
Age at screening		
Mean — yr	17±12	15±10
Median (range) — yr	13.5 (4–54)	13.0 (4–58)
Distribution — no. (%)		
<12 yr	14 (39)	10 (33)
≥12 to <18 yr	9 (25)	14 (47)
≥18 yr	13 (36)	6 (20)
Age at onset of disease manifestation — yr		
Mean	8±8	5±5
Median (range)	5.0 (0–42)	4.0 (0–20)
Sex — no. (%)		
Male	18 (50)	15 (50)
Female	18 (50)	15 (50)
Race — no. (%)†		
White	27 (75)	28 (93)
Other	9 (25)	2 (7)
Height <5th percentile in patients ≤18 yr of age — no./total no. (%)	3/26 (12)	3/24 (12)
LIPA mutation — no. (%)		
Homozygous for c894 G→A	11 (31)	10 (33)
Compound heterozygous for c894 G→A	17 (47)	18 (60)
Other mutation	8 (22)	2 (7)
Alanine aminotransferase		
Mean — U/liter	105±45	99±42
Median (range) — U/liter	90.0 (52–212)	86.5 (50–237)
≥3× ULN — no. (%)‡	10 (28)	8 (27)
Aspartate aminotransferase		
Mean — U/liter	87±34	78±35
Median (range) — U/liter	74.5 (41–173)	71.0 (39–220)
≥3× ULN — no. (%)§	7 (19)	2 (7)
γ-glutamyltransferase		
Mean — U/liter	52±46	52±60
Median (range) — U/liter	37.5 (14–239)	34.0 (13–333)
Elevated level — no. (%)¶	13 (36)	12 (40)
Total bilirubin — μmol/liter		
Mean	18±16	19±16
Median (range)	13.5 (6–76)	13.0 (5–80)
Hepatic fat content — %‖		
Mean	8.7±4.0	8.2±2.8
Median (range)	7.7 (3.3–25.4)	7.9 (2.2–13.1)
Liver biopsy — no./total no. (%)**		
Fibrosis	19/19 (100)	13/13 (100)
Bridging fibrosis	10/19 (53)	5/13 (38)

Table 1. (Continued.)

Characteristic	Sebelipase Alfa (N=36)	Placebo (N=30)
Cirrhosis	5/19 (26)	5/13 (38)
Liver volume — multiple of the normal value††		
Mean	1.4±0.4	1.4±0.3
Median (range)	1.4 (0.8–2.9)	1.4 (1.1–2.2)
Total cholesterol — mg/dl		
Mean	252.5±60.7	296.7±75.4
Median (range)	253.0 (121–355)	278.0 (191–440)
LDL cholesterol		
Mean — mg/dl	189.9±57.2	229.5±70.0
Median (range) — mg/dl	193.0 (70–280)	213.0 (135–378)
≥190 mg/dl — no. (%)	18 (50)	20 (67)
Non-HDL cholesterol — mg/dl		
Mean	220.5±61.4	263.8±75.4
Median (range)	223.5 (93–332)	241.5 (155–408)
HDL cholesterol — mg/dl		
Mean	32.4±7.1	33.4±7.4
Median (range)	32.0 (18–48)	33.5 (16–47)
Triglycerides		
Mean — mg/dl	152.8±54.4	174.4±65.9
Median (range) — mg/dl	138.0 (65–307)	170.0 (66–361)
≥200 to <500 mg/dl — no. (%)	6 (17)	8 (27)
Lipid-lowering medication — no. (%)		
Statin	14 (39)	9 (30)
Other	3 (8)	1 (3)
≥1 medication	15 (42)	11 (37)

* Plus–minus values are means ±SD. No difference between groups reached statistical significance as prespecified in the statistical analysis plan ($P \leq 0.05$). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† Race was self-reported.

‡ The upper limit of the normal range for alanine aminotransferase that was used by the central laboratory was 34 U per liter for female patients 4 to 69 years of age and male patients 4 to 10 years of age and 43 U per liter for male patients 10 to 69 years of age. Information provided by the central laboratory included overlapping age ranges.

§ The normal range for aspartate aminotransferase that was used by the central laboratory was 10 to 48 U per liter for female patients 4 to 7 years of age, 10 to 40 U per liter for those 7 to 18 years of age, and 9 to 34 U per liter for those 18 to 59 years of age; for male patients, the normal range was 10 to 59 U per liter for those 4 to 7 years of age, 10 to 40 U per liter for those 7 to 18 years of age, and 11 to 36 U per liter for those 18 to 59 years of age. Information provided by the central laboratory included overlapping age ranges.

¶ The upper limit of the normal range for γ-glutamyltransferase that was used by the central laboratory for female patients was 24 U per liter for those 4 to 10 years of age, 33 U per liter for those 10 to 18 years of age, and 49 U per liter for those 18 to 59 years of age; for male patients, the upper limit of the normal range was 24 U per liter for those 4 to 10 years of age, 51 U per liter for those 10 to 18 years of age, and 61 U per liter for those 18 to 59 years of age. Information provided by the central laboratory included overlapping age ranges.

‖ Data were missing for one patient in the sebelipase alfa group and for four in the placebo group. There was no significant difference in the mean percentage of hepatic fat content at baseline between patients who used lipid-lowering medication and those who did not (9% and 8%, respectively).

** Fibrosis was defined by an Ishak score of 1 or more, on a scale from 0 to 6, with higher scores indicating a greater degree of fibrosis. Bridging fibrosis was defined by an Ishak score of 3 or 4, and cirrhosis by an Ishak score of 5 or 6.

†† Data were missing for three patients in the sebelipase alfa group and for two in the placebo group.

Table 2. Primary and Secondary Efficacy Assessments.*

End Point	No. of Patients	Sebelipase Alfa	Placebo	P Value
Primary end point: normalization of alanine aminotransferase level — no./total no. (%)	66	11/36 (31)	2/30 (7)	0.03
Secondary end points				
Change from baseline in LDL cholesterol level — percentage points	66	−28.4±22.3	−6.2±13.0	<0.001
Change from baseline in non-HDL cholesterol level — percentage points	66	−28.0±18.6	−6.9±10.9	<0.001
Normalization of aspartate aminotransferase level — no./total no. (%)	65†	15/36 (42)	1/29 (3)	<0.001
Change from baseline in triglyceride level — percentage points	66	−25.5±29.4	−11.1±28.8	0.04
Change from baseline in HDL cholesterol level — percentage points	66	19.6±16.8	−0.3±12.4	<0.001
Change from baseline in hepatic fat content — percentage points‡	57§	−32.0±26.8	−4.2±15.6	<0.001
Reduction in steatosis — no./total no. (%)¶	26‖	10/16 (62)	4/10 (40)	0.42
Change from baseline in liver volume — percentage points	60**	−10.3±10.5	−2.7±10.1	—††

* Plus–minus values are means ±SD. The primary and secondary end-point results are presented in order of the prespecified fixed-sequence hypothesis-testing sequence for statistical significance. Fisher's exact test was used to analyze normalization of the alanine aminotransferase level and liver histologic end points, and the Wilcoxon rank-sum test was used for all other end points. Normalization of the alanine and aspartate aminotransferase levels was defined by the central laboratory.

† One patient in the placebo group had a normal aspartate aminotransferase level at baseline.

‡ Hepatic fat content was measured by means of multi-echo gradient-echo MRI.

§ Data were missing for four patients in the sebelipase alfa group and for five in the placebo group. MRI was not performed in patients with medical implants or in children requiring sedation.

¶ Reduction in steatosis was defined as an absolute decrease of 5 percentage points or more from baseline in the morphometric assessment of the hepatic fat content.

‖ Paired biopsy samples were required in patients 18 years of age or older unless contraindicated and were optional in patients younger than 18 years of age.

** Data were missing for three patients in the sebelipase alfa group and for three in the placebo group.

†† The P value could not be interpreted as significant owing to lack of statistical significance of end point above, according to prespecified fixed-sequence hypothesis-testing method.

double-blind period. Two of these events occurred in the sebelipase alfa group, including one that was considered to be related to the study drug: an infusion-associated reaction that was atypical in terms of timing relative to infusion (8.5 hours after) and in terms of the symptoms; the reaction resolved rapidly after a single dose of oral diphenhydramine.

A total of 5 of 35 patients in the sebelipase alfa group had one or more positive antidrug-antibody tests during the 20-week study period. Titers were generally low and unsustained, and the development of antidrug antibody did not have any effect on safety or efficacy variables.

OPEN-LABEL PERIOD

In addition to the improvements with sebelipase alfa that were observed during the double-blind period, further reductions were observed during the open-label period in the LDL cholesterol level (mean reduction from baseline, −44.1 percentage points after 36 weeks of sebelipase alfa treatment vs. −28.9 percentage points at the last visit in the double-blind period) (Fig. 1B) and the non-HDL cholesterol level (mean reduction from baseline, −41.5 percentage points after 36 weeks of sebelipase alfa treatment vs. −28.3 percentage points at the last visit in the double-blind period). The alanine aminotransferase and LDL

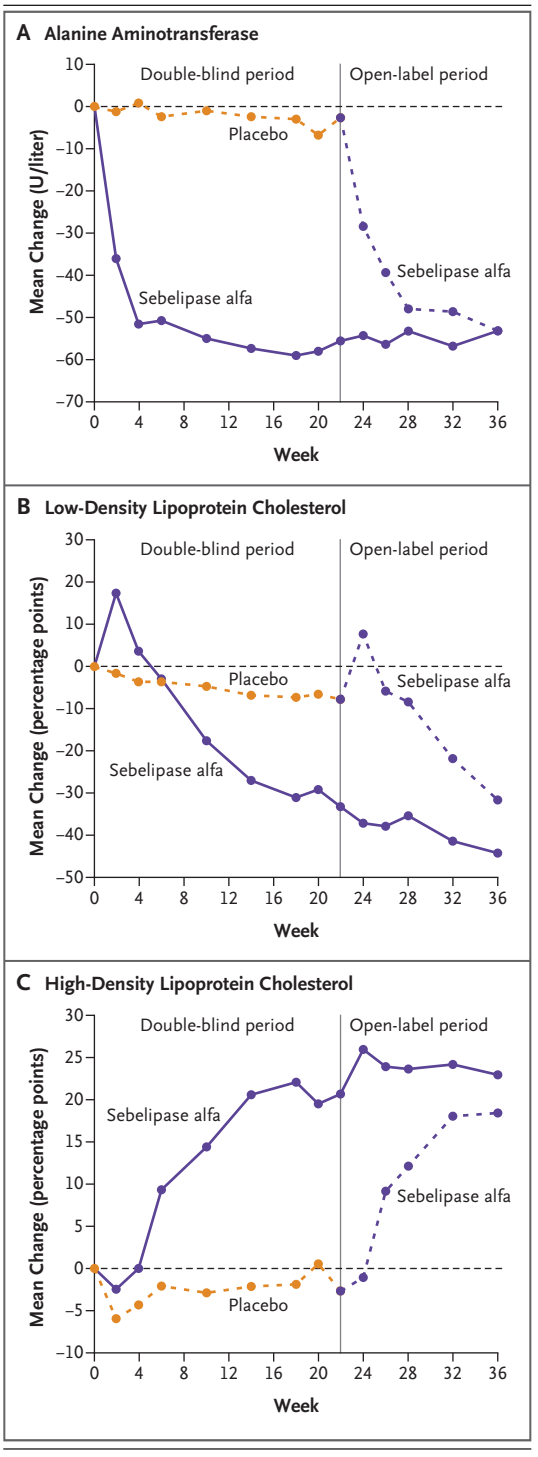

Figure 1. Effects of Sebelipase Alfa on Levels of Alanine Aminotransferase, Low-Density Lipoprotein Cholesterol, and High-Density Lipoprotein Cholesterol.

The trial design included a 20-week double-blind placebo-controlled period and an ongoing open-label period; data from the open-label period were available through the week 36 visit. The upper limit of the normal range for alanine aminotransferase was 34 U per liter for female patients 4 to 69 years of age and male patients 4 to 10 years of age and 43 U per liter for male patients 10 to 69 years of age. Information provided by the central laboratory included overlapping age ranges. The vertical line between week 20 and week 24 indicates the switch to the open-label period.

cholesterol levels that were persistently elevated in patients in the placebo group during the double-blind period decreased markedly with the switch to sebelipase alfa (Fig. 1A and 1B). The safety profile in the open-label period was consistent with that in the double-blind period, and no serious adverse events were considered by the site investigator to be related to the study drug.

DISCUSSION

Lysosomal acid lipase deficiency is an underrecognized genetic cause of cirrhosis and severe dyslipidemia that can, according to reports, cause atherosclerotic cardiovascular disease early in life.[3,5,12-15] Although statins and other lipid-lowering medications may reduce LDL cholesterol levels, levels remain high and there is continued progression to cirrhosis.[3,5] In the current study, fibrosis and cirrhosis were seen in patients at an early age at a substantially higher frequency than that observed in patients with other chronic noncholestatic liver diseases. For example, in a study involving 67 children with biopsy-proven nonalcoholic fatty liver disease, clinically significant fibrosis was seen in only 15% of the patients and cirrhosis was not observed in any patient.[16] As is the case with other chronic liver diseases, the progression of fibrosis is probably related to the persistence of the injurious agent, because current therapies for lysosomal acid lipase deficiency do not appear to reduce the abnormal lysosomal lipid levels in the liver substantially.[3,17] Characteristics at baseline, including portal hypertension, hyperbilirubinemia, thrombocytopenia, disturbed coagulation, splenomegaly, and short stature, provide evidence of progression to advanced liver disease.[18]

Enzyme-replacement therapies have substan-

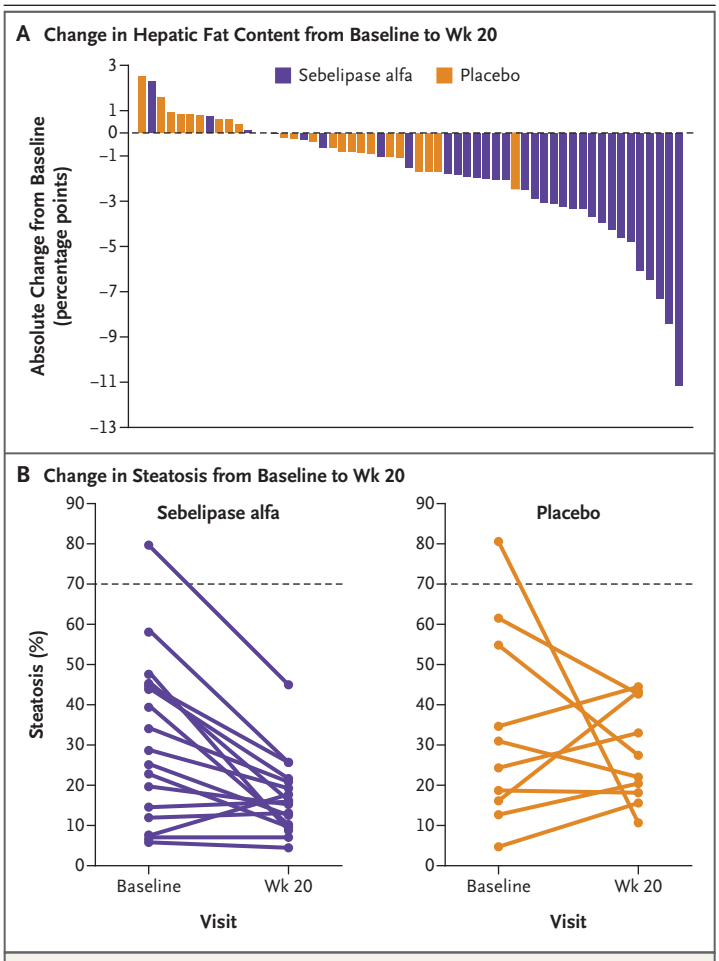

Figure 2. Effects of Sebelipase Alfa on Hepatic Fat.

Panel A shows changes in absolute hepatic fat content, as assessed by means of multi-echo gradient-echo MRI, in individual patients. Panel B shows changes in steatosis, as assessed by means of morphometry, in individual patients.

tially changed the outlook for patients with lysosomal storage disorders.[19] The results of our study showed the effectiveness and safety of enzyme-replacement therapy with sebelipase alfa in children and adults with lysosomal acid lipase deficiency. Significantly greater improvements, as compared with placebo, were seen in the primary end point and six consecutive secondary efficacy end points. The significant reductions in hepatic fat content, as assessed by means of multi-echo gradient-echo MRI, were consistent with the mechanism of action of sebelipase alfa in decreasing accumulated tissue lipid. Improvement in an orthogonal measure of hepatic fat content, microvesicular steatosis as assessed by means of morphometry, was not significant, possibly owing to small sample size. The mean baseline hepatic fat content of 8.7% in the sebelipase alfa group and 8.2% in the placebo group, as assessed by means of multi-echo gradient-echo MRI, was relatively low, as compared with values that have been described in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Given the marked differences in the composition and subcellular localization of lipids between lysosomal acid lipase deficiency and nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, absolute values for these patients cannot be meaningfully compared.[20,21]

Sebelipase alfa was associated with significant reductions in the LDL cholesterol level, with a decrease from baseline of 28.4 percentage points by week 20, as compared with a decrease of 6.2 percentage points in the placebo group. These reductions were accompanied by significant decreases in the triglyceride level and increases in the HDL cholesterol level. The continued reduction over time in the LDL cholesterol level between week 20 and week 36 is similar to findings in a long-term dosing study with sebelipase alfa.[9] Transient asymptomatic increases in the blood cholesterol and triglyceride levels were observed during the first 2 to 4 weeks of sebelipase alfa therapy. These observations are consistent with findings of earlier clinical trials of sebelipase alfa and are probably related to the mobilization of cholesterol and triglycerides into the circulation from hydrolysis of accumulated substrate in the tissues.[6,8]

Infusions with sebelipase alfa did not engender reactions that required routine premedication. One patient treated with sebelipase alfa did not complete the double-blind period because dosing was paused pending further investigation of an infusion-associated reaction. This patient successfully restarted therapy during the open-label period. Antidrug-antibody titers developed in few patients and were generally low and transient, with no apparent effect on the treatment response or safety profile, including infusion-associated reactions.

Our study has some limitations. The heterogeneous event and disease-progression rates and predominantly pediatric population precluded

assessment of some clinical-trial outcomes, such as long-term progression of liver disease, cardiovascular events, and mortality. In addition, although the study design controlled for the confounding effects of lipid-lowering medications and confirmed that sebelipase alfa reduced LDL cholesterol levels regardless of baseline status with regard to the use of lipid-lowering medication, the potential additional benefits of combining sebelipase alfa with lipid-lowering medications on the LDL cholesterol–lowering effect was not formally addressed in this study.

In conclusion, cirrhosis and severe dyslipidemia often develop at an early age in patients with lysosomal acid lipase deficiency. Enzyme replacement with sebelipase alfa in affected children and adults was superior to placebo in producing significant reductions in serum aminotransferase levels, disease-related lipid abnormalities, and hepatic fat content. The broad range of effects is consistent with a mechanism of action that addresses the enzyme deficiency and resultant lysosomal lipid accumulation that causes this multisystem disease. Because lysosomal cholesteryl esters, triglycerides, or both appear to be potent inducers of liver fibrosis (100% of the patients who underwent biopsy in the current study had evidence of fibrosis, and cirrhosis appeared within months after birth in the most severely affected patients),[4,22] the marked reductions in aminotransferase levels and other markers of hepatic disease and in hepatic fat content seen in this study suggest that sebelipase alfa may have potential value in reducing the risk of fibrosis and progression to cirrhosis among patients with lysosomal acid lipase deficiency.

Table 3. Adverse Events.

Event	Sebelipase Alfa (N=36)	Placebo (N=30)
	number (percent)	
Any adverse event during 20-wk double-blind period	31 (86)	28 (93)
Most common events during 20-wk double-blind period*		
Headache	10 (28)	6 (20)
Pyrexia	7 (19)	6 (20)
Diarrhea	6 (17)	5 (17)
Oropharyngeal pain	6 (17)	1 (3)
Upper respiratory tract infection	6 (17)	6 (20)
Epistaxis	4 (11)	6 (20)
Nasopharyngitis	4 (11)	3 (10)
Abdominal pain	3 (8)	1 (3)
Asthenia	3 (8)	1 (3)
Constipation	3 (8)	1 (3)
Cough	3 (8)	3 (10)
Nausea	3 (8)	2 (7)
Vomiting	3 (8)	3 (10)
Adverse event related to study drug	5 (14)	6 (20)
Severe adverse event	3 (8)	1 (3)
Infusion-associated reaction	2 (6)	4 (13)
Event leading to paused dosing	1 (3)†	0
Serious adverse event	2 (6)†‡	1 (3)§
Serious adverse event related to study drug	1 (3) †	0
Adverse event leading to death	0	0

* The most common adverse events during the 20-week double-blind period were defined as those reported by three or more patients in the sebelipase alfa group.
† One patient paused dosing during the double-blind study period after the second infusion, owing to an infusion-associated reaction. The patient restarted therapy during the open-label period.
‡ One patient had gastritis.
§ One patient had a motor vehicle accident.

Supported by Synageva BioPharma (now part of Alexion Pharmaceuticals). The study at Mount Sinai was supported by a grant (UL1TR000067) from the National Center for Research Resources, National Institutes of Health; and the study at Boston Children's Hospital, by a National Center for Advancing Translational Sciences grant (8UL1TR000170) from the Harvard Catalyst Clinical and Translational Science Center.

Dr. Burton reports receiving consulting fees from BioMarin Pharmaceutical, Shire, REGENXBIO, and Hyperion Therapeutics (now Horizon Pharma), lecture fees from Genzyme and Shire, and grant support from Genzyme, BioMarin Pharmaceutical, Shire, Synageva BioPharma, Ultragenyx Pharmaceutical, and Cytonet; Dr. Feillet, receiving fees for serving on advisory boards from Shire, BioMarin Pharmaceutical, Genzyme, and Merck Serono, and travel support from BioMarin Pharmaceutical, Genzyme, and Merck Serono; Drs. Burrow and Valayannopoulos, receiving grant support from Synageva BioPharma; Dr. Consuelo-Sánchez, receiving lecture fees from Synageva BioPharma; Dr. Kane, receiving grant and travel support from Synageva BioPharma; Dr. Eckert, being a former employee of Synageva BioPharma; Drs. Yang, Rojas-Caro, and Quinn, being employees of and holding stock options in Synageva BioPharma; and Dr. Quinn, being a named inventor on a patent (U.S. Patent No. 8,663,631) held by Synageva BioPharma related to the use of sebelipase alfa. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Elizabeth Daro-Kaftan, Ph.D., of Peloton Advantage for editorial and medical writing support (funded by Synageva BioPharma) and the following investigators in the Acid Lipase Replacement Investigating Safety and Efficacy (ARISE) trial: Martin Bialer, M.D., Ph.D., Norberto Bernardo Guelbert, M.D., Maria Kostyleva, M.D., Vera Malinova, M.D., Elaine Murphy, M.B., B.Ch., Yusof Rahman, M.B., B.Ch., José Pastor, M.D., Joanna Taybert, M.D., Ph.D., and Mikio Zeniya, M.D., Ph.D.

APPENDIX

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