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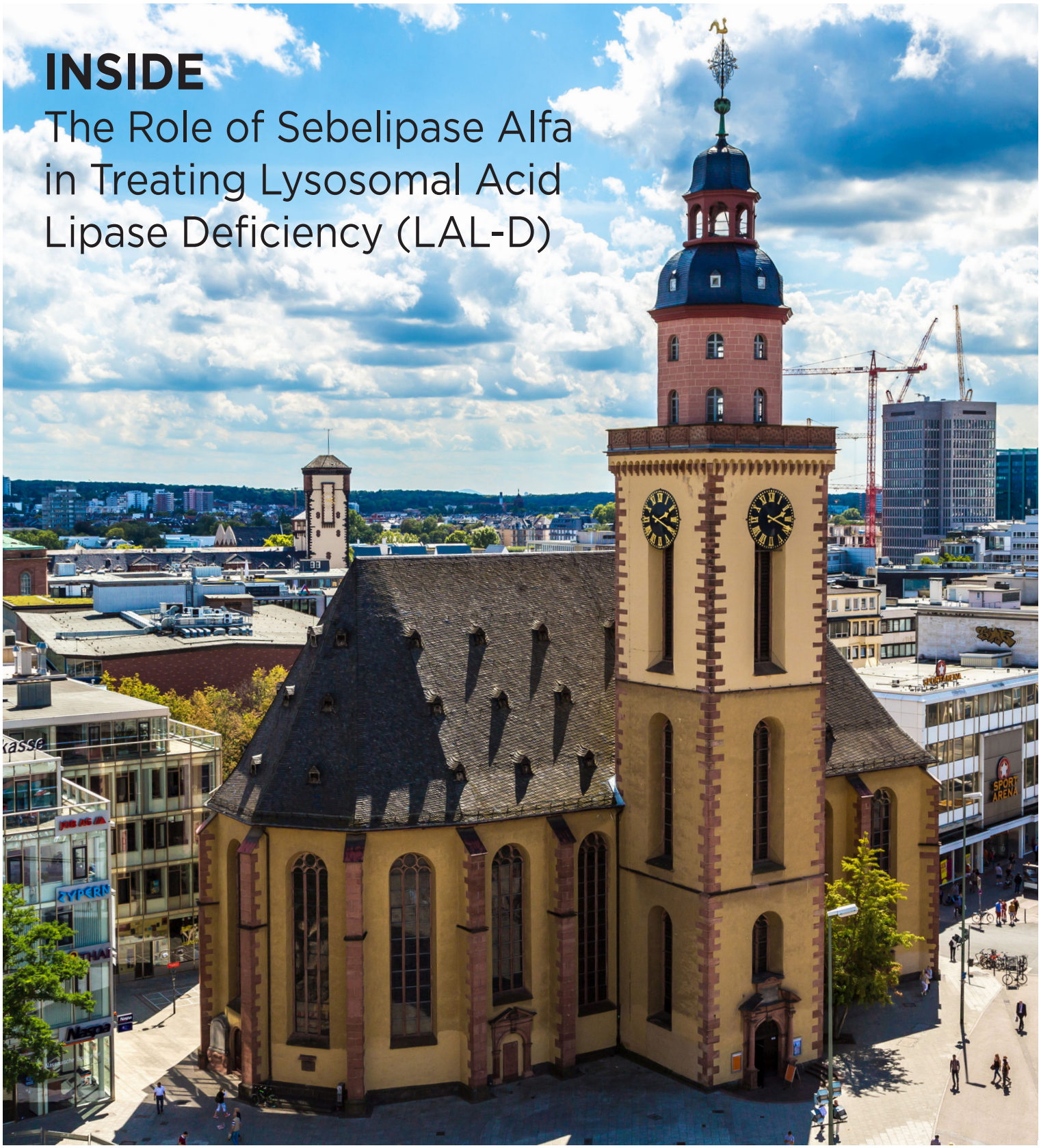

INSIDE

The Role of Sebelipase Alfa in Treating Lysosomal Acid Lipase Deficiency (LAL-D)

THE ROLE OF SEBELIPASE ALFA IN TREATING LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D)

Summary of presentations from the Alexion-Sponsored Educators Forum on LAL-D, held in Frankfurt, Germany, on 29th and 30th October 2015

Speakers

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MEETING SUMMARY

Lysosomal acid lipase deficiency (LAL-D), historically known as Wolman's disease or cholesteryl ester storage disease, is a severe, underdiagnosed, and rare disease associated with significant morbidity and premature mortality. LAL is involved in lipid hydrolysis, and deficiency induces lipid metabolism abnormalities, which affect multiple organ systems including the liver, cardiovascular system, spleen, and gastrointestinal (GI) system.

The most rapidly progressive cases of LAL-D are apparent during infancy. In these cases, the disease progresses very rapidly and is likely to be fatal within the first 6 months of life. At the same time, LAL-D can also progress less rapidly, in which case clinically severe manifestations may not be observed until later in childhood or adulthood. Low awareness of the disease contributes to under and misdiagnosis of LAL-D.

LAL-D can be difficult to distinguish from other conditions as the signs and symptoms are non-specific and overlap with more commonly occurring liver or lipid abnormalities such as heterozygous familial hypercholesterolaemia and non-alcoholic fatty liver disease (NAFLD). When LAL-D is suspected, it can be rapidly diagnosed using a dry blood spot enzymatic test.

Sebelipase alfa is a LAL enzyme replacement. It is the first drug therapy for the treatment of LAL-D and was recently approved in the European Union and the USA. Sebelipase alfa has been shown to both improve survival and slow disease-progression markers in patients with LAL-D.

Lysosomal Acid Lipase Deficiency: A Progressive Disease Associated with Multiorgan Damage and Premature Mortality

Doctor Florian Abel

LAL-D is a rare and progressive genetic disease that was first characterised in the mid-1900s.[1,2] The disease was previously known as Wolman's disease in infants, and as cholesteryl ester storage disease in children and adults. However, it is now known that these conditions are both manifestations of the same disease.[2] LAL-D affects lipid metabolism and consequently causes damage to multiple organ systems, including the cardiovascular system, liver, spleen, and GI system.[1,2] Typical clinical symptoms in infants include growth failure, persistent vomiting, diarrhoea, hepatosplenomegaly, adrenal calcification, and abdominal distension.[1,2] If LAL-D is suspected, it is essential to obtain a prompt diagnosis because the disease leads to a rapid deterioration of the patient's condition and is usually fatal in infants,[2] with a median age at death of 3.7 months.[3] Although progression is less rapid in older children and adults, the effects of LAL-D are still severe and remain associated with significant morbidities and premature mortality.[1,2] For example, approximately 50% of patients progress to fibrosis, cirrhosis, or liver transplant within 3 years of symptom onset (Data on file, Alexion 2015).

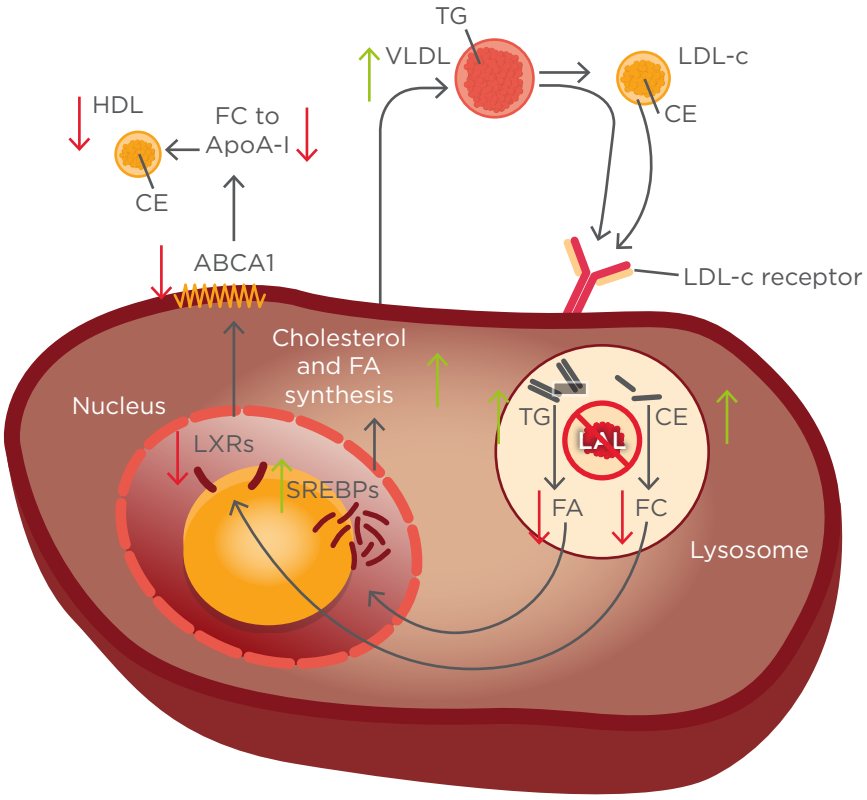

Figure 1: Effect of LAL-D on lipid metabolism in plasma and hepatocytes.[5]

Receptors on the hepatocyte (most notably the LDL-c receptor) facilitate uptake of cholesterol and triglycerides via LDL and VLDL, which are then delivered to lysosomes. Under normal conditions, LAL would hydrolyse the lipids to release free FAs and free cholesterols that the cell can use for various functions. If LAL activity is diminished, these lipids are not hydrolysed resulting in an accumulation of CEs and TGs in the lysosomes. This leads to a compensatory increase of synthesis of free FAs and free cholesterol in the hepatocyte through the SREBP pathway, which are released from the hepatocyte and can eventually re-enter the cycle. In parallel, plasma levels of HDL cholesterol are reduced due to a reduced efflux of cholesterol through decreased expression of ABCA1, downregulated through the LXR pathway.

ABCA1: ATP-binding cassette transporter A1; ApoA-I: apolipoprotein A-I; CE: cholesteryl ester; FC: free cholesterol; FA: fatty acids; HDL: high-density lipoprotein; LAL: lysosomal acid lipase; LDL-c: low-density lipoprotein cholesterol; LXR: liver X receptor; SREBPs: sterol regulatory element-binding proteins; TG: triglycerides; VLDL: very-low-density lipoprotein.

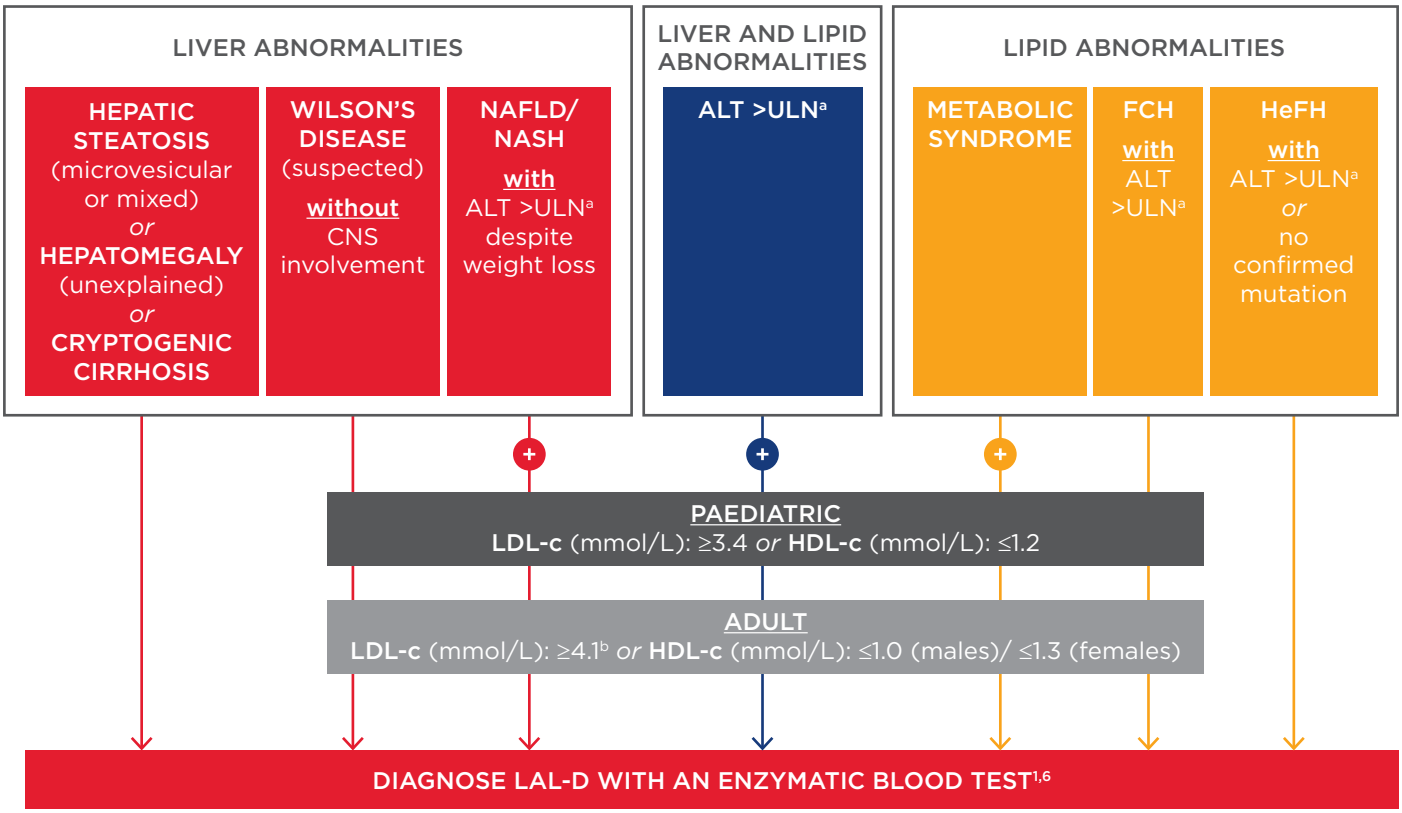

Figure 2: High-risk patient groups for LAL-D.

ALT: alanine aminotransferase; CNS: central nervous system; FCH: familial combined hyperlipidaemia; HDL-c: high-density lipoprotein cholesterol; HeFH: heterozygous familial hypercholesterolaemia; LAL-D: lysosomal acid lipase deficiency; LDL-c: low-density lipoprotein cholesterol; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; ULN: upper limit of normal.

a) Age and gender-specific.[2]

b) LDL-c ≥3.4 mmol/L in patients on lipid-lowering medications.[2]

Currently, published literature regarding patients with LAL-D includes case studies and clinical trials, the data from which represent approximately 300 patients. Estimates of prevalence vary widely, ranging from 1:130,000 to 1:300,000 depending on location and ethnicity.[2,4] Paediatric patients represent a substantial proportion of disease burden, with the first reported manifestations of LAL-D occurring at a median age of 5 years.[2] However, it is likely that the burden in adults is greater than that currently reported due to under and misdiagnosis. LAL-D in children and adults can be challenging to diagnose as many of the signs and symptoms of the disease are shared with more frequently occurring lipid disorders and liver diseases, such as heterozygous familial hypercholesterolaemia or NAFLD.[1,2]

Pathophysiology

LAL-D is an autosomal, recessive, lysosomal-storage disorder caused by mutations of the *LIPA* gene that result in little or no LAL activity.[2] The function of LAL is to process cholesteryl esters and triglycerides within lysosomes. This leads to the release of free cholesterol and free fatty acids that the cell can use for various essential functions. In the absence of LAL, lipids accumulate in the lysosome. The lack of free cholesterol or free fatty acid release leads to the upregulation of the expression of low-density lipoprotein (LDL) receptors on the cell surface, and the synthesis and packaging of cholesterol in the hepatocytes, as shown in Figure 1.[1,2,5] Dyslipidaemia and widespread abnormal fat deposition in organs ensue as a result of progressive lipid accumulation. This results in microvesicular liver steatosis, accelerated atherosclerosis, malabsorption, and ultimately severe organ damage.[1]

Almost all patients with LAL-D experience liver manifestations (86% of patients) and/or cardiovascular manifestations including lipid level

abnormalities (87% of patients).[1] In the liver, LAL-D manifests as microvesicular or mixed steatosis, fatty liver, hepatomegaly, and elevated transaminases, progressing to fibrosis and/or micronodular cirrhosis, and eventually portal hypertension and liver failure.[1,2] Life-threatening liver damage can occur at a very young age in patients with LAL-D. The youngest reported death due to liver disease occurred at 7 years of age, and one case of microvesicular steatosis *in utero* has been reported.[1] In the cardiovascular system, progressive damage is caused as a result of dyslipidaemia and accelerated atherosclerosis, which can lead to coronary artery disease, stroke, and/or myocardial infarction.[1] Manifestations in the spleen are also important; they include splenomegaly, hypersplenism, thrombocytopaenia, and anaemia.[1,6] Almost one quarter of patients report GI symptoms such as abdominal pain, emesis, gallbladder dysfunction, diarrhoea, GI bleeding, and malabsorption.[1,2] Effects on the GI system contribute to failure to thrive in infants and children, including low body mass index and short stature.[2,7]

Diagnosis

Diagnosis of LAL-D can be challenging.[1,2,7] The LAL-D patient population is disproportionately younger than the general population, although it is likely that LAL-D is under or misdiagnosed in older patients.[2,8] This is because the disease can easily be confused with other conditions that are more likely to occur later in life, and which share signs and symptoms with LAL-D.[1]

When LAL-D is suspected, it can be diagnosed quickly with a dry blood spot test to detect LAL enzyme activity and/or by genetic testing. The most frequent mutation observed in white, Caucasian patients is the c.894G>A mutatation of the *LIPA* gene (either homozygous or compound heterozygous), but it should be noted that this mutation may not be as common in patients with other ethnic and racial backgrounds.[4] Testing for LAL-D should be performed in patients with liver and/or lipid abnormalities as per the criteria outlined in Figure 2.

One of the key conditions with symptoms that overlap with those of LAL-D is NAFLD, although certain risk factors may help to distinguish between the two. Patients with NAFLD tend to be older than those with LAL-D as NAFLD is uncommon in children <10 years of age. Patients with NAFLD also tend to be overweight or obese, whereas LAL-D patients generally do not. A liver biopsy to confirm the type and degree of liver steatosis or fibrosis can help to diagnose NAFLD; however, prior to this, LAL-D should be ruled out using a blood test.[9,10]

Wilson's disease also presents symptoms common to LAL-D but in Wilson's disease there is frequently a central nervous system (CNS) component that is not present with LAL-D. This can assist in the differential diagnosis in adults. A LAL-D test should be performed in infants and children when Wilson's disease is suspected, as the CNS component of Wilson's disease or other unique differential diagnostic criteria may not be evident.[11,12] Other common misdiagnoses include Gaucher's disease, Niemann–Pick type B,[13,14] heterozygous familial hypercholesterolaemia, familial defective apolipoprotein B, fibrosing cholestatic hepatitis, and polygenic hypercholesterolaemia.[2] LAL-D should also be tested for when any of these diseases are suspected.

Treatment

Sebelipase alfa therapy is a unique enzyme replacement therapy for the treatment of LAL-D, which addresses the underlying pathophysiology of the disease. It has been shown to improve survival in infants,[15] and the signs and symptoms of the disease in children and adults.[15-18] Sebelipase alfa is currently the only treatment option that addresses the underlying pathophysiology of the disease. There are also supportive treatment options that have been used to provide relief from the signs and symptoms of LAL-D. These supportive options include use of a low-fat diet,[19] use of lipid-lowering agents such as statins,[2,5] liver transplantation,[2] and haematopoietic stem cell transplantation.[2] However, no well-controlled studies have proven that any of these treatments are safe or effective in patients with LAL-D.[2,5,19]

Sebelipase Alfa for the Treatment of LAL-D

Professor Barbara K. Burton

Sebelipase alfa is a recombinant human LAL that replicates the enzyme activity in patients with LAL-D. It binds to cell surface receptors via glycans expressed on the protein, and is internalised into lysosomes where it catalyses the hydrolysis of cholesteryl esters and triglycerides to free cholesterol and free fatty acids.[5]

Sebelipase alfa was approved in the European Union on 28 August 2015 [20] and in the USA[21] on 8 December 2015, for patients of any age with LAL-D. In infants presenting with LAL-D during the first 6 months of life, sebelipase alfa should be administered once weekly as an intravenous infusion at a dose of 1 mg/kg, which can be escalated to 3 mg/kg once weekly in patients who do not achieve optimal response. In paediatric and adult patients, the approved dose is 1 mg/kg as an intravenous infusion given once every other week. No dose escalation strategy has been tested in this group. Infusions of sebelipase alfa should be administered over a period of approximately 2 hours, but this may be shortened to 1 hour once patient tolerability has been established. Sebelipase alfa is contraindicated in patients who experience life-threatening hypersensitivity to sebelipase alfa or have an allergy to egg or any of the inactive ingredients. To minimise the risk of hypersensitivity reactions, patients should be observed for at least 1 hour after the first infusion of sebelipase alfa has concluded, or after a dose escalation.

Clinical Trial Programme

To date, eight clinical investigations, either natural history studies or clinical trials involving sebelipase alfa, have been initiated, as follows:

- LAL-1-NH01 (NCT01358370; completed) - a chart review to establish the natural history of LAL-D in 35 infants[3]
- LAL-2-NH01 (NCT01528917; completed) - a chart review to establish the natural history of LAL-D in 49 children and adults[8]
- LAL-CL01 (NCT01307098; completed) - a Phase I trial in nine adult patients[16]
- LAL-CL04 (NCT01488097; ongoing) - an extension study of LAL-CL01[16,17]
- LAL-CL02/ARISE (NCT01757184; ongoing) - a Phase III trial in 66 children and adults[18]
- LAL-CL03 (NCT01371825; ongoing) - a Phase II/III trial in nine infants[15]
- LAL-CL06 (NCT02112994; ongoing) - a study including children and adults
- LAL-CL08 (NCT02193867; recruiting) - an ongoing study in infants

Table 1: Summary of efficacy endpoint results in the ARISE trial.[18]

Endpoint	Sebelipase alfa N=36	Placebo N=30	P-value
Primary endpoint			
Normalisation of ALT level, n/N (%)	11/36 (31)	2/30 (7)	0.03
Secondary endpoints			
Change from baseline in LDL cholesterol level, percentage points	−28.4±22.3	−6.2±13.0	<0.001
Change from baseline in non-HDL cholesterol level, percentage points	−28.0±18.6	−6.9±10.9	<0.001
Normalisation of AST level, n (%)	15/36 (42)	1/29 (3)[a]	<0.001
Change from baseline in triglyceride level, percentage points	−25.5±29.4	−11.1±28.8	0.04
Change from baseline in HDL cholesterol, percentage points	19.6±16.8	−0.3±12.4	<0.001
Change from baseline in hepatic fat content, percentage points[b]	−32.0±26.8[c]	−4.2±15.6[d]	<0.001
Reduction in steatosis, n (%)[e]	10/16 (62)	4/10 (40)	0.42
Change from baseline in liver volume, percentage points	−10.3±10.5[f]	−2.7±10.1[g]	–[h]

Values are mean ±SD unless otherwise stated.
[a]one patient in the placebo group had a normal AST level at baseline; [b]measured using multiple gradient-echo magnetic resonance imaging; [c]N=32; [d]N=25; [e]paired biopsy samples were required in patients ≥18 years of age unless contraindicated and were optional in patients <18 years of age; [f]N=33; [g]N=27; [h]the p-value could not be interpreted as significant owing to the lack of statistical significance of the endpoint above according to the pre-specified fixed-sequence, hypothesis-testing method.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
From a Phase III Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency.[18] Copyright © 2015 Massachussets Medical Society. Reprinted with permission from Massachusetts Medical Society.

Key results: infants (LAL-CL03)[15]

LAL-CL03 was a multicentre, open-label, dose-escalation, Phase II/III trial in infants with growth failure or other evidence of rapidly progressing LAL-D. It was considered unethical to perform a placebo-controlled study, and therefore the results were compared with findings from the chart review study LAL-1-NH01. Nine infants were included in the LAL-CL03 trial for a duration of ≥24 months and investigations are continuing in surviving patients. The primary endpoint, survival at 1 year, was met in 6 of the 9 infants included in the study. In comparison, none of the 21 infants included in LAL-1-NH01 who had early growth failure and were not treated with either a haematopoietic stem cell transplant or liver transplant reached 1 year of age.[3] Improvements in liver function were also observed after 1 year, with decreases in baseline levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of 34.0 U/L and 44.5 U/L, respectively. After 1 year, mean weight-for-age percentile improved from 12.74% at baseline to 29.83% and mean serum albumin level increased from 26.7 g/L at baseline to 38.7 g/L. A number of adverse events (AEs) were reported in the study and, because of the low number of patients, all AEs experienced by one or more patients were reported as 'very common'. Many of the AEs reported were typical complaints associated with infancy. The main concern associated with sebelipase alfa was the possibility of a life-threatening allergic reaction during or after treatment infusion.[20,21]

Key results: children and adults (LAL-CL02/ARISE)[18]

ARISE was a multicentre, randomised, placebo-controlled, double-blind, 20-week, Phase III clinical trial designed to assess the efficacy and safety of sebelipase alfa in children and adults with LAL-D. An open-label, observational extension is ongoing, in which all patients are being treated with sebelipase alfa. The study included male and female patients aged ≥4 years if they had confirmed enzyme activity-based diagnosis of LAL-D using the dried-blood spot assay.[22] Patients were also required to have an ALT level ≥1.5-times the upper limit of normal and any patients using lipid-lowering medications were required to use them at a stable dose for at least 6 weeks before screening, and to continue on this dose during the study.

During the double-blind treatment period, 36 patients were randomised to receive sebelipase alfa, and 30 were randomised to placebo. The baseline characteristics across the groups were considered to be generally well balanced, although there were minor differences that were considered to be unavoidable due to the low number of patients. The mean (±SD) age of patients at screening was 17 (±12) and 15 (±10) years in the sebelipase alfa and placebo arms, respectively. Gender distribution was equal in both treatment arms and the majority of patients were white and of European ancestry. Most patients had the c.894G>A mutatation (either homozygous or compound heterozygous). The mean (±SD) ALT level was 105 (±45) U/L in the sebelipase alfa arm and 99 (±42) U/L in the placebo arm. Patients in both arms had elevated levels of LDL/non-high-density lipoprotein (HDL) cholesterol and triglycerides, and decreased levels of HDL cholesterol compared with the general population.

The primary endpoint was normalisation of ALT at 20 weeks. This was achieved in 31% of patients in the active treatment arm and 7% of patients in the placebo arm; the treatment difference was statistically significant (p=0.027) (Table 1) and improvements were observed within 2 weeks of treatment initiation (Alexion, data on file). Normalisation of AST was assessed as a secondary endpoint and was achieved in 42% of patients treated with sebelipase alfa and 3% of patients in the placebo arm; the treatment difference was statistically significant (p=0.0003). With respect to prespecified, key, secondary, efficacy end points, improvements in lipid levels and reduction in hepatic fat content were observed (p<0.001 for all comparisons, except p=0.04 for triglycerides), as shown in Table 1.

AEs were reported by 31/36 patients (86%) treated with sebelipase alfa and 28/30 patients (93%) in the placebo arm during the double-blind treatment period. All AEs reported in two or more patients were reported as common due to the low number of patients. AEs considered by the investigators to be related to the study drug were reported in five patients in the sebelipase alfa group and six in the placebo group. A total of three patients experienced serious AEs, two in the sebelipase alfa group (n=1 infusion associated reaction, n=1 gastritis), and one in the placebo group (motor vehicle accident). The infusion associated reaction occurred after the second infusion and was the only serious AE considered related to the study drug; the patient restarted treatment during the open-label extension. No AEs leading to death were reported.

The implications of this study are that treatment with sebelipase alfa provides significant improvements in liver function, serum lipid levels, and hepatic fat content versus placebo, and that the side-effect profile of sebelipase alfa is acceptable. These findings support the efficacy, safety, and tolerability findings of the Phase I/II trial and extension study in adults, and also support efficacy and safety in children. Further improvements in lipid levels have been observed during the open-label study extension.[18]

Summary of Findings from the Clinical Trial Programme

In summary, these trials have demonstrated that sebelipase alfa therapy improves survival in infants with rapidly progressive LAL-D. In addition, when compared with placebo, children and adults who received sebelipase alfa experienced significant improvements in ALT levels, liver fat content, spleen volume, and cholesterol levels. No data are currently available on the longer-term effects of sebelipase alfa, such as potential reversal or stabilisation of liver fibrosis. As with all enzyme replacement treatments, development of antibodies is a potential risk.[18] To monitor and assess this risk, Alexion are providing a service to enable physicians to monitor their patients for the development of antibodies to sebelipase alfa.[20]

Patient's Perspective

Mister Brett Billmeyer

Mr Billmeyer was one of the first people recruited to the sebelipase alfa clinical trial programme in 2011 and is a patient advocate running the LAL Solace organisation.

In 1993 and at the age of 23 years, Mr Billmeyer was informed of an abnormality after donating blood but did not act upon this. In 2001, Mr Billmeyer's elevated cholesterol levels led him to visit a physician, who prescribed diet and exercise, but no further investigations were performed due to the lack of other concerning risk factors. However, Mr Billmeyer already led what he considered to be a healthy and active lifestyle, he regularly participated in sports and was active in his work as a police officer. By 2007, Mr Billmeyer's cholesterol levels had risen above 300 mg/dL, and another physician prescribed statins and performed further investigations. Liver function tests showed above normal ALT and AST levels, although not dramatically so. An ultrasound identified gallstones, and although none were found during surgery, the surgeon observed that Mr Billmeyer had an extremely fatty liver. As a result, Mr Billmeyer was referred to various specialists over the course of the next 2 years. Various potential conditions were suggested, including Wilson's disease, NAFLD, non-alcoholic steatohepatitis, and John–Gilbert's syndrome. LAL-D was diagnosed after a blood test at the age of 39 years. This long period between manifestation of symptoms and confirmation of LAL-D attests to the difficulty of diagnosing this condition in adults.

Mr Billmeyer's initial reaction was shock and concern, particularly after reading negative information online which indicated a very short life expectancy. Due to this concern, Mr Billmeyer began to research clinical trials and consequently came across the sebelipase alfa clinical trial programme. Mr Billmeyer was treated with sebelipase alfa while participating in the clinical trial programme and continues to be treated with the drug. In 2014, his liver had recovered from extreme fat content with microvesicular steatosis and fibrosis (identified in a previous biopsy in 2007) and his condition was lowered to mild microvesicular steatosis with no fibrosis. He has now been in treatment for over 4 years, and at the last test his HDL cholesterol levels were in normal range (previously below average) and his LDL cholesterol level was 39 mg/dL. At the time of his last test, he was being treated with a statin, but has since discontinued this and awaits his next lipid tests to see the impact of this change in treatment. Mr Billmeyer reported feeling healthy, both before and after LAL-D diagnosis, and has not had any adverse reactions to treatment with sebelipase alfa.

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