

**Sebelipase alfa** (reassessment after expiry of the deadline (lysosomal acid lipase deficiency))

Resolution of: 3 June 2021  
Entry into force on: 3 June 2021  
BAnz AT 09 08 2021 B1

Valid until: unlimited

**Therapeutic indication (according to the marketing authorisation of 28 August 2015):**

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

**Therapeutic indication of the resolution (resolution of 3/6/2021):**

see therapeutic indication according to marketing authorisation.

**1. Extend of the additional benefit and significance of the evidence:**

Sebelipase alfa is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months):

**Extend of the additional benefit and significance of the evidence of sebelipase alfa:**

Hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))

**Extend of the additional benefit and significance of the evidence of sebelipase alfa:**

Hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

## Study results according to endpoints:<sup>1</sup>

a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months):

### Summary of results of relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	∅	There are no evaluable data.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

Study results of the single-arm studies LAL-CL03 and LAL-CL08 with sebelipase alfa and their indirect comparisons with the observational study LAL-1-NH01 for the endpoint Mortality

	LAL-CL03 <sup>1)</sup> N = 9	LAL-CL08 <sup>2)</sup> N = 10	LAL-1- NH01 <sup>3)4)</sup> N = 25	LAL-CL03 vs LAL-1-NH01	LAL-CL08 vs LAL-1-NH01
Endpoint Time	Number of deaths n (%)			Hazard ratio <sup>5)</sup> (95% CI) <sup>6)</sup> ; p value <sup>7)</sup> ;	
<b>Mortality</b>					
<b>Number of deaths</b>					
up to the age of 12 months	3 (33)	1 (10)	24 (96)	0,17 (0.05; 0.59); 0,0017	0,04 (0.01; 0.29); <0.0001
up to the age of 24 months	4 (44)	2 (20)	25 (100)	0,17 (0.06; 0.53); 0,0008	0,05 (0.01; 0.24); <0.0001
up to the age of 36 months	4 (44)	2 (20)	25 (100)	0,17 (0.06; 0.53); 0,0008	0,05 (0.01; 0.24); <0.0001
up to the age of 48 months	4 (44)	--	25 (100)	0,17 (0.06; 0.53); 0,0008	--
up to the age of 60 months	4 (44)	--	25 (100)	0,17 (0.06; 0.53); 0,0008	--

<sup>1)</sup>Data from the dossier assessment of the G-BA (published on 15 March 2021), and from the amendment to the dossier assessment, unless otherwise indicated.

Endpoint Study	Sebelipase alfa		
	Time	N <sup>8)</sup>	z-score
<b>Morbidity</b>			
<b>Age-related weight (z-scores)</b>			
<i>LAL-CL03 study N = 9</i>			
Baseline <sup>9)</sup> MV (SD) Median (min; max)	8	-1.9 (1.6) -1.9 [-4.8; 0.7]	-
Week 240 MV (SD) Median (min; max)	5	-0.2 (1.4) -0.7 [-1.4; 1.9]	1.8 (1.2) 1.1 [0.5; 3.4]
<i>LAL-CL08 study N = 10</i>			
Baseline <sup>9)</sup> MV (SD) Median (min; max)	10	-2.3 (1.6) -2.5 [-4.5; 0.8]	
Week 156 MV (SD) Median (min; max)	5	0.5 (0.6) 0.7 [-0.5; 1.1]	2.8 (1.1) 2.7 [1.7; 4.7]
<b>Weight in relation to length (z-scores)</b>			
<i>LAL-CL03 study N = 9</i>			
Baseline <sup>9)</sup> MV (SD) Median (min; max)	8	-0.5 (1.5) -0.5 [-3.1; 1.4]	
Week 240 MV (SD) Median (min; max)	5	0.2 (1.1) 0.2 [-1.0; 1.4]	1.0 (2.2) 1.0 [-1.2; 4.4]
<i>LAL-CL08 study N = 10</i>			
Baseline <sup>9)</sup> MV (SD) Median (min; max)	9	-1.6 (2.0) -2.3 [-3.8; 2.5]	-
Week 156 MV (SD) Median (min; max)	5	0.8 (0.5) 1.0 [0.2; 1.3]	2.5 (2.4) 2.9 [-1.4; 5.1]
<b>Body Mass Index (z-scores)</b>			
<i>LAL-CL03 study N = 9</i>			
Baseline <sup>9)</sup> MV (SD) Median (min; max)	8	-1.3 (1.5) -1.0 [-4.1; 0.3]	
Week 240 MV (SD) Median (min; max)	5	0.4 (1.2) 0.4 [-1.1; 1.6]	2.0 (1.8) 1.3 [0.1; 4.4]
<i>LAL-CL08 study N = 10</i>			
Baseline <sup>9)</sup> MV (SD) Median (min; max)	8	-1.9 (1.9) -2.6 [-4.4; 1.6]	
Week 156 MV (SD) Median (min; max)	5	0.9 (0.5) 1.0 [0.4; 1.5]	2.9 (2.3) 3.2 [-0.6; 5.9]

Endpoint Study	Sebelipase alfa				
	N <sup>8)</sup>	N <sup>10)</sup>	Normal <sup>11)</sup> n (%) <sup>12)</sup>	Noticeable <sup>11)</sup> n (%) <sup>12)</sup>	Not testable <sup>11)</sup> n (%) <sup>12)</sup>
<b>Denver II development test</b>					
<i>LAL-CL03 study N = 9</i>					
Denver II - Fine motor skills and adaptation					
Baseline <sup>9)</sup>	3	9	_13)	_13)	_13)
Week 216	4	5	4 (80.0)	0 (0.0)	0 (0.0)
Denver II - Gross motor skills					
Baseline <sup>9)</sup>	3	9	_13)	_13)	_13)
Week 216	4	5	4 (80.0)	0 (0.0)	0 (0.0)
Denver II - Language ability					
Baseline <sup>9)</sup>	3	9	_13)	_13)	_13)
Week 216	4	5	4 (80.0)	0 (0.0)	0 (0.0)
Denver II - Social contacts					
Baseline <sup>9)</sup>	3	9	_13)	_13)	_13)
Week 216	4	5	4 (80.0)	0 (0.0)	0 (0.0)
<i>LAL-CL08 study; N=10</i>					
Denver II - Total Score <sup>14)</sup>					
Baseline <sup>9)15)</sup>	6	10	_13)	_13)	_13)
Week 144 <sup>16)</sup>	5	7	2 (28.6)	3 (42.9)	0 (0.0)
<b>Quality of life</b>					
There are no evaluable data.					
Endpoint	LAL-CL03 (VITAL) <sup>11)</sup> N = 9 n (%)		LAL-CL08 <sup>2)</sup> N = 10 n (%)		
<b>Side effects</b>					
AE	9 (100)		10 (100)		
Severe AE	4 (44) <sup>17)</sup>		7 (70) <sup>18)</sup>		
SAE	9 (100)		10 (100)		
AE, which led to the discontinuation of the study medication	0 (0)		6 (60) <sup>19)</sup>		
<sup>1)</sup> Evaluation based on the FAS. The median duration of exposure (min; max) to SA was 241.7 weeks (0; 262). <sup>2)</sup> Evaluation based on the FAS. The median duration of exposure (min; max) to SA was 147.6 weeks (3; 160). <sup>3)</sup> No data are available on the duration of observation in the retrospective LAL-1-NH01 study (N=21; N=25). <sup>4)</sup> Individuals who were untreated and had early failure to thrive. Untreated is defined as individuals who have had no preparatory procedures for hematopoietic stem cell or liver transplantation. Data on the observation period are not available. <sup>5)</sup> Data from module 4. The hazard ratio was determined using the Cox method. <sup>6)</sup> Data from module 4. Confidence intervals were calculated using the Clopper-Pearson method. <sup>7)</sup> The p-value was determined by a log-rank test. <sup>8)</sup> Number of people included in the analysis. <sup>9)</sup> Baseline corresponds to the last measurement before the first SA infusion. <sup>10)</sup> Number of subjects with available data or who have not died or dropped out of the study. Two individuals died at 4.9 months and 13.8 months of age, respectively. Due to the sponsor's decision (market approval of the investigational drug), two subjects switched to the commercially available therapy after 123 and 156 weeks, respectively, which prevented the endpoint from being assessed for these subjects during the course of the study. <sup>11)</sup> Based on demographic norm values, the testing personnel evaluates for each test item whether the result for the corresponding age group of the respective child fell within the associated normal range or was to be rated as noticeable.					

The 4 test areas were classified as "normal", "noticeable" or "not testable". A result was categorised as "untestable" if it was not possible to administer the test to a child.

- <sup>12)</sup> Percentages refer to the FAS population minus deceased participants.  
<sup>13)</sup> No presentation is made as the return rate (<70%) was not met.  
<sup>14)</sup> The results from the study report were presented. These are different from those in Module 4.  
<sup>15)</sup> In Module 4, information is provided on the screening visit instead of baseline. Data from 7 individuals were available for screening. 4 persons (40%, related to the FAS population) were assigned to the test result "noticeable", two persons (20%) to the test result "normal" and one person (10%) to the test result "not testable".  
<sup>16)</sup> Inconsistent information between the benefit dossier (Module 4) and the study report. Data in the table refer to the study report. According to Module 4, data were available for four individuals (66.7%) at week 144: One person (10%) was assigned to the test result "normal", 3 persons (70%) to the test result "noticeable" and no person (0%) to the test result "not testable".  
<sup>17)</sup> The severity of AE was determined using CTCAE version 4.0.  
<sup>18)</sup> The severity of AE was determined using "Clinical Data Interchange Standards Consortium Study Data Tabulation Model" standard terminology v3.1.1.  
<sup>19)</sup> There is inconsistent information in the study records as 0 (0%) individuals are reported here. The explanation for the 6 (60%) subjects includes permanent discontinuation of study medication or withholding of medication.

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; FAS: Full analysis set; CI: Confidence interval; MV: Mean value; SA: Sebelipase alfa; SD: Standard deviation; SAE: (Serious) adverse events; AE: Adverse event

### Register ALX-LALD-501

Side effects	
Global patients with at least one ...	Ever treated with sebelipase alfa <sup>1)</sup>
	N = 18 <sup>2)</sup> n (%)
AE	9 (50)
Severe AE <sup>3)</sup>	2 (11)
SAE	6 (33)
AE, which led to the discontinuation of the study medication <sup>4)</sup>	1 (6)

<sup>1)</sup> All AE from inclusion in the registry were recorded for the safety population. This included all individuals who had ever been treated with sebelipase alfa without having a confirmed diagnosis of LAL.  
<sup>2)</sup> Data on observation time are not available for the safety population (n = 18). Patients with LAL deficiency in infancy (ever treated with SA, n = 16) were followed in the registry for a median (min; max) of 1.1 years (0.0; 2.9) until the data cut-off point. The total median (min; max) treatment time with SA for individuals with LAL deficiency in infancy was 4.1 years (2.5; 8.8).  
<sup>3)</sup> The severity of AE was determined using "Clinical Data Interchange Standards Consortium Study Data Tabulation Model" standard terminology v3.1.1.  
<sup>4)</sup> Data from module 4.

Abbreviations: LAL: Lyosomal Acid Lipase; SAE: (Serious) adverse events; AE: Adverse event

b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))

### Summary of results of relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant difference for the benefit assessment.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

LAL-CL02 (ARISE) study: RCT, sebelipase alfa (SA) vs placebo (PBO); double-blind study phase over 20 weeks

Endpoint	Sebelipase alfa (N = 36)		Placebo (N = 30)		
<b>Mortality</b>					
There were no deaths.					
	Sebelipase alfa		Placebo		SA vs. PBO
Endpoint Time	n <sup>1</sup> /N <sup>2</sup>	MV (SD)	n <sup>1</sup> /N <sup>2</sup>	MV (SD)	Change from baseline MD; p value <sup>3</sup>
<b>Morbidity</b>					
<b>FACIT-Fatigue<sup>4</sup></b>					
Baseline <sup>5</sup>	13/13	44.3 (6.55)	7/7	38.6 (12.66)	-
Week 20 <sup>6/7</sup>	13/13	44.2 (8.01)	7/7	38.6 (11.65)	-0.,2; 0.8731

	Sebelipase alfa N = 36		Placebo N = 30		RR [95% CI] <sup>10)</sup> p value <sup>11)</sup> ;	
	Share with available data <sup>8)</sup> n	Share with normalisation <sup>9)</sup> n (%)	Share with available data <sup>8)</sup> n	Share with normalisation <sup>9)</sup> n (%)		
<b>ALT normalisation - shown in addition</b>						
Week 20 <sup>6)12)</sup>	36	11 (31)	30	2 (7)	4.58 [1.10; 19.09] 0.037 <sup>13)</sup>	
	Sebelipase alfa N = 36		Placebo N = 30		MD (SE) [95% CI] p value <sup>3)</sup> ;	
Endpoint Time	n	MV (SD)	n	MV (SD)	Absolute	Percentage
<b>LDL-C concentration changes - supplementary presentation</b>						
Baseline <sup>5)</sup> LDL-C concentration (mg/dl) <sup>14)</sup>	36	189.9 (57.2)	30	229.5 (70.0)		
Week 20 <sup>6)15)</sup> LDL-C concentration (mg/dl) <sup>14)</sup>	36	138.8 (66.4)	30	213.3 (65.9)	-34.9 (10.12) [-55.16; -14.72] 0.0001	-22.2 (4.61) [-31.33; -12.90] < 0.0001
Absolute change		-51.1 (45.5)		-16.2 (34.7)		
Percentage change		-28.4 (22.3)		-6.2 (13.0)		
	Sebelipase alfa		Placebo		SA vs. PBO	
Endpoint Time	n <sup>1)/N<sup>16)</sup></sup>	MV (SD)	n <sup>1)/N<sup>16)</sup></sup>	MV (SD)	Change from baseline MD; p value <sup>3)</sup>	
<b>Quality of life</b>						
<b>CLDQ<sup>17)</sup></b>						
CLDQ - Total score						
Baseline <sup>5)</sup>	13/13	6.03 (0.79)	7/7	5.23 (1.44)	-	
Week 20 <sup>6)7)</sup>	13/13	6.14 (0.83)	7/7	5.54 (1.30)	-0,2; 0,8734	
CLDQ - abdominal symptomatology						
Baseline <sup>5)</sup>	13/13	6.28 (1.00)	7/7	5.19 (2.26)	-	
Week 20 <sup>6)7)</sup>	13/13	6.38 (0.94)	7/7	5.19 (1.96)	0,10; 0,8351	
CLDQ - Activity						
Baseline <sup>5)</sup>	13/13	6.33 (1.17)	7/7	5.96 (1.21)	-	
Week 20 <sup>6)7)</sup>	13/13	6.52 (0.95)	7/7	6.20 (0.99)	-0,05; 0,8351	
CLDQ - emotional function						
Baseline <sup>5)</sup>	13/13	5.51 (1.23)	7/7	4.83 (1.97)	-	
Week 20 <sup>6)7)</sup>	13/13	5.58 (1.15)	7/7	5.27 (1.61)	-0,37; 0,7506	
CLDQ - Fatigue						
Baseline <sup>5)</sup>	13/13	5.48 (1.04)	7/7	4.37 (1.89)	-	
Week 20 <sup>6)7)</sup>	13/13	5.72 (1.11)	7/7	5.17 (1.71)	-0,55; 0,5207	

QLDQ - systematic symptomatology					
Baseline <sup>5)</sup>	13/13	6.25 (0.86)	7/7	5.77 (1.24)	-
Week 20 <sup>6)7)</sup>	13/13	6.14 (0.92)	7/7	5.86 (0.96)	-0,20; 0,7796
CLDQ - Anxiety and concerns					
Baseline <sup>5)</sup>	13/13	6.32 (0.94)	7/7	5.29 (1.21)	-
Week 20 <sup>6)7)</sup>	13/13	6.45 (1.05)	7/7	5.60 (2.04)	-0,19; 0,5731
PedsQL <sup>18)</sup>					
PedsQL - Total score (23 items)					
Baseline <sup>5)</sup>	23/25	83.37 (13.74)	23/23	81.01 (15.55)	-
Week 20 <sup>6)19)</sup>	22/25	81.92 (12.93)	23/23	80.38 (13.46)	-1,75; 0,6908
PedsQL - Physical Health Summary Scale (8 items) <sup>20)</sup>					
Baseline <sup>5)</sup>	23/25	88.20 (10.45)	23/23	84.93 (14.71)	-
Week 20 <sup>6)19)</sup>	22/25	86.94 (9.09)	23/23	85.21 (12.89)	-2,84; 0,1983
PedsQL - Psychosocial health summary scale (15 items)					
Baseline <sup>5)</sup>	23/25	80.79 (17.57)	23/23	78.92 (16.76)	-
Week 20 <sup>6)19)</sup>	22/25	79.24 (16.84)	23/23	77.82 (15.46)	-1,17; 0,9547
PedsQL - Emotional Functioning Scale (5 items)					
Baseline <sup>5)</sup>	23/25	78.70 (17.20)	23/23	78.70 (18.29)	-
Week 20 <sup>6)19)</sup>	22/25	78.40 (21.51)	23/23	76.30 (19.84)	1,5; 0,8553
PedsQL - Social Functioning Scale (5 items)					
Baseline <sup>5)</sup>	23/25	88.0 (24.67)	23/23	85.0 (17.90)	-
Week 20 <sup>6)19)</sup>	22/25	86.1 (20.58)	23/23	88.0 (15.13)	-5,0; 0,1369
PedsQL - School Functioning Scale (5 items)					
Baseline <sup>5)</sup>	23/25	75.7 (17.21)	23/23	73.0 (21.41)	-
Week 20 <sup>6)19)</sup>	22/25	73.2 (19.67)	23/23	69.1 (17.03)	0,0; 0,5801
Endpoint	Sebelipase alfa N = 36 n (%)	Placebo N = 30 n (%)	RR [95% CI] <sup>11)</sup> p value <sup>11)</sup>		
Side effects <sup>21)</sup>					
AE	31 (86)	28 (93)	-		
Severe AE	3 (8)	1 (3)	2.50 [0.27; 22.81] 0.417		
SAE	2 (6)	1 (3)	1.67 [0.16; 17.49] 0,670		
EU, which led to the discontinuation of the study medication	1 (3)	0 (0)	no data		
Infusion-associated reaction	2 (6)	4 (13)	no data		
<sup>1)</sup> Number of people included in the analysis. <sup>2)</sup> Number of individuals who are ≥ 17 years of age at the time of consent. <sup>3)</sup> The p-value for the treatment difference was calculated using Wilcoxon rank sum test. Data on the standard error (SE) are not available. Analyses that took into account adjustment for stratification variables were not presented. <sup>4)</sup> The FACIT-Fatigue consists of 13 items that are answered on a scale of 0-4 (0 = never; 4 = very much) and ask about the intensity of fatigue as well as the weakness and difficulty to perform daily activities due to fatigue within the last 7 days.					



The FACIT-Fatigue scale is then inversely applied to a total score of 0-52, with 0 being the worst score and 52 being the best score (a higher score indicates a lower expression of fatigue).

- 5) Baseline corresponds to the last measurement before the first infusion with SA. If multiple measurements are available prior to study treatment, the average of up to three most recent measurements is used as the baseline value.
- 6) If the value was not available at study week 20, the last available measurement was used according to SAP. The last available measurement and week 20 may differ if some individuals had their last available measurement in a different visit before week 20.
- 7) Values were available at week 20 for all individuals in the SA and PBO groups.
- 8) Individuals with a normal ALT level at baseline were excluded from the ALT normalisation analysis. This was not true for any individual in the study.
- 9) Was defined a priori as primary endpoint as ALT normalisation ("normal" as  $\leq$  ULN and "abnormal" as  $>$  ULN) at week 20. If the final assessment of ALT normalisation occurs less than 10 weeks (70 days) after the first dose, the individual will be considered a non-responder in the analysis at the time of the last available measurement.
- 10) Post hoc calculated for module 4. It is unclear whether adjustment was made for the a priori defined stratification variables.
- 11) Post hoc calculated for module 4. The p-value was determined using Wald test from the log-binomial model. It is unclear whether adjustment was made for the a priori defined stratification variables.
- 12) Values were available at week 20 for all individuals in the PBO group. No values were available at week 20 for 2 individuals in the SA group, so the latest available values were used.
- 13) A priori, the treatment difference was calculated using the Fischer exact test. Here the p-value was 0.027.
- 14) LDL concentrations were calculated using the Friedewald equation.
- 15) Values at week 20 were available for 29 subjects in the PBO group and 35 subjects in the intervention group, so the latest available values were used.
- 16) Number of individuals in the specified treatment group who are  $\geq$  17 years of age at the time of informed consent at CLDQ and between 5 and  $\leq$  18 years of age at PedQL (FAS sub-population).
- 17) The CLDQ includes 29 items answered on a scale of 1-7 (1 = at all times/always; 7 = at no time/never). The individual domains and the total score have a range of 1 to 7, with a higher score indicating a higher quality of life.
- 18) The PedsQL includes a total of 23 items. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function (never), 4 = worst function (always)); the values are then inverted into a scale from 1 to 100. Higher scores indicate a higher quality of life.
- 19) Values were available at week 20 for all individuals in the PBO group. No values were available at week 20 for 4 individuals in the SA group, so the latest available values were used.
- 20) The scores of the Physical Health Summary Scale (8 items) are equal to the Physical Functioning Scale domain (8 items). A separate presentation is not provided.
- 21) The study duration of the double-blind phase was 20 weeks. However, concrete data on the actual exposure times could not be identified. However, only one person in the intervention group and nobody in the control group dropped out of the double-blind study phase. It is assumed that the median exposure times are sufficiently comparable between the treatment arms. AEs for the double-blind phase from receipt of the investigational product until the end of the double-blind phase were presented.

Abbreviations: ALT: Alanine aminotransferase; CLDQ: Chronic Liver Disease Questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; FAS: Full analysis set; n. d.: no data; CI: Confidence interval; LDL-C: Low-density lipoprotein; MV: Mean value; MD: Mean difference; PBO: Placebo; PedsQL: Paediatric Quality of Life Inventory; RR: relative risk; SA: Sebelipase alfa; SAP: Statistical Analysis Plan; SD: Standard deviation. (SE) Standard error; SAE: serious AE; AE: adverse event; ULN: Upper Limit of Normal

LAL-CL02 (ARISE): Single-arm study phase from week 22; all patients included in the RCT receive sebelipase alfa (SA)

Endpoint	SA/SA (N = 36) <sup>1)</sup>		PBO/SA (N = 30) <sup>2)</sup>	
<b>Mortality<sup>3)</sup></b>				
No deaths have occurred.				
Endpoint category Endpoint	SA/SA (N = 36) <sup>1)</sup>		PBO/SA (N = 30) <sup>2)</sup>	
	n <sup>4)</sup> /N <sup>5)</sup>	MV (SD)	n <sup>4)</sup> /N <sup>5)</sup>	MV (SD)
<b>Morbidity</b>				
<b>FACIT-Fatigue<sup>6)</sup></b> last evaluable visit in week 148/196 (SA/SA) or week 100/148 (PBO/SA) <sup>8)</sup>				
Change from baseline <sup>7)</sup>	10/13	-0.5 (9.68)	7/7	3.6 (4.50)

Endpoint category Endpoint	SA/SA (N = 36) <sup>1)</sup>		PBO/SA (N = 30) <sup>2)</sup>	
	n <sup>4)</sup> /N <sup>5)</sup>	MV (SD)	n <sup>4)</sup> /N <sup>5)</sup>	MV (SD)
<b>LDL-C concentration change - shown in addition</b> last evaluable visit in week 148/172 (SA/SA) or week 100/124 (PBO/SA) <sup>8)</sup>				
Change from baseline <sup>7)</sup> absolute percentage	27/36	-57.2 (40.2) -31.3 (17.3)	27/30	-64.8 (36.5) -32.3 (17.5)
<b>Quality of life</b>				
<b>CLDQ</b> <sup>9)</sup> - change from baseline <sup>7)</sup> ; last evaluable visit in week 148/196 (SA/SA) or week 100/148 (PBO/SA) <sup>8)</sup>				
Total score	10/13	-0.05 (0.60)	7/7	0.40 (0.56)
Abdominal symptomatology	10/13	-0.37 (1.01)	7/7	0.43 (0.85)
Activity	10/13	-0.03 (0.55)	7/7	0.57 (1.00)
Emotional function	10/13	0.03 (1.26)	7/7	-0.16 (1.15)
Fatigue	10/13	0.08 (1.39)	7/7	0.23 (0.41)
Systematic symptomatology	10/13	0.10 (0.93)	7/7	0.43 (0.47)
Anxiety and concerns	10/13	-0.12 (0.96)	7/7	0.91 (1.75)
<b>PedsQL</b> <sup>10)</sup> - change to baseline <sup>7)</sup> ; last evaluable visit in week 124/172 (SA/SA) or week 52/100 (PBO/SA) <sup>8)</sup>				
Total score	19/25	-2.80 (9.76)	17/23	4.35 (8.19)
Summation scale - Physical health <sup>14</sup>	19/25	-1.2 (12.33)	17/23	2.4 (5.36)
Summation scale - psychosocial health	19/25	-3.68 (14.07)	17/23	19
Summation scale - Emotional Functioning Scale	19/25	7.1 (19.03)	17/23	3.2 (16.20)
Summation scale - Social function scale	19/25	2.1 (14.84)	17/23	5.0 (12.12)
Summation scale - school function scale <sup>11)</sup>	19/25	-6.1 (14.20)	17/23	7.9 (11.87)

Endpoint Endpoint category	SA/SA		PBO/SA	
	N	Patients with event n (%)	N	Patients with event n (%)
<b>Side effects</b>				
Severe AE <sup>15)</sup>	36	3 (8)	30	3 (10)
SAE	36	6 (17)	30	5 (17)
AE that led to discontinuation of study medication	36	0 (0.0)	30	0 (0.0)
AE of special interest: IAR	36	3 (8)	30	10 (33)

- <sup>1)</sup> SA/SA Treatment Sequence: Treatment with SA from study week 0.
- <sup>2)</sup> PBO/SA treatment sequence: Treatment with PBO from study week 0 followed by treatment with sebelipase alfa.
- <sup>3)</sup> Deaths were recorded through security.
- <sup>4)</sup> Number of people included in the analysis.
- <sup>5)</sup> Number of individuals in the specified treatment group who were of the following ages at the time of informed consent: FACIT fatigue and CLDQ  $\geq 17$  years; PedsQL between 5 and  $\leq 18$  years (ES sub-population).
- <sup>6)</sup> The FACIT-Fatigue consists of 13 items that are answered on a scale of 0-4 (0 = never; 4 = very much) and ask about the intensity of fatigue as well as the weakness and difficulty to perform daily activities due to fatigue within the last 7 days. The FACIT-Fatigue scale is then inversely applied to a total score of 0-52, with 0 being the worst score and 52 being the best score (a higher score indicates a lower expression of fatigue).
- <sup>7)</sup> Baseline corresponds to the last measurement before the first infusion with sebelipase alfa. If multiple measurements are available prior to study treatment, the average of up to 3 most recent measurements is used as the baseline value. For the PBO/SA treatment sequence, the last up to 3 non-missing assessments must occur within 45 days.
- <sup>8)</sup> For the analyses of the open-label study phase data, subjects were compared by time since the first dose of sebelipase alfa. In all analyses, a shift in visits was made for individuals randomised to placebo (PBO/SA group) for whom study visits were scheduled in the open-label phase relative to week 22. No shift in visits was performed for those randomised to sebelipase alfa (SA group). However, it remains unclear how the shift in visits was made, given that some of them span more than 22 weeks in the PBO group compared with the SA group.
- <sup>9)</sup> The CLDQ includes 29 items answered on a scale of 1-7 (1 = at all times/always; 7 = at no time/never). The individual domains and the total score have a range of 1 to 7, with a higher score indicating a higher quality of life.
- <sup>10)</sup> The PedsQL includes a total of 23 items. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function (never), 4 = worst function (always)); the values are then inserted into a scale from 1 to 100. Higher scores indicate a higher quality of life.
- <sup>11)</sup> The scores of the Physical Health Summary Scale (8 items) are equal to the Physical Functioning Scale domain (8 items). A separate presentation is not provided.
- <sup>12)</sup> The median (min; max) exposure duration of the LAL-CL03 study was 241.7 weeks (0; 262).
- <sup>13)</sup> The median exposure duration of the LAL-CL08 study was 147, 6 weeks (3; 160).
- <sup>14)</sup> The severity of AE was determined using CTCAE version 4.0.
- <sup>15)</sup> The severity of AE was determined using "Clinical Data Interchange Standards Consortium Study Data Tabulation Model" standard terminology v3.1.1.
- <sup>16)</sup> There is inconsistent information in the study records as 0 (0 %) individuals are reported here. The explanation for the 6 (60 %) subjects includes permanent discontinuation of study medication or withholding of medication.

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; CLDQ: Chronic Liver Disease Questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; FAS: Full analysis set; n. d.: no data; CI: Confidence interval; LDL-C: Low-density lipoprotein; MV: Mean value; MD: Mean difference; PBO: Placebo; PedsQL: Paediatric Quality of Life Inventory; RR: relative risk; SA Sebelipase alfa; SAP: Statistical Analysis Plan; SD: Standard deviation. (SE) Standard error; SAE: serious AE; AE: adverse event.

LAL-CL06: Single-arm intervention study with sebelipase alfa up to 144 weeks

Endpoint category		Sebelipase alfa N = 31 <sup>1)</sup>			
<b>Mortality<sup>2)</sup></b>					
No deaths have occurred.					
		Sebelipase alfa Patients ≤ 18 years; N = 22			
Endpoint Time	N <sup>3)</sup>	Percentile <sup>4)</sup>	Absolute changes from baseline	Percentage change from baseline	
<b>Morbidity</b>					
<b>Age-dependent weight (percentile)</b>					
Baseline <sup>5)</sup> MV (SD) Median (min; max)	22	29.0 (28.6) 18.4 [0.4; 99.6]		-	
Week 144 MV (SD) Median (min; max)	17	29.7 (27.3) 26.0 [0.0; 83.4]	3.8 (12.4) 0.8 [-13.6; 40.3]	43.2 (166.1) 1.8 [-89.0; 631.7]	
<b>Age-dependent BMI (percentile)</b>					
Baseline <sup>5)</sup> MV (SD) Median (min; max)	22	46.4 (27.5) 49.6 [6.2; 99.5]			
Week 144 MV (SD) Median (min; max)	17	41.6 (26.3) 42.9 [6.3; 92.4]	-2.6 (30.0) -0.5 [-63.5; 57.3]	26.5 (118.4) -1.0 [-89.7; 415.2]	
		Sebelipase alfa Patients ≤ 6 years; N = 8			
Endpoint Time	N <sup>3)</sup>	Normal <sup>6)</sup> n (%) <sup>7)</sup>	Noticeable <sup>6)</sup> n (%) <sup>7)</sup>	Not testable <sup>6)</sup> n (%) <sup>7)</sup>	
<b>Denver II Developmental Test - Total Score</b>					
Baseline <sup>5)</sup>	7	6 (75)	1 (12.5)	0 (0)	
Week 96	6	6 (75)	0 (0)	0 (0)	

		Sebelipase alfa N = 36		
Endpoint Time	N <sup>3)</sup>	LDL-C concentration at the visits	Absolute changes from baseline	Percentage changes compared to baseline
<b>LDL-C concentration changes - supplementary presentation</b>				
Baseline <sup>5)</sup> MV (SD) Median (min; max)	30	159.7 (57.0) 160 [18; 282]		
Week 96 MV (SD) Median (min; max)	25	131.7 (51.6) 133.0 [40; 277]	-40.2 (48.6) -45.2 [-117; 142]	-22.5 (31.1) -27.5 [-53; 105]
		Sebelipase alfa Patients between 5 and ≤ 18 years; N=18		
Endpoint Time	N <sup>8)</sup>	MV (SD)	Change from baseline, MV (SD)	
<b>Quality of life</b>				
<b>PedsQL<sup>9)</sup></b>				
PedsQL- total score (23 items) <sup>4)</sup>				
Baseline <sup>5)</sup>	14	80.9 (14.97)	-	
Week 96	16	80.2 (11.59)	1.7 (10.77)	
PedsQL - Physical Health Summary Scale (8 items) <sup>10)</sup>				
Baseline <sup>5)</sup>	14	85.9 (19.14)	-	
Week 96	16	87.3 (10.79)	3.4 (17.93)	
PedsQL - Psychosocial health summary scale (15 items)				
Baseline <sup>5)</sup>	14	78.2 (16.07)	-	
Week 96	16	76.5 (14.63)	0.8 (12.94)	
PedsQL - Emotional Functioning Scale (5 items)				
Baseline <sup>5)</sup>	14	79.6 (18.45)	-	
Week 96	16	78.1 (16.42)	2.7 (15.22)	
PedsQL - Social Functioning Scale (5 items)				
Baseline <sup>5)</sup>	14	85.0 (17.76)	-	
Week 96	16	83.4 (22.49)	2.7 (23.24)	
PedsQL - School Functioning Scale (5 items)				
Baseline <sup>5)</sup>	14	70.0 (20.10)	-	
Week 96	16	67.8 (16.83)	-3.1 (21.46)	
Endpoint category Endpoint	N	Patients with event n (%)		
<b>Side effects</b>				
Severe AE <sup>11)</sup>	31	4 (13)		
SAE	31	10 (32)		

Endpoint category Endpoint	N	Patients with event n (%)
AE that led to discontinuation of study medication	31	1 (3)
AE of special interest: IAR	31	3 (10)

<sup>1)</sup> The median (min; max) exposure duration of the LAL-CL06 study was 144 weeks (61; 145).  
<sup>2)</sup> According to Module 4, deaths were recorded through security.  
<sup>3)</sup> Number of people included in the analysis.  
<sup>4)</sup> Percentiles were calculated for the endpoint based on standardised age and sex norms ("weight for age", WFA) from WHO (individuals ≤ 24 months) or the centres for Disease Control and Prevention (CDC) (individuals ≥ 24 months to 18 years).  
<sup>5)</sup> Baseline corresponds to the mean of the 3 last measurements before the first SA infusion.  
<sup>6)</sup> Based on demographic norm values, the testing personnel evaluates for each test item whether the result for the corresponding age group of the respective child fell within the associated normal range or was to be rated as noticeable. The 4 test areas were classified as "normal", "noticeable" or "not testable". A result was categorised as "untestable" if it was not possible to administer the test to a child.  
<sup>7)</sup> Percentages refer to the number of persons for whom a measurement was possible (N=8)  
<sup>8)</sup> Number of persons with available data for the respective visit.  
<sup>9)</sup> The PedsQL includes a total of 23 items. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function (never), 4 = worst function (always)); the values are then inverted into a scale from 1 to 100. Higher scores indicate a higher quality of life.  
<sup>10)</sup> The Physical Health Summary Scale scores (8 items) also correspond to the Physical Functioning Scale domain (8 items). A separate presentation is not provided.  
<sup>11)</sup> The severity of AE was determined using "Clinical Data Interchange Standards Consortium Study Data Tabulation Model" standard terminology v3.1.1.

Abbreviations: BMI: Body Mass Index; FAS: Full analysis set; MV: Mean; LDL-C: Low-density lipoprotein cholesterol; PedsQL: Paediatric Quality of Life Inventory; SA: Sebelipase alfa; SD: Standard deviation; SAE: (Serious) adverse events; AE: Adverse event

#### Register ALX-LALD-501

Side effects	
Global patients with at least one ...	Ever treated with sebelipase alfa <sup>1)</sup>
	N = 118 <sup>2)</sup> n (%)
AE	41 (35)
Severe AE <sup>3)</sup>	2 (2)
SAE	10 (9)
AE, which led to the discontinuation of the study medication <sup>4)</sup>	0 (0)

<sup>1)</sup> All AE from inclusion in the registry were recorded for the safety population. This included all individuals who had ever been treated with sebelipase alfa without having a confirmed diagnosis of LAL.  
<sup>2)</sup> Data on the observation period are not available for the safety population (n = 118) or for the study population (n = 113). The median total treatment time with SA for individuals with childhood and adult LAL deficiency (n = 113) was 3.67 years.  
<sup>3)</sup> The severity of AE was determined using "Clinical Data Interchange Standards Consortium Study Data Tabulation Model" standard terminology v3.1.1.  
<sup>4)</sup> Data from module 4.

Abbreviations: LAL: Lysosomal Acid Lipase; SAE: (Serious) adverse events; AE: Adverse event

## 2. Number of patients or demarcation of patient groups eligible for treatment

- a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months)

approx. 5 to 10 patients

- b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))

approx. 30 to 60 patients

## 3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Kanuma (active ingredient: sebelipase alfa) at the following publicly accessible link (last access: 10 February 2021):

[https://www.ema.europa.eu/en/documents/product-information/kanuma-epar-product-information\\_de.pdf](https://www.ema.europa.eu/en/documents/product-information/kanuma-epar-product-information_de.pdf)

Treatment with sebelipase alfa should only be initiated and monitored by specialists who are experienced in the treatment of patients with LAL deficiency, metabolic disorders or chronic liver disease.

## 4. Treatment costs

### Annual treatment costs:

- a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months)

Designation of the therapy	Annual treatment costs/patient
Sebelipase alfa	378,917.57 - € 7,578,351.38

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 April 2021).

Costs for additionally required SHI services: not applicable

- b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))

Designation of the therapy	Annual treatment costs/patient
Sebelipase alfa	€ 189,822.43 - € 2,277,869.15

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 May 2021).

Costs for additionally required SHI services: not applicable