

**Clinical trial results:**
A Multicenter, Open-Label Study of Sebelipase Alfa in Patients with Lysosomal Acid Lipase Deficiency
Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2011-004287-30 |
| Trial protocol | DK ES GB IT DE BE HR NL |
| Global end of trial date | 28 December 2017 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 |
| This version publication date | 24 February 2019 |
| First version publication date | 21 July 2018 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set <p>This update includes new data and changes in presentation of current data. All new data originates from the same clinical study report source as the original posting. The new data involves end point 5, with new/different data to accommodate the change in end point title. Changes in presentation of data for the Subject disposition and the Adverse events (AEs) were respectively made to provide a more clear account of the study's variable dosing and to ensure presentation of AEs per intervention.</p> |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | LAL-CL06 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02112994 |
| WHO universal trial number (UTN) | U1111-1152-7171 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Alexion Pharmaceuticals Inc. |
| Sponsor organisation address | 100 College St., New Haven, United States, 06510 |
| Public contact | European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com |
| Scientific contact | European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001331-PIP01-12 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

| | |
|--|-----|
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
|--|-----|

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 April 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and efficacy of sebelipase alfa in a broad population of participants with lysosomal acid lipase deficiency.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 24 June 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | Croatia: 2 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Brazil: 2 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Mexico: 4 |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Country: Number of subjects enrolled | Turkey: 1 |
| Country: Number of subjects enrolled | United States: 3 |
| Worldwide total number of subjects | 31 |
| EEA total number of subjects | 18 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 16 |
| Adolescents (12-17 years) | 6 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 21 study centers were initiated in 15 countries, including Australia, Belgium, Brazil, Canada, Croatia, Denmark, Germany, Italy, Mexico, Netherlands, Russia, Spain, Turkey, United Kingdom (UK), and the United States. Seventeen study centers screened at least 1 participant in all of these countries, except the UK and the Netherlands.

Pre-assignment

Screening details:

The study consisted of a screening period of up to 45 days. The maximum duration of a participant's participation in the study, inclusive of screening and follow-up visits, was approximately 155 weeks.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

None (Open Label)

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 2-<4 Years |

Arm description:

This subgroup is part of the full analysis set and includes only participants between the ages of 2 and 4 years old who initiated intravenous (IV) treatment with sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) every other week (qow). Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg every week (qw) was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sebelipase Alfa |
| Investigational medicinal product code | |
| Other name | SBC-102 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

All eligible participants received repeat IV infusions of sebelipase alfa at an initial dose of 1 mg/kg qow. Sequential dose escalation to 3 mg/kg qow and 3 mg/kg qw was permitted based on evidence of disease progression. Dose decreases were permitted in the event of poor tolerability or in participants who achieved clinical stability on a dose of 3 mg/kg qw. Consecutive infusions were to be administered at least 7 days apart (for qow dosing) and at least 5 days apart (qw dosing).

| | |
|------------------|------------|
| Arm title | 4-18 Years |
|------------------|------------|

Arm description:

This subgroup is part of the full analysis set and includes only participants between the ages of 4 and 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local

drug availability and study participation status.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sebelipase Alfa |
| Investigational medicinal product code | |
| Other name | SBC-102 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

All eligible participants received repeat IV infusions of sebelipase alfa at an initial dose of 1 mg/kg qow. Sequential dose escalation to 3 mg/kg qow and 3 mg/kg qw was permitted based on evidence of disease progression. Dose decreases were permitted in the event of poor tolerability or in participants who achieved clinical stability on a dose of 3 mg/kg qw. Consecutive infusions were to be administered at least 7 days apart (for qow dosing) and at least 5 days apart (qw dosing).

| | |
|------------------|-----------|
| Arm title | >18 Years |
|------------------|-----------|

Arm description:

This subgroup is part of the full analysis set and includes only participants greater than 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sebelipase Alfa |
| Investigational medicinal product code | |
| Other name | SBC-102 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

All eligible participants received repeat IV infusions of sebelipase alfa at an initial dose of 1 mg/kg qow. Sequential dose escalation to 3 mg/kg qow and 3 mg/kg qw was permitted based on evidence of disease progression. Dose decreases were permitted in the event of poor tolerability or in participants who achieved clinical stability on a dose of 3 mg/kg qw. Consecutive infusions were to be administered at least 7 days apart (for qow dosing) and at least 5 days apart (qw dosing).

| Number of subjects in period 1 | 2-<4 Years | 4-18 Years | >18 Years |
|--|-------------------|-------------------|-------------------|
| Started | 6 | 16 | 9 |
| Received at Least 1 Dose of Study Drug | 6 | 16 | 9 |
| Received 0.35 mg/kg qow | 0 ^[1] | 0 ^[2] | 1 ^[3] |
| Received 1 mg/kg qow | 6 | 16 | 9 |
| Received 1 mg/kg qw | 1 ^[4] | 1 ^[5] | 0 ^[6] |
| Received 3 mg/kg qow | 3 ^[7] | 5 ^[8] | 3 ^[9] |
| Received 3 mg/kg qw | 2 ^[10] | 1 ^[11] | 1 ^[12] |
| Completed 96-week Treatment Period | 6 | 14 | 8 |
| Completed | 6 | 13 | 6 |
| Not completed | 0 | 3 | 3 |
| Consent withdrawn by subject | - | 1 | 1 |

| | | | |
|---------------------|---|---|---|
| Liver Transplant | - | 1 | - |
| Progressive Disease | - | - | 1 |
| Pregnancy | - | 1 | 1 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This Milestone represents 1 of the 5 different doses of the study. Dosing was variable and on an individual, per participant basis. All participants began treatment with the study drug at a dose of 1 mg/kg every other week. Dose escalations/reductions could be considered if the participant met protocol-defined criteria. Not all participants in the arm received all 5 different doses.

Baseline characteristics

Reporting groups

| Reporting group title | Overall Trial |
|---|---------------|
| Reporting group description: | |
| Pediatric and adult participants initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qow was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status. | |

| Reporting group values | Overall Trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 31 | 31 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 16 | 16 | |
| Adolescents (12-17 years) | 6 | 6 | |
| Adults (18-64 years) | 9 | 9 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 16.92 | | |
| standard deviation | ± 14.678 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | 12 | |
| Male | 19 | 19 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | 6 | |
| Not Hispanic or Latino | 25 | 25 | |
| Race | | | |
| Units: Subjects | | | |
| White | 27 | 27 | |
| Other | 4 | 4 | |

End points

End points reporting groups

| | |
|-----------------------|------------|
| Reporting group title | 2-<4 Years |
|-----------------------|------------|

Reporting group description:

This subgroup is part of the full analysis set and includes only participants between the ages of 2 and 4 years old who initiated intravenous (IV) treatment with sebelipase alfa at a dose of 1 milligram/kilogram (mg/kg) every other week (qow). Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg every week (qw) was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

| | |
|-----------------------|------------|
| Reporting group title | 4-18 Years |
|-----------------------|------------|

Reporting group description:

This subgroup is part of the full analysis set and includes only participants between the ages of 4 and 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

| | |
|-----------------------|-----------|
| Reporting group title | >18 Years |
|-----------------------|-----------|

Reporting group description:

This subgroup is part of the full analysis set and includes only participants greater than 18 years old who initiated IV treatment with sebelipase alfa at a dose of 1 mg/kg qow. Participants were considered for a dose adjustment at the discretion of the Investigator and in consultation with the Sponsor. Dose escalation to 3 mg/kg qow was considered if pre-defined dose-escalation criteria were met. If these criteria continued to be met, a subsequent dose escalation to 3 mg/kg qw was considered. Dose decreases as low as 0.35 mg/kg qow were permitted based upon evidence of intolerance to sebelipase alfa treatment. Participants who completed the 96-week treatment period were permitted to continue receiving sebelipase alfa in an expanded treatment period for up to 48 weeks, pending local drug availability and study participation status.

| | |
|----------------------------|-------------------|
| Subject analysis set title | Full Analysis Set |
|----------------------------|-------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All participants who received at least 1 infusion of sebelipase alfa. The full analysis set was used for analysis of safety and efficacy.

| | |
|----------------------------|------------------------|
| Subject analysis set title | Pediatric Participants |
|----------------------------|------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

This sub-group is part of the full analysis set and includes only those participants 18 years old or younger.

Primary: Participants Experiencing Severe Treatment-emergent Adverse Events (TEAEs)

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|-----------------|---|
| End point title | Participants Experiencing Severe Treatment-emergent Adverse Events (TEAEs) ^[1] |
|-----------------|---|

End point description:

The number of participants experiencing severe TEAEs is presented for each age group who received sebelipase alfa in this open-label study. Information on AEs was obtained at each scheduled contact with the participant (or participant's parent or legal guardian), by specific questioning and, as appropriate, by examination. An AE was defined as any untoward medical occurrence in a participant that did not necessarily have to have a causal relationship with the administration of the study drug. An AE therefore could have been any unfavorable and unintended sign, symptom or disease temporally associated with the use of the study drug, whether or not considered related to the medicinal product. Pre-existing

conditions that worsened in severity during the course of the study were reported as AEs. AEs were recorded from the date of informed consent until completion of the follow-up phone call at 4 weeks after the last infusion of sebelipase alfa administered.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Week 144 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analyses were not conducted on any of the reported safety data.

| End point values | 2-<4 Years | 4-18 Years | >18 Years | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 16 | 9 | |
| Units: Participants | 1 | 1 | 2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change In Serum Lipids From Baseline To Week 144

| | |
|-----------------|--|
| End point title | Percent Change In Serum Lipids From Baseline To Week 144 |
|-----------------|--|

End point description:

The effect of sebelipase alfa on lipid metabolism was evaluated by measuring the change from baseline to Week 144 in 4 serum lipids: low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); non-HDL-C; triglycerides. Blood samples for these clinical laboratory tests were collected at scheduled time points and analyzed by a central laboratory.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 144 | |

| End point values | 2-<4 Years | 4-18 Years | >18 Years | |
|-------------------------------|-------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 ^[2] | 12 ^[3] | 2 ^[4] | |
| Units: Percent Change | | | | |
| median (full range (min-max)) | | | | |
| LDL-C | -37.5 (-52 to 25) | -29.2 (-59 to 23) | -22.5 (-37 to -8) | |
| HDL-C | 76.5 (30 to 132) | 24.2 (-4 to 90) | 6.1 (-10 to 22) | |
| Non-HDL-C | -39.1 (-53 to 29) | -26.7 (-62 to 19) | -22.1 (-33 to -11) | |
| Triglycerides | -48.3 (-61 to 11) | -15.8 (-74 to 112) | -22.0 (-25 to -19) | |

Notes:

[2] - N=5 for all 4 measurements

[3] - N=12 for all 4 measurements

[4] - N=2 for all 4 measurements

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Testing Positive For Anti-drug Antibodies (ADAs)

| | |
|-----------------|---|
| End point title | Participants Testing Positive For Anti-drug Antibodies (ADAs) |
|-----------------|---|

End point description:

The impact of ADAs on the safety and immunogenicity of sebelipase alfa was evaluated by testing for ADAs in participants who received sebelipase alfa in this open-label study. Blood samples for assessment were collected prior to study infusions at Week 2, Week 4, Week 8, Week 12, and every 12 weeks thereafter. Participants testing positive for ADAs were also tested for the presence of neutralizing antibodies that inhibited sebelipase alfa enzyme activity and/or cellular uptake. Any participant experiencing a moderate or severe infusion-associated reaction (IAR) was to have an additional assessment of ADAs at the next study visit (prior to study drug infusion); these participants were to also have serum samples collected at 1 to 2 hours after IAR onset and at the next study visit (prior to study drug infusion) for analysis of serum tryptase. The number of participants who became ADA positive and who tested positive for neutralizing antibodies are presented.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 144

| End point values | Full Analysis Set | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 31 ^[5] | | | |
| Units: Participants | | | | |
| ADA Positive | 2 | | | |
| Neutralizing Antibodies Positive | 0 | | | |

Notes:

[5] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change In Body Mass Index (BMI)-For-Age Percentile From Baseline To Week 144 in Pediatric Participants

| | |
|-----------------|--|
| End point title | Percent Change In Body Mass Index (BMI)-For-Age Percentile From Baseline To Week 144 in Pediatric Participants |
|-----------------|--|

End point description:

To evaluate the effects of sebelipase alfa on growth parameters in pediatric participants (≤ 18 years old) presenting with evidence of growth delay, the percent change in the anthropometric parameter of BMI-for-age percentile from Baseline to Week 144 is reported. Anthropometric parameters were plotted on standard growth curves. When possible, historical data on growth parameters was also incorporated into the analyses. Percentiles and Z-scores for BMI-for-age were determined using standard growth charts appropriate to a participant's age on the date of the assessment: the World Health Organization standard growth chart for participants ≤ 2 years of age and the Centers for Disease Control standard growth chart for participants > 2 years of age.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 144

| End point values | Pediatric Participants | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 17 ^[6] | | | |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | 26.45 (± 118.432) | | | |

Notes:

[6] - Pediatric Participants (≤18 years old)

Statistical analyses

No statistical analyses for this end point

Secondary: Shift In Child-Pugh Status From Baseline To Week 144

| | |
|---|--|
| End point title | Shift In Child-Pugh Status From Baseline To Week 144 |
| End point description: | |
| In order to evaluate the effects of sebelipase alfa on liver function, the number of participants with a shift in Child-Pugh status from Baseline to Week 144 is reported. The status is based on the Child-Pugh score, which is used in clinical practice to assess prognosis in individuals with chronic liver disease. Laboratory data were used in derivation of the score by summing individual scores (scored 1–3, with 3 indicating most severe) from clinical laboratory test results and physical examinations, including total serum bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy. The total score was used to determine the Child-Pugh status, reported as Class A (score of 5 or 6), Class B (score of 7 to 9), or Class C (score of 10 to 15). Higher scores and higher categories represented a worse outcome. Data reported as 1 of 2 types of shifts in class: No Change from Baseline; Decline from Baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 144 | |

| End point values | Full Analysis Set | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: Participants | | | | |
| No Change: A to A | 16 | | | |
| No Change: B to B | 1 | | | |
| Decline: A to B | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening (up to 45 days prior to start of treatment) to Week 144.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | 0.35 mg/kg QOW |
|-----------------------|----------------|

Reporting group description:

This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 0.35 mg/kg qow.

| | |
|-----------------------|---------------|
| Reporting group title | 1.0 mg/kg QOW |
|-----------------------|---------------|

Reporting group description:

This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 1.0 mg/kg qow.

| | |
|-----------------------|--------------|
| Reporting group title | 1.0 mg/kg QW |
|-----------------------|--------------|

Reporting group description:

This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 1.0 mg/kg qw.

| | |
|-----------------------|---------------|
| Reporting group title | 3.0 mg/kg QOW |
|-----------------------|---------------|

Reporting group description:

This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 3.0 mg/kg qow.

| | |
|-----------------------|--------------|
| Reporting group title | 3.0 mg/kg QW |
|-----------------------|--------------|

Reporting group description:

This reporting group is based on the safety set and includes AEs with onset during the administration of IV treatment of sebelipase alfa at a dose of 3.0 mg/kg qw.

| Serious adverse events | 0.35 mg/kg QOW | 1.0 mg/kg QOW | 1.0 mg/kg QW |
|---|----------------|-----------------|---------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 8 / 31 (25.81%) | 0 / 2 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Shock | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Liver transplant | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serious adverse events | | | |
| 3.0 mg/kg QOW | 3.0 mg/kg QW | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 0 / 4 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |

| | | | |
|---|----------------|---------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Shock | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Liver transplant | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |

| | | | |
|---|----------------|---------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | 0.35 mg/kg QOW | 1.0 mg/kg QOW | 1.0 mg/kg QW |
|---|----------------|------------------|---------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 30 / 31 (96.77%) | 0 / 2 (0.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Vascular disorders | | | |

| | | | |
|--|---------------|------------------|---------------|
| Haematoma | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 15 / 31 (48.39%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 26 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Vaccination site erythema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 7 / 31 (22.58%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 13 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 31 (16.13%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 21 | 0 |
| Oropharyngeal pain | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Catarrh | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |

| | | | |
|--|---------------|-----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 31 (12.90%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Bone contusion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Face injury | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Arthropod bite | | | |

| | | | |
|------------------------------|---------------|------------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Concussion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Forearm fracture | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scratch | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Left ventricular dilatation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 10 / 31 (32.26%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 27 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypoaesthesia | | | |

| | | | |
|--------------------------------------|---------------|------------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Macrocytosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 12 / 31 (38.71%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 23 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 11 / 31 (35.48%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 17 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 9 / 31 (29.03%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 20 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 31 (16.13%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastritis | | | |

| | | | |
|--|---------------|-----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Oral contusion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tongue eruption | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 31 (12.90%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 20 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eczema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash | | | |

| | | | |
|---|--------------------|------------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 4 | 0 / 2 (0.00%) 0 |
| Rash papular subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 1 / 31 (3.23%) 1 | 0 / 2 (0.00%) 0 |
| Skin lesion subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 2 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 11 | 0 / 2 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 31 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 2 (0.00%) 0 |
| Endocrine disorders Delayed puberty subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 31 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 2 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 3 | 0 / 2 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 2 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 13 / 31 (41.94%) 29 | 0 / 2 (0.00%) 0 |

| | | | |
|---|--------------------|-----------------------|--------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 7 / 31 (22.58%) 8 | 0 / 2 (0.00%) 0 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 6 / 31 (19.35%) 9 | 0 / 2 (0.00%) 0 |
| Pharyngitis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 6 / 31 (19.35%) 8 | 0 / 2 (0.00%) 0 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 7 / 31 (22.58%) 14 | 0 / 2 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 2 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 31 (9.68%) 4 | 0 / 2 (0.00%) 0 |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 31 (9.68%) 3 | 0 / 2 (0.00%) 0 |
| Eye infection subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 3 | 0 / 2 (0.00%) 0 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 31 (9.68%) 5 | 0 / 2 (0.00%) 0 |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 1 / 31 (3.23%) 1 | 0 / 2 (0.00%) 0 |
| Otitis media acute subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 31 (9.68%) 3 | 0 / 2 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 31 (9.68%) 5 | 0 / 2 (0.00%) 0 |

| | | | |
|---|---------------|----------------|---------------|
| Sinusitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 31 (9.68%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 31 (6.45%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 31 (3.23%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gastritis viral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 31 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|--------------------|----------------------|--------------------|
| Tracheitis subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 31 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Varicella zoster virus infection subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 31 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 4 / 31 (12.90%) 5 | 0 / 2 (0.00%) 0 |
| Iron deficiency subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 31 (6.45%) 2 | 0 / 2 (0.00%) 0 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 31 (0.00%) 0 | 0 / 2 (0.00%) 0 |

| | | | |
|---|----------------------|---------------------|--|
| Non-serious adverse events | 3.0 mg/kg QOW | 3.0 mg/kg QW | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 10 / 11 (90.91%) | 4 / 4 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 3 | 0 / 4 (0.00%) 0 | |
| Vascular disorders | | | |
| Haematoma subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 5 | 0 / 4 (0.00%) 0 | |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 4 (0.00%) 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------------|---------------------|--|
| Pyrexia subjects affected / exposed occurrences (all) | 4 / 11 (36.36%) 4 | 1 / 4 (25.00%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 4 (0.00%) 0 | |
| Vaccination site erythema subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 4 (0.00%) 0 | |
| Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 4 (25.00%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 4 (25.00%) 1 | |
| Epistaxis subjects affected / exposed occurrences (all) | 3 / 11 (27.27%) 13 | 1 / 4 (25.00%) 1 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 4 (25.00%) 1 | |
| Catarrh subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 4 (0.00%) 0 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Bronchospasm subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 4 (0.00%) 0 | |

| | | | |
|---|----------------|----------------|--|
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) | |
| occurrences (all) | 1 | 1 | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) | |
| occurrences (all) | 1 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) | |
| occurrences (all) | 1 | 2 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| C-reactive protein increased | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Protein total decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 0 / 4 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bone contusion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Face injury | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 3 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 2 | |
| Scratch | | | |

| | | | |
|--------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin abrasion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Wound | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Left ventricular dilatation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Macrocytosis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |

| | | |
|-----------------------------|-----------------|----------------|
| Diarrhoea | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 4 (25.00%) |
| occurrences (all) | 4 | 1 |
| Abdominal pain | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 |
| Vomiting | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 4 (25.00%) |
| occurrences (all) | 2 | 1 |
| Abdominal pain upper | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 |
| Constipation | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nausea | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 4 (25.00%) |
| occurrences (all) | 4 | 1 |
| Dental caries | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastritis | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 |
| Gingival bleeding | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Toothache | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oral contusion | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 |
| Tongue eruption | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 |

| | | | |
|--|-----------------|----------------|--|
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 4 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) | |
| occurrences (all) | 4 | 3 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Petechiae | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) | |
| occurrences (all) | 4 | 1 | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |

| | | | |
|--|---|---|--|
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Endocrine disorders Delayed puberty subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 4 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 | 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) | 4 / 11 (36.36%) 6 2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 | 3 / 4 (75.00%) 4 2 / 4 (50.00%) 3 2 / 4 (50.00%) 2 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 | |

| | | |
|-----------------------------|-----------------|----------------|
| Bronchitis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Ear infection | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Eye infection | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 1 |
| Influenza | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oral herpes | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 |
| Otitis media acute | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Rhinitis | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) |
| occurrences (all) | 6 | 0 |
| Sinusitis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Urinary tract infection | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 |
| Acute sinusitis | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastroenteritis viral | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 4 (25.00%) |
| occurrences (all) | 2 | 3 |
| Hordeolum | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 |

| | | | |
|---|-----------------|----------------|--|
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Gastritis viral | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 4 (25.00%) | |
| occurrences (all) | 0 | 1 | |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Iron deficiency | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 4 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypomagnesaemia | | | |

| | | | |
|-----------------------------|----------------|---------------|--|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 02 February 2015 | <ul style="list-style-type: none">– Removed 'seroconversion rate' and 'time to seroconversion' from the immunogenicity outcome variables. The intent was to characterize ADAs for all isotypes. In this study, a participant was considered to be ADA positive if they had at least 1 positive ADA titer at any time during the study. However, a single positive ADA result would not necessarily imply that a participant had seroconverted. Moreover, analysis of tolerization (for which no standard definition exists) would not be appropriate to these circumstances.– Limited liver biopsy by the transjugular method to participants with advanced liver disease (as local facilities permitted), rather than recommending this for all study participants.– Updated the guidance on the management of IARs based on clinical experience in other ongoing studies with sebelipase alfa.– Clarified that AEs collected during hospitalization would be assessed and reported.– Clarified that AEs occurring after signing the informed consent but before the first dose of study drug would only be recorded if deemed related to study procedures or requirements. |
| 07 December 2015 | <ul style="list-style-type: none">- Clarified that the minimum duration of treatment would be "at least 52 weeks." This clarification was added in response to Pediatric Committee comments on the paediatric investigation plan request for modification.- Added a pharmacokinetics (PK) profile for participants receiving a dose decrease (the protocol already required a PK profile for participants receiving a dose increase), and added an ADA assessment prior to the first infusion at the new dose for all participants receiving a dose modification (increase or decrease). These additional data will support an evaluation of the relationship between immunogenicity, sebelipase alfa exposure, and clinical response during long-term treatment with sebelipase alfa. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported