



## Clinical trial results:

**A multicenter, Phase 2, randomized, open label, active-controlled, parallel-group study investigating the safety, tolerability, and efficacy of different dose levels of ACP-001 administered once weekly versus standard daily rhGH replacement therapy in pre-pubertal children with Growth Hormone Deficiency (GHD)**

### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2012-002787-27       |
| Trial protocol           | HU DE CZ GR BG SI FR |
| Global end of trial date | 22 July 2015         |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 04 February 2017 |
| First version publication date | 04 February 2017 |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | ACP-001_CT-004 |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01947907 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                                  |
|------------------------------|------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Ascendis Pharma A/S                                                                                              |
| Sponsor organisation address | Tuborg Boulevard 5, Hellerup, Denmark, DK-2900                                                                   |
| Public contact               | Michael Beckert,<br>VP Clinical Development<br>, Ascendis Pharma A/S, +49 172 155 2596,<br>mb@ascendispharma.com |
| Scientific contact           | Michael Beckert,<br>VP Clinical Development<br>, Ascendis Pharma A/S, +49 172 155 2596,<br>mb@ascendispharma.com |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| 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? | No |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 28 January 2016 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 22 July 2015    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 22 July 2015    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To compare the safety and PK/PD profile of three different ACP-001 doses to that of a commercially available standard daily rhGH formulation in pre-pubertal children with growth failure due to GHD.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 16 July 2013 |
| 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 | Belarus: 8             |
| Country: Number of subjects enrolled | Poland: 1              |
| Country: Number of subjects enrolled | Bulgaria: 1            |
| Country: Number of subjects enrolled | Greece: 3              |
| Country: Number of subjects enrolled | Hungary: 1             |
| Country: Number of subjects enrolled | Egypt: 7               |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | Turkey: 3              |
| Country: Number of subjects enrolled | Ukraine: 7             |
| Country: Number of subjects enrolled | Romania: 3             |
| Worldwide total number of subjects   | 55                     |
| EEA total number of subjects         | 9                      |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                     | 55 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 170 subjects from 38 initiated centers were screened for inclusion into the study of which 115 subjects were classified as screen failures. A total of 55 subjects were randomized at 20 centers in 10 countries located in Europe and North Africa (EEA and non-EEA).

### Pre-assignment

Screening details:

A total of 170 subjects from 30 recruiting centers were screened for inclusion into the study of which 115 subjects were classified as screen failures.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 55 |
| Number of subjects completed | 53 |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 2 |
|----------------------------|---------------------------------|

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 1 |
|------------------|----------|

Arm description:

ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | ACP-001              |
| Investigational medicinal product code |                      |
| Other name                             | TransCon PEG hGH     |
| Pharmaceutical forms                   | Powder for injection |
| Routes of administration               | Subcutaneous use     |

Dosage and administration details:

ACP-001 was administered in a weekly dose strength equivalent to 0.14 mg rhGH/kg/week, for 26 weeks. Provided in glass vials, reconstituted with sterile water for injection, administered in the morning hours.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 2 |
|------------------|----------|

Arm description:

ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | ACP-001              |
| Investigational medicinal product code |                      |
| Other name                             | TransCon PEG hGH     |
| Pharmaceutical forms                   | Powder for injection |
| Routes of administration               | Subcutaneous use     |

Dosage and administration details:

ACP-001 was administered in a weekly dose strength equivalent to 0.21 mg rhGH/kg/week, for 26

weeks. Provided in glass vials, reconstituted with sterile water for injection, administered in the morning hours.

|                                                                                      |                      |
|--------------------------------------------------------------------------------------|----------------------|
| <b>Arm title</b>                                                                     | Cohort 3             |
| Arm description:<br>ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week |                      |
| Arm type                                                                             | Experimental         |
| Investigational medicinal product name                                               | ACP-001              |
| Investigational medicinal product code                                               |                      |
| Other name                                                                           | TransCon PEG hGH     |
| Pharmaceutical forms                                                                 | Powder for injection |
| Routes of administration                                                             | Subcutaneous use     |

Dosage and administration details:

ACP-001 was administered in a weekly dose strength equivalent to 0.30 mg rhGH/kg/week, for 26 weeks. Provided in glass vials, reconstituted with sterile water for injection, administered in the morning hours.

|                                                                                         |                                               |
|-----------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>Arm title</b>                                                                        | Cohort 4                                      |
| Arm description:<br>Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week |                                               |
| Arm type                                                                                | Active comparator                             |
| Investigational medicinal product name                                                  | Genotropin®                                   |
| Investigational medicinal product code                                                  |                                               |
| Other name                                                                              |                                               |
| Pharmaceutical forms                                                                    | Powder and solvent for solution for injection |
| Routes of administration                                                                | Subcutaneous use                              |

Dosage and administration details:

Genotropin® was administered daily in a standard daily dose of 0.03 mg rhGH/kg/day (equivalent to 0.21 mg rhGH/kg/week), for 26 weeks. Provided as sterile white lyophilized powder dispensed in a two-chamber cartridge, administered with an injection device in the evening hours.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Cohort 1 | Cohort 2 | Cohort 3 |
|-----------------------------------------------------|----------|----------|----------|
| Started                                             | 12       | 14       | 14       |
| Completed                                           | 12       | 14       | 14       |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Cohort 4 |
|-----------------------------------------------------|----------|
| Started                                             | 13       |
| Completed                                           | 13       |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: During the pre-assignment period 2 subjects withdrew the consent.

## Baseline characteristics

### Reporting groups

|                                                                     |          |
|---------------------------------------------------------------------|----------|
| Reporting group title                                               | Cohort 1 |
| Reporting group description:                                        |          |
| ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week    |          |
| Reporting group title                                               | Cohort 2 |
| Reporting group description:                                        |          |
| ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week    |          |
| Reporting group title                                               | Cohort 3 |
| Reporting group description:                                        |          |
| ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week    |          |
| Reporting group title                                               | Cohort 4 |
| Reporting group description:                                        |          |
| Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week |          |

| Reporting group values                             | Cohort 1 | Cohort 2 | Cohort 3 |
|----------------------------------------------------|----------|----------|----------|
| Number of subjects                                 | 12       | 14       | 14       |
| Age categorical                                    |          |          |          |
| Units: Subjects                                    |          |          |          |
| In utero                                           | 0        | 0        | 0        |
| Preterm newborn infants (gestational age < 37 wks) | 0        | 0        | 0        |
| Newborns (0-27 days)                               | 0        | 0        | 0        |
| Infants and toddlers (28 days-23 months)           | 0        | 0        | 0        |
| Children (2-11 years)                              | 12       | 14       | 14       |
| Adolescents (12-17 years)                          | 0        | 0        | 0        |
| Adults (18-64 years)                               | 0        | 0        | 0        |
| From 65-84 years                                   | 0        | 0        | 0        |
| 85 years and over                                  | 0        | 0        | 0        |
| Age continuous                                     |          |          |          |
| Units: years                                       |          |          |          |
| arithmetic mean                                    | 7.98     | 8.24     | 7.32     |
| standard deviation                                 | ± 2.889  | ± 2.13   | ± 2.784  |
| Gender categorical                                 |          |          |          |
| Units: Subjects                                    |          |          |          |
| Female                                             | 3        | 4        | 5        |
| Male                                               | 9        | 10       | 9        |
| Race                                               |          |          |          |
| Units: Subjects                                    |          |          |          |
| White                                              | 12       | 14       | 14       |
| Baseline IGF-I SDS                                 |          |          |          |
| Units: --                                          |          |          |          |
| arithmetic mean                                    | -2.034   | -2.017   | -2.19    |
| standard deviation                                 | ± 0.7429 | ± 0.7713 | ± 0.7169 |
| Baseline Height SDS                                |          |          |          |
| Units: --                                          |          |          |          |
| arithmetic mean                                    | -3.05    | -2.75    | -3.17    |

|                                                                                                        |         |         |        |
|--------------------------------------------------------------------------------------------------------|---------|---------|--------|
| standard deviation                                                                                     | ± 1.127 | ± 0.383 | ± 1.04 |
| Screening Peak GH Levels                                                                               |         |         |        |
| The highest GH peak serum level of the two GH stimulation tests at Screening was used for calculation. |         |         |        |
| Units: ng/mL                                                                                           |         |         |        |
| arithmetic mean                                                                                        | 5.09    | 5.16    | 4.44   |
| standard deviation                                                                                     | ± 3.169 | ± 2.598 | ± 2.77 |

| Reporting group values                                                                                 | Cohort 4 | Total |  |
|--------------------------------------------------------------------------------------------------------|----------|-------|--|
| Number of subjects                                                                                     | 13       | 53    |  |
| Age categorical                                                                                        |          |       |  |
| Units: Subjects                                                                                        |          |       |  |
| In utero                                                                                               | 0        | 0     |  |
| Preterm newborn infants<br>(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)                                                                                  | 13       | 53    |  |
| Adolescents (12-17 years)                                                                              | 0        | 0     |  |
| Adults (18-64 years)                                                                                   | 0        | 0     |  |
| From 65-84 years                                                                                       | 0        | 0     |  |
| 85 years and over                                                                                      | 0        | 0     |  |
| Age continuous                                                                                         |          |       |  |
| Units: years                                                                                           |          |       |  |
| arithmetic mean                                                                                        | 7.53     |       |  |
| standard deviation                                                                                     | ± 2.483  | -     |  |
| Gender categorical                                                                                     |          |       |  |
| Units: Subjects                                                                                        |          |       |  |
| Female                                                                                                 | 3        | 15    |  |
| Male                                                                                                   | 10       | 38    |  |
| Race                                                                                                   |          |       |  |
| Units: Subjects                                                                                        |          |       |  |
| White                                                                                                  | 13       | 53    |  |
| Baseline IGF-I SDS                                                                                     |          |       |  |
| Units: --                                                                                              |          |       |  |
| arithmetic mean                                                                                        | -2.502   |       |  |
| standard deviation                                                                                     | ± 0.896  | -     |  |
| Baseline Height SDS                                                                                    |          |       |  |
| Units: --                                                                                              |          |       |  |
| arithmetic mean                                                                                        | -3.27    |       |  |
| standard deviation                                                                                     | ± 1.077  | -     |  |
| Screening Peak GH Levels                                                                               |          |       |  |
| The highest GH peak serum level of the two GH stimulation tests at Screening was used for calculation. |          |       |  |
| Units: ng/mL                                                                                           |          |       |  |
| arithmetic mean                                                                                        | 5.15     |       |  |
| standard deviation                                                                                     | ± 3.068  | -     |  |

### Subject analysis sets

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type  | Safety analysis     |

Subject analysis set description:

The Safety Analysis Set (SAS) includes all patients who receive at least one dose of planned study medication.

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

Subject analysis set description:

The Full Analysis Set (FAS) includes all patients who are randomized, receive at least one dose of planned study medication and provide a baseline and at least one post-baseline height measurement value.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Per Protocol Analysis Set |
| Subject analysis set type  | Per protocol              |

Subject analysis set description:

Patients with major protocol deviations or premature termination of the treatment due to reasons that were definitely not related to study medication will be excluded from the Per-Protocol (PP) analysis. Major protocol deviations will be detailed in the Protocol Deviation Plan and will include aspects of:

- o availability of measurements,
- o non-compliance with respect to assigned study medication, assigned dose level and / or dose regimen,
- o non-compliance to visit schedule (flexibility defined by visit windows),
- o failure to satisfy inclusion or exclusion criteria,
- o taking any not permitted concomitant medication during the study,
- o other parameters.

| Reporting group values                             | Safety Analysis Set | Full Analysis Set | Per Protocol Analysis Set |
|----------------------------------------------------|---------------------|-------------------|---------------------------|
| Number of subjects                                 | 53                  | 53                | 51                        |
| Age categorical                                    |                     |                   |                           |
| Units: Subjects                                    |                     |                   |                           |
| In utero                                           | 0                   | 0                 | 0                         |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                 | 0                         |
| Newborns (0-27 days)                               | 0                   | 0                 | 0                         |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                 | 0                         |
| Children (2-11 years)                              | 53                  | 53                | 51                        |
| Adolescents (12-17 years)                          | 0                   | 0                 | 0                         |
| Adults (18-64 years)                               | 0                   | 0                 | 0                         |
| From 65-84 years                                   | 0                   | 0                 | 0                         |
| 85 years and over                                  | 0                   | 0                 | 0                         |
| Age continuous                                     |                     |                   |                           |
| Units: years                                       |                     |                   |                           |
| arithmetic mean                                    | 7.76                | 7.76              | 7.76                      |
| standard deviation                                 | ± 2.53              | ± 2.53            | ± 2.542                   |
| Gender categorical                                 |                     |                   |                           |
| Units: Subjects                                    |                     |                   |                           |
| Female                                             | 15                  | 15                | 15                        |
| Male                                               | 38                  | 38                | 36                        |
| Race                                               |                     |                   |                           |
| Units: Subjects                                    |                     |                   |                           |
| White                                              | 53                  | 53                | 51                        |
| Baseline IGF-I SDS                                 |                     |                   |                           |
| Units: --                                          |                     |                   |                           |
| arithmetic mean                                    |                     |                   |                           |
| standard deviation                                 | ±                   | ±                 | ±                         |
| Baseline Height SDS                                |                     |                   |                           |
| Units: --                                          |                     |                   |                           |
| arithmetic mean                                    |                     |                   |                           |

|                                                                                                        |   |   |   |
|--------------------------------------------------------------------------------------------------------|---|---|---|
| standard deviation                                                                                     | ± | ± | ± |
| Screening Peak GH Levels                                                                               |   |   |   |
| The highest GH peak serum level of the two GH stimulation tests at Screening was used for calculation. |   |   |   |
| Units: ng/mL                                                                                           |   |   |   |
| arithmetic mean                                                                                        |   |   |   |
| standard deviation                                                                                     | ± | ± | ± |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Cohort 1                  |
| Reporting group description:<br>ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Cohort 2                  |
| Reporting group description:<br>ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Cohort 3                  |
| Reporting group description:<br>ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                           |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Cohort 4                  |
| Reporting group description:<br>Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                           |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Safety Analysis Set       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Safety analysis           |
| Subject analysis set description:<br>The Safety Analysis Set (SAS) includes all patients who receive at least one dose of planned study medication.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                           |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Full Analysis Set         |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Full analysis             |
| Subject analysis set description:<br>The Full Analysis Set (FAS) includes all patients who are randomized, receive at least one dose of planned study medication and provide a baseline and at least one post-baseline height measurement value.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                           |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Per Protocol Analysis Set |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Per protocol              |
| Subject analysis set description:<br>Patients with major protocol deviations or premature termination of the treatment due to reasons that were definitely not related to study medication will be excluded from the Per-Protocol (PP) analysis. Major protocol deviations will be detailed in the Protocol Deviation Plan and will include aspects of: <ul style="list-style-type: none"><li>o availability of measurements,</li><li>o non-compliance with respect to assigned study medication, assigned dose level and / or dose regimen,</li><li>o non-compliance to visit schedule (flexibility defined by visit windows),</li><li>o failure to satisfy inclusion or exclusion criteria,</li><li>o taking any not permitted concomitant medication during the study,</li><li>o other parameters.</li></ul> |                           |

### Primary: Incidence of anti-hGH binding antibody formation

|                                                                                                                                        |                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| End point title                                                                                                                        | Incidence of anti-hGH binding antibody formation <sup>[1]</sup> |
| End point description:<br>Number of subjects with positive results for Anti-hGH binding antibodies at two consecutive post-dose visits |                                                                 |
| End point type                                                                                                                         | Primary                                                         |
| End point timeframe:<br>Visit 2 - Visit 5                                                                                              |                                                                 |

#### 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: As this is an exploratory study, no hypothesis tests were performed.

| End point values                                | Cohort 1        | Cohort 2        | Cohort 3        | Cohort 4        |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                              | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                     | 12              | 14              | 14              | 13              |
| Units: Number of subjects with positive results | 1               | 0               | 0               | 0               |

## Statistical analyses

No statistical analyses for this end point

### Primary: Incidence of anti-hGH neutralizing antibody formation

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Incidence of anti-hGH neutralizing antibody formation <sup>[2]</sup> |
|-----------------|----------------------------------------------------------------------|

End point description:

Number of subjects with positive results for anti-hGH neutralizing antibodies at two consecutive post-dose visits

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Visit 2 - Visit 5

Notes:

[2] - 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: As this is an exploratory study, no hypothesis tests were performed.

| End point values                                | Cohort 1        | Cohort 2        | Cohort 3        | Cohort 4        |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                              | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                     | 12              | 14              | 14              | 13              |
| Units: Number of subjects with positive results | 0               | 0               | 0               | 0               |

## Statistical analyses

No statistical analyses for this end point

### Primary: Local tolerability (assessed by the patient and the investigator)

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Local tolerability (assessed by the patient and the |
|-----------------|-----------------------------------------------------|

End point description:

Overview of subject number of local tolerability assessment results

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment and continues until the end of the patient's participation in the study

Notes:

[3] - 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: As this is an exploratory study, no hypothesis tests were performed.

| End point values                    | Cohort 1        | Cohort 2        | Cohort 3        | Cohort 4        |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 12              | 14              | 14              | 13              |
| Units: Number of Subjects with ISRs | 7               | 6               | 6               | 6               |

## Statistical analyses

No statistical analyses for this end point

### Primary: Cmax of hGH

|                 |                            |
|-----------------|----------------------------|
| End point title | Cmax of hGH <sup>[4]</sup> |
|-----------------|----------------------------|

End point description:

As part of the following endpoint:

PK profile of serum hGH from ACP-001 treated patients compared between ACP-001 dose groups and to the PK profile of hGH from the daily rhGH group during V1 and V3

Uncorrected Cmax (maximum value of concentration) values at Week 13

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[4] - 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: As this is an exploratory study, no hypothesis tests were performed.

| End point values                     | Cohort 1         | Cohort 2         | Cohort 3        | Cohort 4          |
|--------------------------------------|------------------|------------------|-----------------|-------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group | Reporting group   |
| Number of subjects analysed          | 12               | 14               | 14              | 13                |
| Units: ng/mL                         |                  |                  |                 |                   |
| arithmetic mean (standard deviation) | 12.558 (± 8.678) | 13.418 (± 9.428) | 31.8 (± 17.499) | 16.612 (± 12.777) |

## Statistical analyses

No statistical analyses for this end point

### Primary: AUC0-168h of hGH

|                 |                                 |
|-----------------|---------------------------------|
| End point title | AUC0-168h of hGH <sup>[5]</sup> |
|-----------------|---------------------------------|

End point description:

As part of the following endpoint:

PK profile of serum hGH from ACP-001 treated patients compared between ACP-001 dose groups and to the PK profile of hGH from the daily rhGH group during V1 and V3.

Uncorrected AUC0-168h (area under the curve from 0h to 168h) values at Week 13

For Cohort 4 AUC0-24h\*7 has been presented

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[5] - 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: As this is an exploratory study, no hypothesis tests were performed.

| End point values                     | Cohort 1           | Cohort 2           | Cohort 3             | Cohort 4           |
|--------------------------------------|--------------------|--------------------|----------------------|--------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group      | Reporting group    |
| Number of subjects analysed          | 12                 | 14                 | 14                   | 13                 |
| Units: h*ng/mL                       |                    |                    |                      |                    |
| arithmetic mean (standard deviation) | 696.34 (± 410.096) | 787.41 (± 483.169) | 2167.43 (± 1064.729) | 556.88 (± 412.618) |

## Statistical analyses

No statistical analyses for this end point

### Primary: Etrough of IGF-I

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Etrough of IGF-I <sup>[6]</sup> <sup>[7]</sup> |
|-----------------|------------------------------------------------|

End point description:

As part of the following endpoint:

PD profile of serum IGF-I during V1 and V3 compared between the ACP-001 dose groups and to the daily rhGH group.

Uncorrected Etrough (the pre-dose efficacy response) values at Week 13

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[6] - 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: As this is an exploratory study, no hypothesis tests were performed.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The difference in the dosing regimen of investigational product and comparator does not enable to consistently compare PD parameters across treatments.

| End point values                     | Cohort 1        | Cohort 2        | Cohort 3         |  |
|--------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type                   | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed          | 12              | 14              | 14               |  |
| Units: ng/mL                         |                 |                 |                  |  |
| arithmetic mean (standard deviation) | 97.17 (± 50.53) | 156 (± 76.235)  | 167.83 (± 74.01) |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Emax of IGF-I

|                 |                                             |
|-----------------|---------------------------------------------|
| End point title | Emax of IGF-I <sup>[8]</sup> <sup>[9]</sup> |
|-----------------|---------------------------------------------|

End point description:

As part of the following endpoint:

PD profile of serum IGF-I during V1 and V3 compared between the ACP-001 dose groups and to the daily rhGH group.

Uncorrected Emax (the maximum observed efficacy response) values at Week 13

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[8] - 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: As this is an exploratory study, no hypothesis tests were performed.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The difference in the dosing regimen of investigational product and comparator does not enable to consistently compare PD parameters across treatments.

| End point values                     | Cohort 1          | Cohort 2        | Cohort 3           |  |
|--------------------------------------|-------------------|-----------------|--------------------|--|
| Subject group type                   | Reporting group   | Reporting group | Reporting group    |  |
| Number of subjects analysed          | 12                | 14              | 14                 |  |
| Units: ng/mL                         |                   |                 |                    |  |
| arithmetic mean (standard deviation) | 209.5 (± 120.189) | 276 (± 126.632) | 289.92 (± 129.469) |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: AUEC0-168h of IGF-I

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | AUEC0-168h of IGF-I <sup>[10]</sup> <sup>[11]</sup> |
|-----------------|-----------------------------------------------------|

End point description:

As part of the following endpoint:

PD profile of serum IGF-I during V1 and V3 compared between the ACP-001 dose groups and to the daily rhGH group.

Uncorrected AUEC0-168 (Area Under the Efficacy Curve (AUC) from 0h to 168h) values at Week 13

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[10] - 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: As this is an exploratory study, no hypothesis tests were performed.

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The difference in the dosing regimen of investigational product and comparator does not enable to consistently compare PD parameters across treatments.

| End point values                     | Cohort 1              | Cohort 2              | Cohort 3              |  |
|--------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type                   | Reporting group       | Reporting group       | Reporting group       |  |
| Number of subjects analysed          | 12                    | 14                    | 14                    |  |
| Units: h*ng/mL                       |                       |                       |                       |  |
| arithmetic mean (standard deviation) | 28526.19 (± 15756.44) | 35591.94 (± 17068.59) | 36066.01 (± 17379.44) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Annualized HV during treatment with ACP-001 or daily rhGH at the end of 6 months, for each ACP-001 dose group and for the daily rhGH dose group

|                                                      |                                                                                                                                                 |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                      | Annualized HV during treatment with ACP-001 or daily rhGH at the end of 6 months, for each ACP-001 dose group and for the daily rhGH dose group |
| End point description:                               |                                                                                                                                                 |
| Descriptive Statistics of Annualized Height Velocity |                                                                                                                                                 |
| End point type                                       | Secondary                                                                                                                                       |
| End point timeframe:                                 |                                                                                                                                                 |
| Baseline to 6 Months (Visit 5)                       |                                                                                                                                                 |

| End point values                     | Cohort 1        | Cohort 2        | Cohort 3        | Cohort 4        |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 12              | 14              | 14              | 13              |
| Units: cm/year                       |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 11.93 (± 4.066) | 12.89 (± 3.464) | 13.85 (± 4.009) | 11.64 (± 3.592) |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study treatment and continues until the end of the patient's participation in the study (until 4 weeks after stop of patient's study participation for serious adverse events).

Adverse event reporting additional description:

Treatment-emergent adverse events are summarized.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description:

ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week

|                       |          |
|-----------------------|----------|
| Reporting group title | Cohort 2 |
|-----------------------|----------|

Reporting group description:

ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week

|                       |          |
|-----------------------|----------|
| Reporting group title | Cohort 3 |
|-----------------------|----------|

Reporting group description:

ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week

|                       |          |
|-----------------------|----------|
| Reporting group title | Cohort 4 |
|-----------------------|----------|

Reporting group description:

Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week

| Serious adverse events                            | Cohort 1       | Cohort 2       | Cohort 3       |
|---------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    | 0              | 0              | 0              |
| Gastrointestinal disorders                        |                |                |                |
| Inguinal hernia                                   |                |                |                |
| subjects affected / exposed                       | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |

| Serious adverse events                            | Cohort 4       |  |  |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 13 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Gastrointestinal disorders                      |                |  |  |
| Inguinal hernia                                 |                |  |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Cohort 1        | Cohort 2        | Cohort 3        |
|-------------------------------------------------------|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                 |                 |
| subjects affected / exposed                           | 7 / 12 (58.33%) | 6 / 14 (42.86%) | 8 / 14 (57.14%) |
| General disorders and administration site conditions  |                 |                 |                 |
| Fatigue                                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 1 / 14 (7.14%)  |
| occurrences (all)                                     | 0               | 0               | 1               |
| Hyperthermia                                          |                 |                 |                 |
| subjects affected / exposed                           | 1 / 12 (8.33%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                                     | 2               | 0               | 0               |
| Pyrexia                                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 1 / 14 (7.14%)  |
| occurrences (all)                                     | 0               | 0               | 1               |
| Immune system disorders                               |                 |                 |                 |
| Food allergy                                          |                 |                 |                 |
| subjects affected / exposed                           | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 1 / 14 (7.14%)  |
| occurrences (all)                                     | 0               | 0               | 1               |
| Respiratory, thoracic and mediastinal disorders       |                 |                 |                 |
| Epistaxis                                             |                 |                 |                 |
| subjects affected / exposed                           | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                                     | 0               | 0               | 0               |
| Oropharyngeal pain                                    |                 |                 |                 |
| subjects affected / exposed                           | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                                     | 0               | 0               | 0               |
| Investigations                                        |                 |                 |                 |
| Blood triglycerides                                   |                 |                 |                 |
| subjects affected / exposed                           | 0 / 12 (0.00%)  | 1 / 14 (7.14%)  | 0 / 14 (0.00%)  |
| occurrences (all)                                     | 0               | 1               | 0               |

|                                                |                 |                 |                 |
|------------------------------------------------|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications |                 |                 |                 |
| Heat exhaustion                                |                 |                 |                 |
| subjects affected / exposed                    | 1 / 12 (8.33%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                              | 1               | 0               | 0               |
| Open wound                                     |                 |                 |                 |
| subjects affected / exposed                    | 0 / 12 (0.00%)  | 1 / 14 (7.14%)  | 0 / 14 (0.00%)  |
| occurrences (all)                              | 0               | 1               | 0               |
| Procedural dizziness                           |                 |                 |                 |
| subjects affected / exposed                    | 1 / 12 (8.33%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                              | 1               | 0               | 0               |
| Congenital, familial and genetic disorders     |                 |                 |                 |
| Thalassaemia beta                              |                 |                 |                 |
| subjects affected / exposed                    | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 1 / 14 (7.14%)  |
| occurrences (all)                              | 0               | 0               | 1               |
| Nervous system disorders                       |                 |                 |                 |
| Headache                                       |                 |                 |                 |
| subjects affected / exposed                    | 2 / 12 (16.67%) | 0 / 14 (0.00%)  | 1 / 14 (7.14%)  |
| occurrences (all)                              | 2               | 0               | 1               |
| Blood and lymphatic system disorders           |                 |                 |                 |
| Anaemia                                        |                 |                 |                 |
| subjects affected / exposed                    | 0 / 12 (0.00%)  | 2 / 14 (14.29%) | 1 / 14 (7.14%)  |
| occurrences (all)                              | 0               | 2               | 1               |
| Iron deficiency anaemia                        |                 |                 |                 |
| subjects affected / exposed                    | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 2 / 14 (14.29%) |
| occurrences (all)                              | 0               | 0               | 2               |
| Ear and labyrinth disorders                    |                 |                 |                 |
| Ear pain                                       |                 |                 |                 |
| subjects affected / exposed                    | 1 / 12 (8.33%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                              | 1               | 0               | 0               |
| Middle ear inflammation                        |                 |                 |                 |
| subjects affected / exposed                    | 0 / 12 (0.00%)  | 0 / 14 (0.00%)  | 0 / 14 (0.00%)  |
| occurrences (all)                              | 0               | 0               | 0               |
| Eye disorders                                  |                 |                 |                 |
| Strabismus                                     |                 |                 |                 |
| subjects affected / exposed                    | 0 / 12 (0.00%)  | 1 / 14 (7.14%)  | 0 / 14 (0.00%)  |
| occurrences (all)                              | 0               | 1               | 0               |
| Gastrointestinal disorders                     |                 |                 |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Anal pruritus               |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Diarrhoea                   |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 14 (0.00%) | 1 / 14 (7.14%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Inguinal hernia             |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Nausea                      |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Vomiting                    |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Endocrine disorders         |                |                |                 |
| Hypothyroidism              |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 14 (7.14%) | 1 / 14 (7.14%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Secondary hyperthyroidism   |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Infections and infestations |                |                |                 |
| Bronchitis                  |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 14 (7.14%) | 2 / 14 (14.29%) |
| occurrences (all)           | 0              | 1              | 2               |
| Nasopharyngitis             |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 0 / 14 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Respiratory tract infection |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 1 / 14 (7.14%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Rhinitis                    |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 14 (0.00%) | 1 / 14 (7.14%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Tonsillitis                 |                |                |                 |

|                                                                                                              |                     |                     |                     |
|--------------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                             | 0 / 12 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)                                            | 0 / 12 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 | 0 / 14 (0.00%)<br>0 |
| Tracheitis<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 12 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Varicella<br>subjects affected / exposed<br>occurrences (all)                                                | 0 / 12 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 | 1 / 14 (7.14%)<br>1 |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1 | 0 / 14 (0.00%)<br>0 | 0 / 14 (0.00%)<br>0 |

|                                                                                                                     |                      |  |  |
|---------------------------------------------------------------------------------------------------------------------|----------------------|--|--|
| <b>Non-serious adverse events</b>                                                                                   | Cohort 4             |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                | 8 / 13 (61.54%)      |  |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0  |  |  |
| Hyperthermia<br>subjects affected / exposed<br>occurrences (all)                                                    | 0 / 13 (0.00%)<br>0  |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                         | 3 / 13 (23.08%)<br>3 |  |  |
| Immune system disorders<br>Food allergy<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 13 (0.00%)<br>0  |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Epistaxis                                                        |                      |  |  |

|                                                |                |  |  |
|------------------------------------------------|----------------|--|--|
| subjects affected / exposed                    | 1 / 13 (7.69%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Oropharyngeal pain                             |                |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Investigations                                 |                |  |  |
| Blood triglycerides                            |                |  |  |
| subjects affected / exposed                    | 0 / 13 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Injury, poisoning and procedural complications |                |  |  |
| Heat exhaustion                                |                |  |  |
| subjects affected / exposed                    | 0 / 13 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Open wound                                     |                |  |  |
| subjects affected / exposed                    | 0 / 13 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Procedural dizziness                           |                |  |  |
| subjects affected / exposed                    | 0 / 13 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Congenital, familial and genetic disorders     |                |  |  |
| Thalassaemia beta                              |                |  |  |
| subjects affected / exposed                    | 0 / 13 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Nervous system disorders                       |                |  |  |
| Headache                                       |                |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Blood and lymphatic system disorders           |                |  |  |
| Anaemia                                        |                |  |  |
| subjects affected / exposed                    | 0 / 13 (0.00%) |  |  |
| occurrences (all)                              | 0              |  |  |
| Iron deficiency anaemia                        |                |  |  |
| subjects affected / exposed                    | 1 / 13 (7.69%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Ear and labyrinth disorders                    |                |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                 |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--|--|
| Ear pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Middle ear inflammation<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                       | 0 / 13 (0.00%)<br>0<br><br>1 / 13 (7.69%)<br>1                                                                                  |  |  |
| Eye disorders<br>Strabismus<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                       | 0 / 13 (0.00%)<br>0                                                                                                             |  |  |
| Gastrointestinal disorders<br>Anal pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Inguinal hernia<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0<br><br>1 / 13 (7.69%)<br>1 |  |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)<br><br>Secondary hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                        | 1 / 13 (7.69%)<br>1<br><br>0 / 13 (0.00%)<br>0                                                                                  |  |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                         | 1 / 13 (7.69%)<br>1                                                                                                             |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| Nasopharyngitis                    |                |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Respiratory tract infection        |                |  |  |
| subjects affected / exposed        | 0 / 13 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Rhinitis                           |                |  |  |
| subjects affected / exposed        | 0 / 13 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Tonsillitis                        |                |  |  |
| subjects affected / exposed        | 0 / 13 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Tooth abscess                      |                |  |  |
| subjects affected / exposed        | 1 / 13 (7.69%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Tracheitis                         |                |  |  |
| subjects affected / exposed        | 0 / 13 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Varicella                          |                |  |  |
| subjects affected / exposed        | 0 / 13 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Decreased appetite                 |                |  |  |
| subjects affected / exposed        | 0 / 13 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                         |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 April 2013 | <p>The Protocol was amended:</p> <p>To address changes in Exclusion criteria</p> <p>To clarify and specify study procedures</p> <p>To add new references</p> <p>To address a change of address</p> <p>To clarify abbreviations and address typographical and grammar mistakes</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported