



## Clinical trial results:

**A randomised, double-blind, placebo-controlled trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in obese children aged 7 to 11 years**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004454-34 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 13 April 2017  |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 25 October 2017 |
| First version publication date | 25 October 2017 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN8022-4181 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02696148     |
| WHO universal trial number (UTN)   | U1111-1162-9171 |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novo Nordisk A/S   |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880  |
| Public contact               | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact           | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |

Notes:

### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000128-PIP02-09 |
| 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                       | 18 September 2017 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 13 April 2017     |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 13 April 2017     |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and tolerability of multiple once-daily doses of liraglutide at doses up to 3.0 mg in obese children aged 7–11 years and at Tanner stage 1.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil. 1 Oct 2013) and ICH Good Clinical Practice (10 Jun 1996) and 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 14 March 2016 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 24 |
| Worldwide total number of subjects   | 24                |
| EEA total number of subjects         | 0                 |

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)                     | 24 |
| 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:

The trial was conducted at 3 sites in the United States.

### Pre-assignment

Screening details:

Not applicable.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

Blinding implementation details:

Liraglutide and placebo were supplied in similar 3 mL FlexPen® devices and were visually identical, and packed and labelled to fulfil the requirements for double-blind procedures. Equal volumes of liraglutide and placebo were administered.

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Liraglutide |

Arm description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Liraglutide            |
| Investigational medicinal product code |                        |
| Other name                             | Saxenda®               |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Liraglutide, 6.0 mg/mL in a 3 mL FlexPen® was administered once daily via subcutaneous (s.c.) abdominal injections in the morning (9 a.m. ±2 hours).

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Liraglutide placebo in a 3 mL FlexPen® was administered once daily via s.c. abdominal injections in the morning (9 a.m.  $\pm$ 2 hours).

| <b>Number of subjects in period 1</b> | Liraglutide | Placebo |
|---------------------------------------|-------------|---------|
| Started                               | 16          | 8       |
| Completed                             | 14          | 6       |
| Not completed                         | 2           | 2       |
| Consent withdrawn by subject          | 1           | -       |
| Lost to follow-up                     | 1           | -       |
| Withdrawal by parent/guardian         | -           | 2       |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Liraglutide |
|-----------------------|-------------|

#### Reporting group description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

#### Reporting group description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

| Reporting group values                | Liraglutide | Placebo | Total |
|---------------------------------------|-------------|---------|-------|
| Number of subjects                    | 16          | 8       | 24    |
| Age Categorical<br>Units: Subjects    |             |         |       |
| Children (2-11 years)                 | 16          | 8       | 24    |
| Age Continuous<br>Units: years        |             |         |       |
| arithmetic mean                       | 9.7         | 10.4    |       |
| standard deviation                    | ± 1.1       | ± 1.1   | -     |
| Gender Categorical<br>Units: Subjects |             |         |       |
| Female                                | 8           | 1       | 9     |
| Male                                  | 8           | 7       | 15    |

## End points

### End points reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Liraglutide |
| Reporting group description:   |             |
| Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks. |             |
| Reporting group title  | Placebo     |
| Reporting group description:   |             |
| Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.  |             |

### Primary: Number of treatment emergent adverse events

|   |  |
|---|--|
| End point title   | Number of treatment emergent adverse events <sup>[1]</sup> |
| End point description:  |  |
| A treatment emergent adverse event (TEAE) was defined as an event that either:<br>1) had an onset time after the first time of exposure to investigational medicinal product (IMP), liraglutide or placebo and no later than the follow-up visit (i.e., 10-17 days after the last dose)<br>2) or had an onset time before the first time of exposure to IMP and increased in severity during the treatment period and no later than the follow-up visit.<br>Results are based on the safety analysis set, which included all subjects who were exposed to at least one dose of the IMP. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Recorded from the time of first dosing and until completion of follow up visit (59-108 days after first dosing)   |  |
| 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.<br>Justification: The primary endpoint investigated safety and was analysed using descriptive statistics, and thus no statistical analysis was performed.   |  |

| End point values            | Liraglutide       | Placebo          |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 16 <sup>[2]</sup> | 8 <sup>[3]</sup> |  |  |
| Units: Number of events     | 37                | 12               |  |  |

Notes:

[2] - Out of 16 subjects analysed, 9 subjects were reported with 37 AEs.

[3] - Out of 8 subjects analysed, 5 subjects were reported with 12 AEs.

### Statistical analyses

No statistical analyses for this end point

---

**Secondary: Area under the liraglutide concentration curve from 0-24 hours (AUC0-24h) at steady state**

---

|                 |  |
|-----------------|--|
| End point title | Area under the liraglutide concentration curve from 0-24 hours (AUC0-24h) at steady state <sup>[4]</sup> |
|-----------------|--|

End point description:

Results are based on the full analysis set, which included all subjects who were randomised and received at least one dose of trial product. Number of subjects analysed = number of subjects contributed to the analysis.

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

End point timeframe:

Following the last dose (49-91 days after first dosing)

Notes:

[4] - 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: For this endpoint, only samples from subjects treated with liraglutide were included. Therefore, the placebo-treated subjects did not contribute to the analyses.

| End point values                         | Liraglutide         |  |  |  |
|--|---------------------|--|--|--|
| Subject group type                       | Reporting group     |  |  |  |
| Number of subjects analysed              | 13                  |  |  |  |
| Units: h x nmol/L                        |                     |  |  |  |
| geometric mean (confidence interval 95%) | 1161 (1002 to 1398) |  |  |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time of first dosing and until completion of follow up visit (59-108 days after first dosing).

Adverse event reporting additional description:

All the following mentioned AEs are treatment emergent, i.e., TEAEs. Results are based on the safety analysis set.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20     |

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Liraglutide |
|-----------------------|-------------|

Reporting group description:

Subjects received liraglutide once daily. Treatment was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. Following was the dose escalation regimen for liraglutide: week 1: 0.3 mg, week 2: 0.6 mg, week 3: 0.9 mg, week 4: 1.2 mg, week 5: 1.8 mg, week 6: 2.4 mg, and week 7: 3.0 mg. The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received liraglutide matching placebo once daily. Each placebo injection volume was based on the correspondent liraglutide dose (0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg). The treatment period consisted of 7 mandatory treatment weeks with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was to be included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Thus, the duration of the treatment period could be prolonged from 7 to 13 weeks, in case a flex week was needed between all 7 treatment weeks.

| Serious adverse events                            | Liraglutide    | Placebo       |  |
|---|----------------|---------------|--|
| Total subjects affected by serious adverse events |                |               |  |
| subjects affected / exposed                       | 0 / 16 (0.00%) | 0 / 8 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0             |  |
| number of deaths resulting from adverse events    | 0              | 0             |  |

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

| Non-serious adverse events                            | Liraglutide     | Placebo        |  |
|---|-----------------|----------------|--|
| Total subjects affected by non-serious adverse events |                 |                |  |
| subjects affected / exposed                           | 9 / 16 (56.25%) | 5 / 8 (62.50%) |  |



|   |   |   |  |
|---|---|---|--|
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0   | 1 / 8 (12.50%)<br>1   |  |
| Injury, poisoning and procedural complications<br>Arthropod bite<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0   | 1 / 8 (12.50%)<br>1   |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1<br><br>2 / 16 (12.50%)<br>3   | 1 / 8 (12.50%)<br>1<br><br>3 / 8 (37.50%)<br>4  |  |
| General disorders and administration site conditions<br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site induration<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site reaction<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0<br><br>1 / 16 (6.25%)<br>1<br><br>2 / 16 (12.50%)<br>2<br><br>1 / 16 (6.25%)<br>1 | 1 / 8 (12.50%)<br>1<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1   | 0 / 8 (0.00%)<br>0  |  |
| Eye disorders<br>Orbital oedema<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1   | 0 / 8 (0.00%)<br>0  |  |
| Gastrointestinal disorders  |   |   |  |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 16 (6.25%)<br>3  | 0 / 8 (0.00%)<br>0  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 16 (12.50%)<br>6 | 0 / 8 (0.00%)<br>0  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 16 (18.75%)<br>3 | 0 / 8 (0.00%)<br>0  |  |
| Salivary hypersecretion<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 16 (6.25%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 4 / 16 (25.00%)<br>5 | 0 / 8 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders   |                      |                     |  |

|  |   |  |  |
|--|---|--|--|
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1   | 0 / 8 (0.00%)<br>0   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle tightness<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0<br><br>1 / 8 (12.50%)<br>1<br><br>1 / 8 (12.50%)<br>1 |  |
| Infections and infestations<br>Gastritis viral<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1<br><br>0 / 16 (0.00%)<br>0<br><br>1 / 16 (6.25%)<br>1 | 0 / 8 (0.00%)<br>0<br><br>1 / 8 (12.50%)<br>1<br><br>0 / 8 (0.00%)<br>0  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 23 February 2016 | <ol style="list-style-type: none"><li>1) A discrepancy in the key inclusion criteria regarding the time of tanner stage was corrected in the summary.</li><li>2) Self-injection with test medium at visit 1 (in week 1) was added to the Flow char for clarification.</li><li>3) The PK sampling time window for liraglutide at visit 12 (follow-up visit) was updated for more flexibility for the subjects.</li><li>4) The subject information (SI)/informed consent (IC) for parents or legally acceptable representative (LARs) was updated with inclusion of the findings from the pre-clinical juvenile toxicity study as per FDA request. The protocol was updated accordingly ensuring the full information is reflected in the protocol.</li><li>5) A discrepancy regarding the number of days from visit 2 (in week 0) to visit 3-8 (in weeks 1-6) was corrected.</li><li>6) The protocol was updated with specifications of procedures in case a subject fails to attend a visit fasting, or has forgotten to perform self-measured plasma glucose (SMPG) and/or withhold their daily liraglutide/liraglutide placebo dose before coming to the trial site.</li></ol> |
| 06 July 2016     | <ol style="list-style-type: none"><li>1) Based on external advisor and Investigators feedback, children with obesity enter puberty earlier than other children. The request to modify the inclusion criterion to allow children with premature adrenarche (development of pubic hair without the children having entered true puberty) was based on the association of this finding with increased body mass index.</li><li>2) The SI/IC for parents or LARs was also updated with the change in inclusion criteria related to Tanner stage 1.</li><li>3) The protocol was updated with information describing that arrangements can be made with the investigator to stay at site overnight before a visit, as needed.</li></ol>  |
| 06 July 2016     | With amendment no. 2, the trial protocol population was modified to include prepubertal children (Tanner stage 1) and prepubertal children with premature adrenarche. This amendment no. 3 updated the trial protocol with information on how to document the exclusion of conditions other than premature adrenache.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported