



Clinical trial results:

A randomised, open-labelled, active-controlled, multinational, dose-escalation trial investigating safety, tolerability, pharmacokinetics and pharmacodynamics of a single dose of long-acting growth hormone (NNC0195-0092) compared to daily dosing of Norditropin® SimpleXx® in children with growth hormone deficiency

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-000013-20 |
| Trial protocol | SI BE AT SE ES FR |
| Global end of trial date | 04 November 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 01 April 2016 |
| First version publication date | 16 May 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN8640-4042 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01973244 |
| WHO universal trial number (UTN) | U1111-1138-2206 |

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) | 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? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 19 March 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 04 November 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and tolerability of a single subcutaneous (s.c.) dose of NNC0195-0092 compared to daily dosing of Norditropin® SimpleXx® for seven days in children with growth hormone deficiency (GHD)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013), ICH Good Clinical Practice (GCP) (1996) and FDA 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

| | |
|---|------------------|
| Actual start date of recruitment | 16 December 2013 |
| 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 | Slovenia: 6 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Belgium: 6 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Israel: 5 |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 4 |
| Worldwide total number of subjects | 32 |
| EEA total number of subjects | 23 |

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) | 32 |
| 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 14 sites in 8 countries.

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 | Not blinded |

Blinding implementation details:

Not applicable.

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 0.02 mg/Kg - NNC0195-0092 |

Arm description:

0.02 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|--|-------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | NNC0195-0092 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.02 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|------------------|---------------------------|
| Arm title | 0.04 mg/Kg - NNC0195-0092 |
|------------------|---------------------------|

Arm description:

0.04 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|--|-------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | NNC0195-0092 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.04 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|------------------|---------------------------|
| Arm title | 0.08 mg/Kg - NNC0195-0092 |
|------------------|---------------------------|

Arm description:

0.08 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|--|-------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | NNC0195-0092 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.08 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|------------------|---------------------------|
| Arm title | 0.16 mg/Kg - NNC0195-0092 |
|------------------|---------------------------|

Arm description:

0.16 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|--|-------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | NNC0195-0092 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.16 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|------------------|-------------------------------------|
| Arm title | 0.03 mg/Kg - Norditropin® SimpleXx® |
|------------------|-------------------------------------|

Arm description:

0.03 mg/Kg, once daily dose of Norditropin® SimpleXx® was administered to subjects subcutaneously, for 7 days.

| | |
|--|-------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Norditropin® SimpleXx® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.03 mg/Kg, once daily dose of Norditropin® SimpleXx® was administered to subjects subcutaneously, for 7 days.

| Number of subjects in period 1 | 0.02 mg/Kg - NNC0195-0092 | 0.04 mg/Kg - NNC0195-0092 | 0.08 mg/Kg - NNC0195-0092 |
|---------------------------------------|------------------------------|------------------------------|------------------------------|
| Started | 6 | 6 | 6 |
| Completed | 6 | 6 | 6 |

| Number of subjects in period 1 | 0.16 mg/Kg - NNC0195-0092 | 0.03 mg/Kg - Norditropin® SimpleXx® |
|---------------------------------------|------------------------------|---|
| | | |
| Started | 6 | 8 |
| Completed | 6 | 8 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | 0.02 mg/Kg - NNC0195-0092 |
| Reporting group description: 0.02 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. | |
| Reporting group title | 0.04 mg/Kg - NNC0195-0092 |
| Reporting group description: 0.04 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. | |
| Reporting group title | 0.08 mg/Kg - NNC0195-0092 |
| Reporting group description: 0.08 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. | |
| Reporting group title | 0.16 mg/Kg - NNC0195-0092 |
| Reporting group description: 0.16 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. | |
| Reporting group title | 0.03 mg/Kg - Norditropin® SimpleXx® |
| Reporting group description: 0.03 mg/Kg, once daily dose of Norditropin® SimpleXx® was administered to subjects subcutaneously, for 7 days. | |

| Reporting group values | 0.02 mg/Kg - NNC0195-0092 | 0.04 mg/Kg - NNC0195-0092 | 0.08 mg/Kg - NNC0195-0092 |
|---------------------------------------|------------------------------|------------------------------|------------------------------|
| Number of subjects | 6 | 6 | 6 |
| Age categorical Units: Subjects | | | |
| Children (2-11 years) | 6 | 6 | 6 |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 5 | 1 |
| Male | 4 | 1 | 5 |
| Height Units: meter | | | |
| arithmetic mean | 1.2 | 1.3 | 1.3 |
| standard deviation | ± 0.1 | ± 0.1 | ± 0.1 |
| Body weight Units: Kg | | | |
| arithmetic mean | 23.1 | 27.8 | 27.1 |
| standard deviation | ± 8.9 | ± 5.6 | ± 7.4 |
| Body mass index (BMI) Units: Kg/m2 | | | |
| arithmetic mean | 15.8 | 17.4 | 16.6 |
| standard deviation | ± 2.2 | ± 3.4 | ± 1.9 |

| Reporting group values | 0.16 mg/Kg - NNC0195-0092 | 0.03 mg/Kg - Norditropin® SimpleXx® | Total |
|------------------------------------|------------------------------|---|-------|
| Number of subjects | 6 | 8 | 32 |
| Age categorical Units: Subjects | | | |
| Children (2-11 years) | 6 | 8 | 32 |

| | | | |
|--|---------------|---------------|----|
| Gender categorical Units: Subjects | | | |
| Female | 1 | 0 | 9 |
| Male | 5 | 8 | 23 |
| Height Units: meter arithmetic mean standard deviation | 1.3 ± 0.1 | 1.3 ± 0.2 | - |
| Body weight Units: Kg arithmetic mean standard deviation | 26.7 ± 6.9 | 26.1 ± 7.5 | - |
| Body mass index (BMI) Units: Kg/m2 arithmetic mean standard deviation | 15.6 ± 1.9 | 16.2 ± 1.4 | - |

End points

End points reporting groups

| | |
|------------------------------|--|
| Reporting group title | 0.02 mg/Kg - NNC0195-0092 |
| Reporting group description: | 0.02 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. |
| Reporting group title | 0.04 mg/Kg - NNC0195-0092 |
| Reporting group description: | 0.04 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. |
| Reporting group title | 0.08 mg/Kg - NNC0195-0092 |
| Reporting group description: | 0.08 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. |
| Reporting group title | 0.16 mg/Kg - NNC0195-0092 |
| Reporting group description: | 0.16 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously. |
| Reporting group title | 0.03 mg/Kg - Norditropin® SimpleXx® |
| Reporting group description: | 0.03 mg/Kg, once daily dose of Norditropin® SimpleXx® was administered to subjects subcutaneously, for 7 days. |

Primary: Incidence of adverse events (AEs)

| | |
|------------------------|---|
| End point title | Incidence of adverse events (AEs) ^[1] |
| End point description: | Incidence of adverse events (AEs) from first administration of trial product and up until day 35 (final visit). |
| End point type | Primary |
| End point timeframe: | From first administration of trial product and up until day 35 (final visit). |

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: The primary endpoint investigates safety and is analysed using descriptive statistics, and thus no statistical analysis is performed.

| End point values | 0.02 mg/Kg - NNC0195-0092 | 0.04 mg/Kg - NNC0195-0092 | 0.08 mg/Kg - NNC0195-0092 | 0.16 mg/Kg - NNC0195-0092 |
|---------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 ^[2] | 6 ^[3] | 6 ^[4] | 6 ^[5] |
| Units: Number of adverse events | 3 | 9 | 3 | 4 |

Notes:

[2] - 3 events were reported in 2 subjects

[3] - 9 events were reported in 4 subjects

[4] - 3 events were reported in 2 subjects

[5] - 4 events were reported in 3 subjects

| End point values | 0.03 mg/Kg - Norditropin® SimpleXx® | | | |
|---------------------------------|-------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 ^[6] | | | |
| Units: Number of adverse events | 2 | | | |

Notes:

[6] - 2 events were reported in 1 subject

Statistical analyses

No statistical analyses for this end point

Secondary: The area under the insulin-like growth factor I (IGF-I) concentration-time curve (AUC 0-168h)

| | |
|------------------------|---|
| End point title | The area under the insulin-like growth factor I (IGF-I) concentration-time curve (AUC 0-168h) |
| End point description: | The area under the insulin-like growth factor I (IGF-I) concentration-time curve (AUC 0-168h) |
| End point type | Secondary |
| End point timeframe: | From 0 to 168 hours after dosing. |

| End point values | 0.02 mg/Kg - NNC0195-0092 | 0.04 mg/Kg - NNC0195-0092 | 0.08 mg/Kg - NNC0195-0092 | 0.16 mg/Kg - NNC0195-0092 |
|---|------------------------------|------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 6 | 6 | 6 |
| Units: ng*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 16153 (\pm 57) | 24199 (\pm 86.6) | 42218 (\pm 28.1) | 34350 (\pm 13.5) |

| End point values | 0.03 mg/Kg - Norditropin® SimpleXx® | | | |
|---|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 | | | |
| Units: ng*h/mL | | | | |
| geometric mean (geometric coefficient of variation) | 34989 (\pm 59.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (up until day 35).

Adverse event reporting additional description:

An adverse event is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | 0.02 mg/Kg - NNC0195-0092 |
|-----------------------|---------------------------|

Reporting group description:

0.02 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|-----------------------|---------------------------|
| Reporting group title | 0.04 mg/Kg - NNC0195-0092 |
|-----------------------|---------------------------|

Reporting group description:

0.04 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|-----------------------|---------------------------|
| Reporting group title | 0.08 mg/Kg - NNC0195-0092 |
|-----------------------|---------------------------|

Reporting group description:

0.08 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously.

| | |
|-----------------------|---------------------------|
| Reporting group title | 0.16 mg/Kg - NNC0195-0092 |
|-----------------------|---------------------------|

Reporting group description:

0.16 mg/Kg, single dose of NNC0195-0092 was administered to subjects subcutaneously..

| | |
|-----------------------|-------------------------------------|
| Reporting group title | 0.03 mg/Kg - Norditropin® SimpleXx® |
|-----------------------|-------------------------------------|

Reporting group description:

0.03 mg/Kg, once daily dose of Norditropin® SimpleXx® was administered to subjects subcutaneously, for 7 days.

| Serious adverse events | 0.02 mg/Kg - NNC0195-0092 | 0.04 mg/Kg - NNC0195-0092 | 0.08 mg/Kg - NNC0195-0092 |
|---|---------------------------|---------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | 0.16 mg/Kg - NNC0195-0092 | 0.03 mg/Kg - Norditropin® SimpleXx® | |
|---|---------------------------|-------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 6 (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 | 0.02 mg/Kg - NNC0195-0092 | 0.04 mg/Kg - NNC0195-0092 | 0.08 mg/Kg - NNC0195-0092 |
|--|--|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 2 / 6 (33.33%) | 4 / 6 (66.67%) | 2 / 6 (33.33%) |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 | 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 |

| Non-serious adverse events | 0.16 mg/Kg - NNC0195-0092 | 0.03 mg/Kg - Norditropin® SimpleXx® | |
|--|------------------------------|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 6 (50.00%) | 1 / 8 (12.50%) | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 8 (0.00%) 0 | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Nausea | 1 / 6 (16.67%) 1 | 1 / 8 (12.50%) 1 | |

| | | | |
|--|--------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 8 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|-----------------|
| Not applicable. |
|-----------------|

Notes: