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	v2 (current)
This version publication date	15 April 2016
First version publication date	16 May 2015
Version creation reason	• Correction of full data set AE data to be updated

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?	Yes
Primary completion date	04 November 2014
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	1.3	1.3	
standard deviation	± 0.1	± 0.2	-
Body weight Units: Kg			
arithmetic mean	26.7	26.1	
standard deviation	± 6.9	± 7.5	-
Body mass index (BMI) Units: Kg/m2			
arithmetic mean	15.6	16.2	
standard deviation	± 1.9	± 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 (± 57)	24199 (± 86.6)	42218 (± 28.1)	34350 (± 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 (± 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	0.04 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 title	0.02 mg/Kg - NNC0195-0092

Reporting group description:

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

Serious adverse events	0.04 mg/Kg - NNC0195-0092	0.08 mg/Kg - NNC0195-0092	0.16 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	0.03 mg/Kg - Norditropin® SimpleXx®	0.02 mg/Kg - NNC0195-0092	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (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	0.04 mg/Kg - NNC0195-0092	0.08 mg/Kg - NNC0195-0092	0.16 mg/Kg - NNC0195-0092
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	3 / 6 (50.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injection site swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Enterobiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Varicella			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	0.03 mg/Kg - Norditropin® SimpleXx®	0.02 mg/Kg - NNC0195-0092	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 6 (33.33%)	
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Enterobiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Varicella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	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: