Clinical trial results:
A multicentre, multinational, randomised, open-labelled, parallel-group, active-controlled trial to compare the safety of once-weekly dosing of somapacitan (NNC0195-0092) with daily Norditropin® FlexPro® for 26 weeks in previously human growth hormone treated adults with growth hormone deficiency

Summary

EudraCT number	2014-000290-39
Trial protocol	SE DK GB
Global end of trial date	04 January 2016

Results information

Result version number	v1 (current)
This version publication date	19 January 2017
First version publication date	19 January 2017

Trial information

Trial identification

Sponsor protocol code	nn8640-4043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02382939
WHO universal trial number (UTN)	U1111-1152-3664
Other trial identifiers	Japanese trial registration number: JapicCTI-152850

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2016
Global end of trial reached?	Yes
Global end of trial date	04 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical safety of once-weekly dosing of somapacitan during 26 weeks of treatment in Adults with growth hormone deficiency subjects previously treated with daily human growth hormone.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and ICH Good Clinical Practice (GCP) (May 1996), ISO 14155 and FDA 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 February 2015
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	Germany: 13
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Sweden: 8
Worldwide total number of subjects	92
EEA total number of subjects	75

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)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	73
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 26 sites in 6 countries. All 26 sites screened and randomised/ assigned patients to treatment. Denmark: 3 sites; France: 5 sites; Germany: 3 sites; Sweden: 3 sites; United Kingdom: 5 sites; Japan: 7 sites.

Pre-assignment

Screening details:

Subjects, who were diagnosed with adults with growth hormone deficiency ≥ 6 months (defined as 180 days) prior to screening and receiving treatment with human growth hormone at least 6 months (defined as 180 days) at screening, were enrolled.

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	Norditropin

Arm description:

Subjects received subcutaneous (s.c.) injections of Norditropin daily for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of Norditropin was 0.2 mg/day (except females on oral oestrogen: 0.3 mg/day; subjects older than 60 years: 0.1 mg/day). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on insulin-like growth factor-I standard deviation score (IGF-I SDS) values:
IGF-I SDS > 3: dose reduction by 0.1 mg/day;
2 < IGF-I SDS ≤ 3: dose reduction by 0.05 mg/day;
0 < IGF-I SDS ≤ 2: No need of dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose increment by 0.1 mg/day;
IGF-I SDS ≤ -2: Dose increment by 0.2 mg/day.
After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The minimum and maximum daily dose was set to 0.05 mg and 1.1 mg (Japan: maximum daily dose was 1.0 mg).

Arm type	Active comparator
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	Norditropin FlexPro 10 mg
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects were trained in the use of the pen-injector and to inject themselves with trial drug under the supervision of the site staff. Norditropin® FlexPro® subjects injected themselves daily s.c. in the evening (standard treatment practice), except during observed trial administrations (where injections were
done in the morning (up to 12 PM noon) and at least 12 hours after injection the evening.

Arm title	Somapacitan

Arm description:

Subjects received s.c. injections of somapacitan once-weekly for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of somapacitan was 1.5 mg/week (except females on oral oestrogen 2.0 mg/week; subjects older than 60 years 1.0 mg/week). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on IGF-I SDS values:

IGF-I SDS > 3: dose reduction by 1 mg;
2 < IGF-I SDS ≤ 3: dose reduction by 0.5 mg;
0 < IGF-I SDS ≤ 2: No need for dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose Increment by 0.7 mg;
IGF-I SDS ≤ -2: Dose Increment by 1.5 mg.
After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The minimum and maximum weekly dose was set to 0.1 mg and 8 mg.

Arm type	Experimental
Investigational medicinal product name	Somapacitan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects were trained in the use of the pen-injector and to inject themselves with trial drug under the supervision of the site staff. Somapacitan subjects injected themselves once-weekly s.c. in the morning (no later than 10 am to ensure consistency of PK/PD with previous trials). On site visit days this could be extended until 12 PM (noon).

Number of subjects in period 1	Norditropin	Somapacitan
Started	31	61
Exposed	31	61
Completed	28	58
Not completed	3	3
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups

Reporting group title	Norditropin

Reporting group description:

Subjects received subcutaneous (s.c.) injections of Norditropin daily for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of Norditropin was 0.2 mg/day (except females on oral oestrogen: 0.3 mg/day; subjects older than 60 years: 0.1 mg/day). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on insulin-like growth factor-I standard deviation score (IGF-I SDS) values:
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-2 < IGF-I SDS ≤ 0: Dose increment by 0.1 mg/day;
IGF-I SDS ≤ -2: Dose increment by 0.2 mg/day.
After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The minimum and maximum daily dose was set to 0.05 mg and 1.1 mg (Japan: maximum daily dose was 1.0 mg).

Reporting group title	Somapacitan

Reporting group description:

Subjects received s.c. injections of somapacitan once-weekly for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of somapacitan was 1.5 mg/week (except females on oral oestrogen 2.0 mg/week; subjects older than 60 years 1.0 mg/week). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on IGF-I SDS values:
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0 < IGF-I SDS ≤ 2: No need for dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose Increment by 0.7 mg;
IGF-I SDS ≤ -2: Dose Increment by 1.5 mg.
After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The minimum and maximum weekly dose was set to 0.1 mg and 8 mg.

Reporting group values	Norditropin	Somapacitan	Total
Number of subjects	31	61	92
Age Categorical Units: Subjects			
18-64 years	23	50	73
≥ 65 years	8	11	19
Age Continuous Units: years			
arithmetic mean	51.7	48.1	
standard deviation	± 17.1	± 16.2	-
Gender Categorical Units: Subjects			
Female	14	28	42
Male	17	33	50

End points

End points reporting groups

Reporting group title	Norditropin

Reporting group description:

Subjects received subcutaneous (s.c.) injections of Norditropin daily for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of Norditropin was 0.2 mg/day (except females on oral oestrogen: 0.3 mg/day; subjects older than 60 years: 0.1 mg/day). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on insulin-like growth factor-I standard deviation score (IGF-I SDS) values:
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2 < IGF-I SDS ≤ 3: dose reduction by 0.05 mg/day;
0 < IGF-I SDS ≤ 2: No need of dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose increment by 0.1 mg/day;
IGF-I SDS ≤ -2: Dose increment by 0.2 mg/day.
After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The minimum and maximum daily dose was set to 0.05 mg and 1.1 mg (Japan: maximum daily dose was 1.0 mg).

Reporting group title	Somapacitan

Reporting group description:

Subjects received s.c. injections of somapacitan once-weekly for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of somapacitan was 1.5 mg/week (except females on oral oestrogen 2.0 mg/week; subjects older than 60 years 1.0 mg/week). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on IGF-I SDS values:
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2 < IGF-I SDS ≤ 3: dose reduction by 0.5 mg;
0 < IGF-I SDS ≤ 2: No need for dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose Increment by 0.7 mg;
IGF-I SDS ≤ -2: Dose Increment by 1.5 mg.
After the last dose adjustment (if any) at week 8, the individual dose level was fixed. The minimum and maximum weekly dose was set to 0.1 mg and 8 mg.

Primary: Incidence of adverse events

End point title	Incidence of adverse events[1]

End point description:

An adverse event can be 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. Total number of adverse events are reported. Analysis was performed on safety analysis set (all randomised subjects that received at least one dose of randomised treatment).

End point type	Primary

End point timeframe:

From baseline to the end of the treatment period (26 weeks)

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 a safety endpoint, no statistical analysis was performed.

End point values	Norditropin	Somapacitan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	61		
Units: adverse events	81	159		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of injection site reactions

End point title	Incidence of injection site reactions[2]

End point description:

Number of total injection site reactions. Analysis was performed on safety analysis set.

End point type	Primary

End point timeframe:

From baseline to the end of the treatment period (26 weeks)

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 a safety endpoint, no statistical analysis was performed.

End point values	Norditropin	Somapacitan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	61		
Units: injection site reactions	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of anti-NNC0195-0092 antibodies

End point title	Occurrence of anti-NNC0195-0092 antibodies[3]

End point description:

Number of subjects with anti-somapacitan (NNC0195-0092) antibodies. Analysis was performed on safety analysis set (subjects who received somapacitan only).

End point type	Secondary

End point timeframe:

From baseline (randomisation) to end of treatment period (26 weeks)

Notes:

[3] - 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 endpoint was assessed in subjects who received only somapacitan. Hence, no results for Norditropin arm are reported.

End point values	Somapacitan			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Treatment Satisfaction Questionnaire for Medication (TSQM) scores (effectiveness, convenience, and global satisfaction scores)

End point title	Change in Treatment Satisfaction Questionnaire for Medication (TSQM) scores (effectiveness, convenience, and global satisfaction scores)

End point description:

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) is a psychometric measure of a patient's satisfaction with medication. It consists of 3 subscales: effectiveness, convenience and global satisfaction. Items are rated on a 5- or 7- point scale according to subjects' experience with the medication. Each domain score can vary from 0 to 100 with higher scores indicating higher effectiveness of treatment, more convenient use of medication and overall greater satisfaction with the treatment. Analysis was performed on full analysis set (all randomised subjects that received at least one dose of randomised treatment). Here, 'n' specifies the number of subjects with data available for specified category.

End point type	Secondary

End point timeframe:

From baseline (randomisation) to end of treatment period (26 weeks)

End point values	Norditropin	Somapacitan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	61		
Units: score on a scale				
arithmetic mean (standard deviation)				
Effectiveness (n=28, 53)	3.8 (± 27.4)	9.7 (± 18.1)		
Convenience (n=28, 55)	3 (± 16.5)	15.3 (± 20.9)		
Global satisfaction (n=28, 54)	-1.2 (± 15.2)	5.4 (± 21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to week 26

Adverse event reporting additional description:

Subjects in the safety analysis set contributed to the evaluation of adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Norditropin

Reporting group description:

Subjects received s.c. injections of Norditropin daily for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of Norditropin was 0.2 mg/day (except females on oral oestrogen: 0.3 mg/day; subjects older than 60 years: 0.1 mg/day). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on IGF-I SDS values:
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0 < IGF-I SDS ≤ 2: No need of dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose increment by 0.1 mg/day;
IGF-I SDS ≤ -2: Dose increment by 0.2 mg/day.
After the last dose adjustment (if any) at Week 8, the individual dose level was fixed. The minimum and maximum daily dose was set to 0.05 mg and 1.1 mg (Japan: maximum daily dose was 1.0 mg).

Reporting group title	Somapacitan

Reporting group description:

Subjects received s.c. injections of somapacitan once-weekly for 26 weeks (8 weeks dose titration followed by 18 weeks fixed dose treatment) followed by 1 week washout. The starting dose of somapacitan was 1.5 mg/week (except females on oral oestrogen 2.0 mg/week; subjects older than 60 years 1.0 mg/week). An individualised dose titration regimen was used. Adjustment of dose was performed at weeks 2, 4, 6 and 8 based on IGF-I SDS values:
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0 < IGF-I SDS ≤ 2: No need for dose adjustment;
-2 < IGF-I SDS ≤ 0: Dose Increment by 0.7 mg;
IGF-I SDS ≤ -2: Dose Increment by 1.5 mg.
After the last dose adjustment (if any) at Week 8, the individual dose level was fixed. The minimum and maximum weekly dose was set to 0.1 mg and 8 mg.

Serious adverse events	Norditropin	Somapacitan	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 31 (6.45%)	4 / 61 (6.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Patella fracture			

subjects affected / exposed	0 / 31 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 31 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	0 / 31 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Short-bowel syndrome			
subjects affected / exposed	1 / 31 (3.23%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Norditropin	Somapacitan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)	30 / 61 (49.18%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 31 (9.68%)	1 / 61 (1.64%)	
occurrences (all)	3	1	
Headache			
subjects affected / exposed	6 / 31 (19.35%)	7 / 61 (11.48%)	
occurrences (all)	10	11	
Sciatica			
subjects affected / exposed	0 / 31 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 31 (3.23%)	4 / 61 (6.56%)	
occurrences (all)	1	5	
Fatigue			
subjects affected / exposed	5 / 31 (16.13%)	6 / 61 (9.84%)	
occurrences (all)	5	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 31 (6.45%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 31 (6.45%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	5 / 61 (8.20%) 5	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 31 (25.81%) 11	12 / 61 (19.67%) 13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2015	Two typing errors in the visit flow chart were corrected. No impact on subject safety or trial procedures: 1) The timing of visit 1 changed to 'minimum 1 day prior to visit 2'. 2) Attend visit fasting: should read 'No' for visit 3 and 'yes' for visit 4. The master PI/informed consent was updated accordingly.
27 January 2015	Changes requested by the Voluntary Harmonisation Procedure were addressed: The guideline for the United Kingdom investigators concerning contraception requirements for study subjects to be identical to the one applicable for the Denmark investigators.
11 May 2015	Updates of procedures as well as clarifications of relevant sections in the protocol: 1) Local tolerability assessments: external review by a dermatologist was added to ensure that the clinical validity of photos supported the AE description. 2) Antibody analysis: process for follow up after last patient last visit of subjects with 2 consecutive positive antidrug antibody results. 3) French health authority: any immediate adverse effects on kidney function (eGFR creatinine ≤60 mL/min/1.73m2) to be reported as a critical laboratory alert. 4)Homeostasis model assessment calculation. 5) Process for tryptase sampling in case of severe hypersensitivity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported