Clinical trial results:
A trial investigating the long-term efficacy and safety of two doses of NN-220 (somatropin [genetical recombination]) in short stature due to Noonan syndrome.

Summary

EudraCT number	2018-000750-22
Trial protocol	Outside EU/EEA
Global end of trial date	12 July 2018

Results information

Result version number	v1 (current)
This version publication date	07 February 2019
First version publication date	07 February 2019

Trial information

Trial identification

Sponsor protocol code	GHLIQUID-4020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01927861
WHO universal trial number (UTN)	U1111-1131-5892
Other trial identifiers	JAPIC: JapicCTI-132336

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (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	27 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2018
Global end of trial reached?	Yes
Global end of trial date	12 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the growth promoting effect of NN-220 (somatropin [genetical recombination]) from baseline to 104 weeks of treatment in short stature due to Noonan syndrome.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (1996) and the Ministry of Health and Welfare (MHW) Ordinance on Good Clinical Practice (1997).

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	19 August 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	Japan: 51
Worldwide total number of subjects	51
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)	51
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 26 sites in Japan.

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	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Blinding implementation details:

Both trial products were indistinguishable from one another. The code for a particular subject could be broken by the investigator if a medical emergency took place.

Arms

Are arms mutually exclusive?	Yes
Arm title	NN-220 0.033 mg/kg/day

Arm description:

The subjects received NN-220 0.033 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase.

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

Dosage and administration details:

NN-220 0.033 mg/kg/day was administered as once daily subcutaneous (s.c.; under the skin) injections by use of prefilled pens, alternating between the upper arm, thigh, abdominal wall or gluteal region. The dose was selected based on the subject’s body weight at each visit.

Arm title	NN-220 0.066 mg/kg/day

Arm description:

The subjects received NN-220 0.066 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase.

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

Dosage and administration details:

NN-220 0.066 mg/kg/day was administered as once daily s.c. injections by use of prefilled pens, alternating between the upper arm, thigh, abdominal wall or gluteal region. The dose was selected based on the subject’s body weight at each visit.

Number of subjects in period 1	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day
Started	25	26
Completed	25	23
Not completed	0	3
Adverse event, non-fatal	-	2
Unclassified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	NN-220 0.033 mg/kg/day
Reporting group description:	
The subjects received NN-220 0.033 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase.	
Reporting group title	NN-220 0.066 mg/kg/day
Reporting group description:	
The subjects received NN-220 0.066 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase.	

Reporting group values	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day	Total
Number of subjects	25	26	51
Age Categorical			
Units: Subjects			
Children (2-11 years)	25	26	51
Age Continuous			
Units: years			
arithmetic mean	6.57	6.06	
standard deviation	± 2.42	± 2.25	-
Gender Categorical			
Units: Subjects			
Female	11	8	19
Male	14	18	32
Height standard deviation score (SDS)			
Units: Standard deviation score			
arithmetic mean	-3.24	-3.25	
standard deviation	± 0.76	± 0.71	-
Insulin-like growth factor I (IGF-I)			
Units: ng/mL			
arithmetic mean	70.2	69.7	
standard deviation	± 35.8	± 35.2	-
Glycosylated haemoglobin A1c (HbA1c)			
Units: Percentage of HbA1c			
arithmetic mean	5.19	5.10	
standard deviation	± 0.19	± 0.29	-

End points

End points reporting groups

Reporting group title	NN-220 0.033 mg/kg/day
Reporting group description:	
The subjects received NN-220 0.033 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase.	
Reporting group title	NN-220 0.066 mg/kg/day
Reporting group description:	
The subjects received NN-220 0.066 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase.	
Subject analysis set title	NN-220 0.033 mg/kg/day
Subject analysis set type	Full analysis
Subject analysis set description:	
The subjects received NN-220 0.033 mg/kg/day for 104 weeks (2 years; pivotal phase).	
Subject analysis set title	NN-220 0.066 mg/kg/day
Subject analysis set type	Full analysis
Subject analysis set description:	
The subjects received NN-220 0.066 mg/kg/day for 104 weeks (2 years; pivotal phase).	
Subject analysis set title	NN-220 0.033 mg/kg/day
Subject analysis set type	Safety analysis
Subject analysis set description:	
The subjects received NN-220 0.033 mg/kg/day for 104 weeks (2 years; pivotal phase).	
Subject analysis set title	NN-220 0.066 mg/kg/day
Subject analysis set type	Safety analysis
Subject analysis set description:	
The subjects received NN-220 0.066 mg/kg/day for 104 weeks (2 years; pivotal phase).	

Primary: Change in height SDS

End point title	Change in height SDS
End point description:	
The change from baseline (week 0) in the height standard deviation score (SDS) after 104 weeks of treatment was analysed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline height SDS as a covariate. Missing values were imputed using the last observation carried forward (LOCF) method. Results are based on the full analysis set (FAS), which included all randomised subjects.	
End point type	Primary
End point timeframe:	
From baseline to 104 weeks of treatment	

End point values	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	26		
Units: Standard deviation score				
least squares mean (standard error)	0.84 (± 0.09)	1.47 (± 0.09)		

Statistical analyses

Statistical analysis title	NN-220 0.066 mg/kg/day vs. NN-220 0.033 mg/kg/day

Statistical analysis description:

The change from baseline (week 0) in the height SDS after 104 weeks of treatment was analysed using an ANCOVA model with treatment as a fixed effect and baseline height SDS as a covariate.

Comparison groups	NN-220 0.033 mg/kg/day v NN-220 0.066 mg/kg/day
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.88

Secondary: Incidence of treatment emergent adverse events (AEs)

End point title	Incidence of treatment emergent adverse events (AEs)

End point description:

A treatment emergent AE (TEAE; for the pivotal phase) was defined as an event that had onset date on or after the date of visit 2 (week 0; start of treatment) and no later than the date of visit 12 (104 weeks; end of pivotal phase). For withdrawal subjects (if any), an AE with onset date no later than 7 days after the last day of NN-220 treatment was included. Results are based on the safety analysis set (SAS), which included all subjects receiving at least one dose of trial product (NN-220 0.033 mg/kg/day and NN-220 0.066 mg/kg/day of NN-220).

End point type	Secondary

End point timeframe:

During 104 weeks of treatment

End point values	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	26		
Units: Events	265	306		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGF-I

End point title	Change in IGF-I

End point description:

Change from baseline (in between week -4 and week 0) in IGF-I was evaluated after 104 weeks of treatment. Missing values were imputed using the LOCF method. Results are based on the SAS.

End point type	Secondary

End point timeframe:

From baseline to 104 weeks of treatment

End point values	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	26		
Units: ng/mL				
arithmetic mean (standard deviation)	90.4 (± 65.5)	159.1 (± 88.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change from baseline (in between week -4 and week 0) in HbA1c was evaluated after 104 weeks of treatment. Results are based on the SAS.

End point type	Secondary

End point timeframe:

From baseline to 104 weeks of treatment

End point values	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	26		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	0.14 (± 0.18)	0.13 (± 0.20)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 234 (208 weeks treatment period + 26 weeks extended treatment period) + 7 days (follow-up period).

Adverse event reporting additional description:

All presented AEs are TEAEs. A TEAE (for the entire trial) was defined as an event that had onset date on or after the date of visit 2 (week 0; start of treatment) and no later than 7 days after the last day of trial product administration. Results are based on the SAS, which included all subjects receiving at least one dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	NN-220 0.033 mg/kg/day

Reporting group description:

The subjects received NN-220 0.033 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase. Treatment was further extended to 234 weeks for subjects who agreed to continue treatment after completion of the extension phase.

Reporting group title	NN-220 0.066 mg/kg/day

Reporting group description:

The subjects received NN-220 0.066 mg/kg/day for 208 weeks (4 years) as per the following sequence: 104 weeks (2 years) in the pivotal phase and 104 weeks (2 years) in the extension phase. Treatment was further extended to 234 weeks for subjects who agreed to continue treatment after completion of the extension phase.

Serious adverse events	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)	10 / 26 (38.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniosynostosis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hamartoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pulmonary artery therapeutic procedure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			

subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supernumerary teeth			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Velopharyngeal incompetence			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Head banging			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Polymyositis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 25 (4.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NN-220 0.033 mg/kg/day	NN-220 0.066 mg/kg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)	26 / 26 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 25 (36.00%)	9 / 26 (34.62%)	
occurrences (all)	24	12	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 25 (12.00%)	2 / 26 (7.69%)	
occurrences (all)	4	3	
Cough			

subjects affected / exposed	6 / 25 (24.00%)	3 / 26 (11.54%)	
occurrences (all)	8	5	
Epistaxis			
subjects affected / exposed	3 / 25 (12.00%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Rhinitis allergic			
subjects affected / exposed	4 / 25 (16.00%)	4 / 26 (15.38%)	
occurrences (all)	4	4	
Rhinorrhoea			
subjects affected / exposed	2 / 25 (8.00%)	3 / 26 (11.54%)	
occurrences (all)	3	3	
Upper respiratory tract inflammation			
subjects affected / exposed	7 / 25 (28.00%)	9 / 26 (34.62%)	
occurrences (all)	35	30	
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 25 (8.00%)	3 / 26 (11.54%)	
occurrences (all)	2	8	
Arthropod sting			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
Chillblains			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Contusion			
subjects affected / exposed	1 / 25 (4.00%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Skin abrasion			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Thermal burn			

subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 25 (24.00%)	2 / 26 (7.69%)	
occurrences (all)	10	5	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	6 / 25 (24.00%)	5 / 26 (19.23%)	
occurrences (all)	11	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	
occurrences (all)	2	10	
Dental caries			
subjects affected / exposed	4 / 25 (16.00%)	4 / 26 (15.38%)	
occurrences (all)	4	11	
Diarrhoea			
subjects affected / exposed	7 / 25 (28.00%)	3 / 26 (11.54%)	
occurrences (all)	12	4	
Enteritis			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Stomatitis			
subjects affected / exposed	0 / 25 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	6	
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	4 / 25 (16.00%)	3 / 26 (11.54%)	
occurrences (all)	9	3	
Skin and subcutaneous tissue disorders			

Dermatitis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	1 / 25 (4.00%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Eczema			
subjects affected / exposed	3 / 25 (12.00%)	8 / 26 (30.77%)	
occurrences (all)	4	13	
Hyperkeratosis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
Miliaria			
subjects affected / exposed	2 / 25 (8.00%)	5 / 26 (19.23%)	
occurrences (all)	2	10	
Rash			
subjects affected / exposed	3 / 25 (12.00%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Urticaria			
subjects affected / exposed	5 / 25 (20.00%)	2 / 26 (7.69%)	
occurrences (all)	8	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 25 (16.00%)	7 / 26 (26.92%)	
occurrences (all)	5	12	
Bronchitis bacterial			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Conjunctivitis			
subjects affected / exposed	5 / 25 (20.00%)	6 / 26 (23.08%)	
occurrences (all)	6	6	
Gastroenteritis			

subjects affected / exposed	8 / 25 (32.00%)	14 / 26 (53.85%)	
occurrences (all)	14	33	
Gingivitis			
subjects affected / exposed	2 / 25 (8.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Hordeolum			
subjects affected / exposed	1 / 25 (4.00%)	3 / 26 (11.54%)	
occurrences (all)	1	5	
Impetigo			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Influenza			
subjects affected / exposed	20 / 25 (80.00%)	18 / 26 (69.23%)	
occurrences (all)	34	31	
Molluscum contagiosum			
subjects affected / exposed	3 / 25 (12.00%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	19 / 25 (76.00%)	21 / 26 (80.77%)	
occurrences (all)	115	121	
Otitis media			
subjects affected / exposed	7 / 25 (28.00%)	8 / 26 (30.77%)	
occurrences (all)	9	9	
Otitis media acute			
subjects affected / exposed	4 / 25 (16.00%)	1 / 26 (3.85%)	
occurrences (all)	6	1	
Pharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	5 / 26 (19.23%)	
occurrences (all)	3	6	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Rhinitis			
subjects affected / exposed	1 / 25 (4.00%)	4 / 26 (15.38%)	
occurrences (all)	1	7	
Sinusitis			

subjects affected / exposed	5 / 25 (20.00%)	2 / 26 (7.69%)	
occurrences (all)	14	2	
Streptococcal infection			
subjects affected / exposed	2 / 25 (8.00%)	3 / 26 (11.54%)	
occurrences (all)	3	4	
Tinea pedis			
subjects affected / exposed	0 / 25 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	9	
Upper respiratory tract infection			
subjects affected / exposed	8 / 25 (32.00%)	9 / 26 (34.62%)	
occurrences (all)	38	43	
Varicella			
subjects affected / exposed	2 / 25 (8.00%)	5 / 26 (19.23%)	
occurrences (all)	2	5	
Metabolism and nutrition disorders			
Hyperinsulinaemia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2013	Specification that randomisation occurred when subject eligibility was confirmed at visit 2 (week 0).
19 August 2013	Corrections of errors in translation of Japanese characters. Correction of error in Protocol section-Methods and assessments (visit 1 (screening visit)) on subject identification numbers.
30 October 2013	Clarification of exclusion criterion 8: Children who had received systemic administration of adrenocortical steroid during the treatment period of greater than or equal to13 weeks were excluded (regardless of the dose level of hydrocortisone). Specification that the investigator was to evaluate and classify the findings from the 12-lead ECG examination, even if corrected QT interval (QTc) greater than 450 msec was defined as "abnormal" referring to the ICH E14 guideline.
07 November 2013	Correction of errors in translation of Japanese characters. Specifications added for assessments to be performed within the visit window stated in the flow chart (oral glucose tolerance test (OGTT), electrocardiogram (ECG), transthoracic echocardiography (TTE) and bone age).
26 April 2016	Update of flowchart to clarify that the informed consent was to be obtained before the screening visit. Specification that the investigator's signature and date for evaluation were mandatory in the daily dosage note. The secondary efficacy endpoints were added to Section 4.2 (endpoints) (i.e. no changes to endpoints). Correction in the protocol Appendix C (reference listing for the dosage scale based on the subject's body weight) and Subject Information/Informed Consent form to elaborate on the NN-220 doses. Information of the doses was insufficient, and therefore explanations of the doses were added.
01 June 2017	Clarification that the extension phase could be further extended to week 234 for subjects who wanted to complete visit 20 (week 208) no later than the end of the month following marketing approval date for use of Norditropin for treatment of 'short stature due to Noonan syndrome' in Japan and who consented to receive the trial products during the period. Clarification of when the test to identify gene mutations that cause Noonan syndrome could be performed during the extension phase and that an informed consent was to be obtained before the genetic test was performed. Clarification that the trial would be classified as a post marketing clinical trial after getting the marketing approval for treatment of 'short stature due to Noonan syndrome' in Japan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported