



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 standard deviation | 6.57 ± 2.42 | 6.06 ± 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 standard deviation | -3.24 ± 0.76 | -3.25 ± 0.71 | - |
| Insulin-like growth factor I (IGF-I) Units: ng/mL arithmetic mean standard deviation | 70.2 ± 35.8 | 69.7 ± 35.2 | - |
| Glycosylated haemoglobin A1c (HbA1c) Units: Percentage of HbA1c arithmetic mean standard deviation | 5.19 ± 0.19 | 5.10 ± 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

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|-----------------|--------|
| 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 occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 26 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 6 / 25 (24.00%) 10 | 2 / 26 (7.69%) 5 | |
| Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all) | 6 / 25 (24.00%) 11 | 5 / 26 (19.23%) 5 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 2 / 26 (7.69%) 10 | |
| Dental caries subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 4 | 4 / 26 (15.38%) 11 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 25 (28.00%) 12 | 3 / 26 (11.54%) 4 | |
| Enteritis subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 1 / 26 (3.85%) 1 | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 1 / 26 (3.85%) 1 | |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 5 / 26 (19.23%) 6 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 26 (7.69%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 9 | 3 / 26 (11.54%) 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 to 13 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