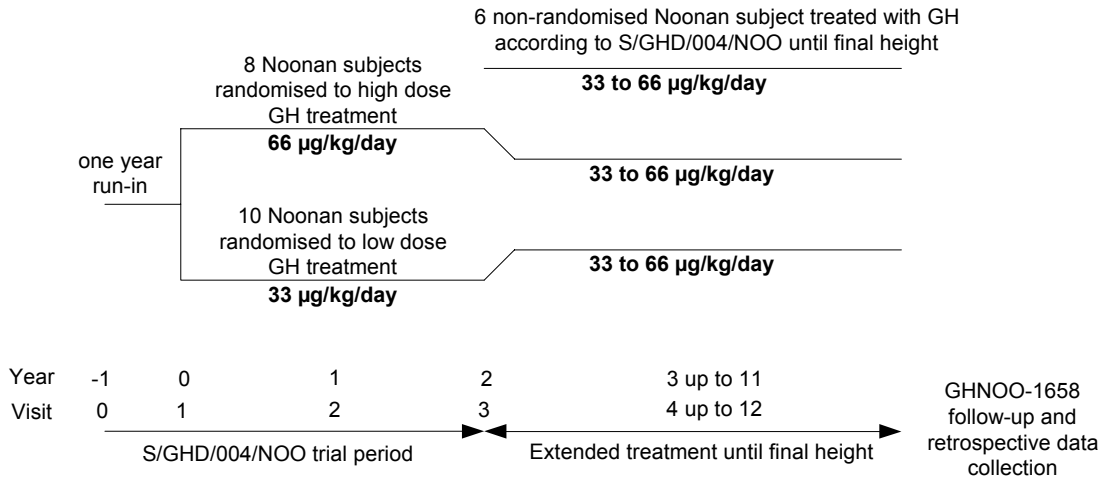
2 Synopsis

Trial Registration ID-number *NA*	***EudraCT number – 2005-000042-37***
Title of Trial Norditropin® Treatment in Subjects with Noonan Syndrome. Effects on Linear Growth and Final Height - Data Collection and Follow-up Visit	
Investigators • Professor [redacted], MD, [redacted] • [redacted], MD, [redacted] • [redacted], MD, [redacted]	
Trial Site [redacted] Sweden	
Publications • Osio D, Dahlgren J, Wikland KA, Westphal O. Improved final height with long-term growth hormone treatment in Noonan syndrome. Acta Paediatr. 2005;94:1232-7.	
Trial Period 30 August to 29 September 2005	**Development Phase** 3b
Objectives **Primary Objective:** • The primary objective of the present trial was to evaluate the effect of Norditropin® on final height in children with Noonan syndrome. **Secondary Objectives:** • Evaluate the effect of Norditropin on height velocity in children with Noonan syndrome • Evaluate the relationship between age at start of treatment and final height and height velocity, respectively • Evaluate the safety of Norditropin treatment in children with Noonan syndrome	

Methodology

The GHNOO-1658 trial was a retrospective data collection from subjects with Noonan syndrome, treated with Norditropin until final height (FH), who were originally enrolled in the S/GHD/004/NOO trial or who had followed the protocol without randomisation (see trial diagram below). The S/GHD/004/NOO trial was a prospective, open label, randomised, parallel group trial assessing the efficacy and safety of Norditropin (33 and 66 µg/kg/day) in children with Noonan syndrome. The children came from several sites in Sweden but they were all assessed at their annual visits at the same site in Gothenburg. Treatment with Norditropin continued until the attainment of final height. The subjects served as their own controls under the assumption that if untreated, she/he would follow her/his previous growth curve according to the national population and to the Noonan population, respectively.



Number of Subjects Planned and Analysed

	Randomised		Not Randomised		
	Norditropin 33 ug/kg/day	Norditropin 66 ug/kg/day	Norditropin 33 ug/kg/day	Norditropin 66 ug/kg/day	Total
Enrolled	10	8	1	5	24
Completed	10(100%)	8(100%)	1(100%)	5(100%)	24(100%)
ITT analysis set	10(100%)	8(100%)			18(75.0%)
Extended ITT analysis set	10(100%)	8(100%)	1(100%)	5(100%)	24(100%)

Diagnosis and Main Criteria for Inclusion

The following inclusion criteria pertained to the GHNOO-1658 trial:

- Informed consent before any trial related activities
- Participation in the original Norditropin study (S/GHD/004/NOO) or following the protocol for S/GHD/004/NOO without being randomised in the trial

The following inclusion criteria pertained to the S/GHD/004/NOO trial:

- Verbal informed consent obtained before any trial-related activities
- Children with Noonan Syndrome. The diagnostic criteria were: Short stature, hypertelorism, low set ears, and one of the following criteria: Ptosis, cubiti valga, testicular dysplasia or hypogonadotroph hypogonadism
- Bone age determination showing no significant acceleration (more than one year above chronological age according to Greulich and Pyle, 1972). Patients showing an accelerated bone age (> chronological age) at the first examination were re-evaluated within 6 weeks before treatment start in order to evaluate the development process
- Age at start of the treatment between 3.00 and 11.99 years
- Prepubertal according to Tanner standards: < stage 2 with testes < 4 mL (boys) and no breast development (girls)
- Height < -2 SD of the used Swedish National growth standards (Karlberg and Taranger, 1976)
- Height velocity (HV) below 1 SD during the 12 months pre-treatment period (Greulich and Pyle, 1972)
- Normal thyroid function
- Normal karyotype
- Available height data since birth
- Parent heights available

Test Product, Dose and Mode of Administration

No trial products were administered in the GHNOO-1658 trial. In the preceding S/GHD/004/NOO trial and its extension period, subjects were treated with freeze dried recombinant human GH (Norditropin®), supplied in vials containing 8 mg. The concentration of Norditropin in the pen system was 4 mg/mL. The subjects were allocated to treatment with either 33 or 66 µg/kg/day. Following Year 2, several subjects had their dosage regimen changed. Norditropin provided by the sponsor (Novo Nordisk AS) and commercially available Norditropin were used throughout the treatment period of up to 11 years.

Duration of Treatment

	Norditropin 33 ug/kg/day	Norditropin 66 ug/kg/day
No. subjects exposed	11	13
Duration of exposure (Weeks)		
N	11	13
Mean (SD)	369 (140)	405 (124)
Median	342	364
Min-Max	107-577	221-605

Reference Therapy, Dose and Mode of Administration, Batch Number

None, each subject's H-SDS at baseline served as control for the given subject.

Criteria for Evaluation – Efficacy

Primary Endpoint:

- Change in H-SDS from start of treatment to FH (ΔFH-SDS) referenced to the national population

Secondary Endpoints:

- ΔFH-SDS referenced to Noonan population
- FH-SDS referenced to national population and Noonan population, respectively
- HV
- Change in HV from start of treatment (ΔHV)
- H-SDS referenced to national population and Noonan population, respectively
- Change in H-SDS from start of treatment (ΔH-SDS) referenced to national population and Noonan population, respectively
- Sitting height
- Number and proportion of subjects with final height SDS above -2 SDS referenced to national population

Criteria for Evaluation – Safety

All safety endpoints were regarded as secondary endpoints:

- Adverse events
- HbA1c
- Fasting blood glucose and insulin
- Haematology, serum biochemistry and urinalysis laboratory variables
- Free thyroxine
- IGF-I and IGF-I SDS
- IGFBP-3 and IGFBP-3 SDS
- Physical examinations, BP and pulse
- Bone age (change in bone age/change in chronological age (ΔBA/ΔCA))
- ECG
- Echocardiography
- PqCT: assessment of bone mineral status
- DXA scan: assessment of body composition and bone mineral status
- Plasma leptin, ghrelin and adiponectin

Statistical Methods

The ITT analysis set comprised all randomised and exposed subjects. An extended version of the ITT analysis set was constructed by addition of the subjects not randomised. This analysis set was denominated extended ITT analysis set and was used for evaluation of the safety endpoints.

The height measurement at the Follow-up visit was defined as FH. The age of the subjects ranged from [redacted] to [redacted] years of age at this visit (25th percentile of the age distribution > 18 years of age for both ITT and extended ITT population).

H-SDS according to the Noonan (Ranke et al. 1988) and national (Wikland et al. 2002) growth reference, respectively, at FH was calculated as signed standard deviations from the mean of the measured heights by gender, at 18 years of age:

$$\text{H-SDS} = (\text{subject's height} - \text{mean}) / \text{SD}$$

For all H-SDS endpoints, other than FH-SDS, H-SDS was calculated as signed standard deviations from the mean of the measured heights by gender and age using the same formula as above.

Since the treatment dose was re-evaluated after two years of treatment, and as some subjects had changed to another dose, a comparison between the treatment groups was not relevant for FH. Hence, the analysis of FH primarily addresses whether FH increased by Norditropin treatment or not.

As no control group was available, the subject's H-SDS at start of treatment acted as the control for the individual subject and FH-SDS was the final outcome.

The primary analysis of the primary endpoint was performed on the FH analysis set and consisted of testing the null hypothesis of no change in H-SDS from start of treatment to FH against the alternative hypothesis that H-SDS did change (ΔFH-SDS=0), using a one-sample t-test.

Exploratory analyses were carried out to explore whether H-SDS at start of treatment, age at start of treatment and gender had any impact on ΔH-SDS using an ANCOVA model.

ΔFH-SDS referenced to the Noonan population was analysed in the same way as the primary endpoint.

The FH-SDS endpoints (referenced to the national population and the Noonan population, respectively) were analysed in the same way as the primary endpoint, with the exception that the null hypothesis of no difference between the study group and the reference population was tested (FH-SDS=0).

Demography of Trial Population at Baseline (ITT Analysis Set)

The two treatment groups were well matched. Age, bone age, height, sitting height and target height were slightly higher in the 33 µg/kg/day group than in the 66 µg/kg/day group (see Table below):

	Norditropin 33 ug/kg/day	Norditropin 66 ug/kg/day	Total
ITT analysis set	10	8	18
Sex (N)			
Female	6	4	10
Male	4	4	8
Age (years)			
Mean	8.9	7.5	8.2
SD	3.0	2.7	2.9
Median	8.3	7.1	7.8
Min-Max	[redacted]	[redacted]	[redacted]
Bone Age (years)			
Mean	6.6	5.1	5.9
SD	3.2	2.3	2.8
Median	6.8	5.0	5.0
Min-Max	3.0-11.5	2.0-9.0	2.0-11.5
Height (cm)			
Mean	116	110	113
SD	13.1	14.4	13.6
Median	114	110	113
Min-Max	96.2-137	89.0-133	89.0-137
Sitting height (cm)			
N	10	8	18
Mean	64.4	60.8	62.8
SD	14.6	6.6	11.6
Median	62.9	60.1	62.4
Min-Max	48.1-99.1	52.1-73.1	48.1-99.1
Start HSDS (Noonan)			
Mean	-0.4	-0.3	-0.4
SD	0.5	0.6	0.6
Median	-0.4	-0.2	-0.3
Min-Max	-1.2-0.2	-1.4-0.5	-1.4-0.5
Start HSDS (National)			
Mean	-3.0	-3.0	-3.0
SD	0.5	0.8	0.6
Median	-3.1	-2.9	-3.0
Min-Max	-3.7--2.1	-4.1--1.7	-4.1--1.7
Target height SDS			
Mean	-0.4	-0.7	-0.5
SD	0.8	1.1	0.9
Median	-0.2	-0.5	-0.2
Min-Max	-1.6-0.8	-2.9-0.3	-2.9-0.8

Efficacy Results (ITT Analysis Set)

Primary Endpoint:

- ΔFH-SDS (national) for the two treatment groups combined was significantly increased: A mean height gain of 1.5 SDS was estimated (95% CI:[1.1; 1.9]; p<0.001). ΔFH-SDS (national) was not significantly affected by baseline H-SDS, age or gender.

Secondary Endpoints:

- ΔFH-SDS (Noonan) for the two treatment groups combined was significantly increased: A mean height gain of 1.6 SDS was estimated (95% CI:[1.1; 2.0]; p<0.001). ΔFH-SDS (Noonan) was not significantly affected by baseline H-SDS, age or gender.
- The estimated mean FH-SDS (national) for the two treatment groups combined was -1.5 SDS (95% CI:[-2.0;-1.0]) and this estimate was significantly different from the national reference population (p<0.001). FH-SDS values within the normal range (> -2 SDS) were reached by 7 out of 10 subjects in the 33 µg/kg/day treatment group and by 5 out of 8 subjects in the 66 µg/kg/day treatment group (FH-SDS values within the normal range were reached by 4 out of the 6 non-randomised subjects). FH-SDS values within the lower limit of the subjects target height SDS (individual target height SDS minus 1.3) were reached by 6 out of 10 subjects in the 33 µg/kg/day treatment group and by 7 out of 8 subjects in the 66 µg/kg/day treatment group (FH-SDS values within the lower limit of target height were reached by 4 out of the 6 non-randomised subjects). H-SDS at baseline had a significant impact on FH-SDS (positive effect, p=0.016), while no significant interaction was seen with baseline age or gender (7 out of the 12 girls and 9 out of the 12 boys reached FH > -2 SDS).
- The estimated mean FH-SDS (Noonan) for the two treatment groups combined was 1.2 (95% CI:[0.7;1.6]) and this estimate was significantly different from the Noonan reference population (p<0.001). H-SDS at baseline had a significant impact on FH-SDS (positive effect, p=0.042), while no significant interaction effect was seen with baseline age or gender.
- The estimated mean HV at Year 1 and Year 2 was 10.1 and 7.6 cm/year with 66 µg/kg/day versus 8.55 and 6.7 cm/year with 33 µg/kg/day. Confidence intervals (95%) overlapped between the two treatment groups.
- The estimated mean ΔHV at Year 1 and Year 2 was 4.8 and 3.1 cm/year with 66 µg/kg/day versus 3.9 and 1.75 cm/year with 33 µg/kg/day. The difference in ΔHV between the two treatment groups did not reach statistical significance. ΔHV was not significantly affected by baseline HV, age or gender.
- The mean H-SDS (national) at start of treatment (Year 0) was -3.0 in both the 33 and the 66 µg/kg/day treatment group. From Year 3 onwards, the mean H-SDS (national) was above -2 for the two treatment groups combined.
- The mean H-SDS (Noonan) at Year 0 was -0.4 and -0.3 in the 33 and the 66 µg/kg/day treatment group, respectively. From Year 3 onwards, the mean H-SDS (Noonan) was > 1 for the two treatment groups combined.
- The estimated mean ΔH-SDS (national) was approximately 0.7 in both treatment groups at Year 1, while at Year 2 the estimates increased to 0.9 and 1.15 in the 33 and the 66 µg/kg/day group, respectively. The mean ΔH-SDS (national) increased each year until Year 6. A significant interaction at Year 1 and Year 2 was observed with age at baseline (negative effect, p<0.01) while no significant interactions were seen with H-SDS at baseline or with gender
- A tendency towards higher estimated mean ΔH-SDS (Noonan) values in the 66 µg/kg/day treatment group than in the 33 µg/kg/day treatment group was seen at Year 1 and Year 2 (0.89 and 1.2 cm/year with 66 µg/kg/day versus 0.75 and 1.0 cm/year with 33 µg/kg). The mean ΔH-SDS (Noonan) increased each year until Year 7. A borderline significant interaction was observed with age at baseline at Year 1 (negative effect, p=0.052) and a significant interaction was observed with H-SDS at baseline at Year 2 (positive effect, p=0.042). No significant interaction was seen with gender.
- The mean sitting height at Year 0 was 64.4 and 60.8 cm in the 33 and the 66 µg/kg/day treatment group, respectively. At Year 1 and Year 2, the estimated mean sitting height was 66.3 and 70.0 cm with 66 µg/kg/day versus 66.0 and 68.65 cm with 33 µg/kg/day. A significant interaction with sitting height at Year 1 and Year 2 was observed with age at baseline (positive effect, p<0.01). No significant interaction was seen with height at baseline or with gender.

Safety Results (Extended ITT Analysis Set)

- The number of adverse events was very low considering the long treatment period (119 events in 179 treatment years). The frequency of adverse events in the 33 µg/kg/day group (53 events in 11 subjects) was comparable to the frequency in the 66 µg/kg/day group (66 events in 13 subjects).
- Infections and infestations was the system organ class with the highest frequency of adverse events (25 events experienced by 8 (73%) of the 11 subjects in the 33 µg/kg/day group and 27 events experienced by 9 (69%) of the 13 subjects in the 66 µg/kg/day group). By preferred term, all these events were singular events, except for upper respiratory tract infection (28 events), gastroenteritis (4 events), ear infection (3 events), and influenza (3 events).
- Cardiac disorders was the system organ class with the second most adverse events reported (3 events experienced by 2 (18%) of the 11 subjects in the 33 µg/kg/day group and 6 events experienced by 5 (39%) of the 13 subjects in the 66 µg/kg/day group). By preferred term, the cardiac disorders included: pulmonary valve stenosis (3 events), ventricular hypertrophy (2 events), left ventricular failure, supraventricular extrasystole, tachycardia, and ventricular wall thickening. A medical history and concomitant illness record of a cardiac disorder was reported at baseline for 6 out of the 7 subjects experiencing one of these adverse events.
- A total of 14 serious adverse events were reported with an even distribution across the two treatment groups. A trial product relationship was considered unlikely, as evaluated by the sponsor and the investigator, for all serious adverse events except for one event of abnormal bone development (difference in bone length). Minor differences in leg bone length are common within the normal population, and abnormal skeletal development is characteristic to Noonan syndrome. However, a causal relationship with Norditropin treatment cannot be ruled out.
- IGF-I SDS values were normalised during Norditropin treatment. The initial increase in IGF-I SDS values was more pronounced in the 66 µg/kg/day treatment group than in the 33 µg/kg/day treatment group. An IGF-I SDS values above the normal reference range (>2 SDS) was only recorded for one subject at one visit.
- Mean IGFBP-3 SDS values increased from the lower normal range to the upper normal range during Norditropin treatment. No apparent difference was seen between the two treatment groups. Five (5) subjects had an IGFBP-3 SDS value above the normal reference range (>2 SDS) during the treatment period.
- HbA1c levels did not increase during the trial. Mean HbA1c levels for the two treatment groups combined ranged from 3.7% (Follow-up Visit) to 4.5% (Year 0 and 2). HbA1c levels above the normal reference range were only recorded for 2 subjects in the 33 µg/kg/day treatment group, the highest measurement being 5.9%.
- Mean fasting blood glucose levels for the two treatment groups combined ranged from 4.1 mmol/L (start of treatment) to 5.5 mmol/L (Year 10, comprising 3 subjects). Mean fasting blood glucose at the Follow-up Visit was 3.7 mmol/L. Fasting blood glucose values above the normal reference range were only recorded for one subject in the 33 µg/kg/day treatment group (6.2 mmol/L).
- The insulin levels increased during treatment. At start of treatment, the mean insulin concentration was 6.7 and 5.2 mU/L in the 33 and the 66 µg/kg/day group, respectively. During treatment the mean insulin concentration for the two treatment groups combined ranged from 10.2 mU/L (Year 7) to 15.0 mU/L (Year 3). At the Follow-up Visit, the mean insulin concentration was 7.1 and 7.4 mU/L in the 33 and the 66 µg/kg/day group, respectively.
- A shift towards higher values, mainly from low to normal, was observed in both treatment groups for haemoglobin. Leucocytes and thrombocytes values were generally missing at start of treatment and normal at Follow-up.
- A shift from high towards normal values was observed in both treatment groups for phosphate. No trends were seen in any of the other serum biochemistry parameters (alanine aminotransferase, lactate dehydrogenase, sodium, calcium and creatinine).
- No difference in levels of free thyroxine between the two treatment groups, nor any change during the treatment period, was observed.
- Bone age (BA) was enhanced compared with chronological age (CA) during Norditropin treatment. However, the BA/CA ratio was below 1 for all subjects at nearly all visits meaning that the enhanced bone age resulted in a normalisation of the subject's BA/CA ratio.
- At the Follow-up Visit, 1 out of 11 subjects in the 33 µg/kg/day treatment group had a not clinically significant abnormal ECG, while 10 subjects had a normal ECG. In the 66 µg/kg/day treatment group, 5 out of 13 subjects had a not clinically significant abnormal ECG, 6 subjects had a normal ECG, and 2 subjects had a clinically significant abnormal ECG.

- No apparent difference between the two treatment groups was observed for any of the PqCT measured bone parameters (trabecular density, total area, cortical area, polar strength strain, total density, marrow area, cortical density of the radius). PqCT measurements of muscle and bone-muscle were similar between the two treatment groups, while the mean fat-muscle ratio was higher in the 33 µg/kg/day treatment group than in the 66 µg/kg/day treatment group (47 versus 34%, respectively). The results did not raise any safety concerns. However, the results were difficult to interpret as baseline information was not available.
- DXA scan results did not raise any safety concerns. However, the results were difficult to interpret as baseline information was not available.
- All leptin measurents were in the normal range (leptin was only measured at the Follow-up Visit).

Conclusions

- The majority of the subjects with Noonan syndrome included in the GHNOO 1658 trial obtained a final height (FH) within the normal range. An FH height gain from baseline of 1.5 and 1.6 SDS was estimated according to the national and the Noonan reference, respectively. These height gains are statistically significant and clinically relevant. A height gain of 1.5 SDS (national) corresponds to a mean height gain of 9.9 cm in boys and 9.1 cm in girls at age 18 years, while a height gain of 1.6 SDS (Noonan) corresponds to a mean height gain of 11.5 cm in boys and 11.0 cm in girls at age 18 years. No difference was observed between the two treatment groups with regard to FH. However, an unbiased comparison of FH between the two treatment groups was not feasible, since the dosage regimens were changed for a substantial number of subjects during the treatment period.
- A comparison of height velocity (HV) between the two treatment groups was feasible within the two first years of treatment for the ITT analysis set. There was no statistically significant difference between the two treatment groups with regard to change in HV from start of treatment, but the results clearly indicated a greater impact on the height acceleration with 66 µg/kg/day as compared with 33 µg/kg/day (4.77 cm/year (95%CI:[3.7; 5.9]) versus 3.93 cm/year (95%CI:[3.0; 4.9]) at Year 1 and 3.13 cm/year (95%CI:[1.6;4.6]) versus 1.56 cm/year (95%:[0.3;2.8]) at Year 2).
- A statistically significant treatment interaction was seen with age at start of treatment for change in H-SDS (national). The younger the age at start of treatment the larger the change in H-SDS (estimated treatment effect: -0.11 and -0.13 at Year 1 and Year 2, respectively). However, a statistically significant treatment interaction with age at start of treatment was not seen with ΔFH-SDS (national and Noonan reference), FH-SDS (national and Noonan reference) or with ΔHV. Hence, the treatment interaction effect with age at start of treatment was not robust.
- Adverse events were few considering the exposure period (119 events in 179 treatment years). The frequency of adverse events was similar across treatment groups. All 14 serious adverse events, except two infections (borrelia and meningitis), were events characteristic of Noonan syndrome. No safety concerns were raised with regard to glucose metabolism, serum biochemistry, haematology or hormones.

The trial was conducted in accordance with ICH Good Clinical Practice and the Declaration of Helsinki