Cover Page for Protocol

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Sponsor trial ID:	GHLIQUID-4020
Official title of study:	A 52-week, Multi-centre, Randomised, Double-blind, Parallel-group, no Treatment Controlled (Open-label) Trial Investigating the Efficacy and Safety of Two Doses of NN-220 in Short Stature With Noonan Syndrome
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16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Protocol originator:
[redacted]
[redacted] Novo Nordisk Pharma Ltd.

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List of abbreviations

AE	adverse event
AGHD	adults with growth hormone deficiency
ALAT	alanine aminotransferase (SGPT: serum glutamino-pyruvic-transaminase)
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ASAT	aspartate aminotransferase (SGOT: serum glutamino-oxaloacetic-transaminase)
AUC	area under the concentration−time curve
BAP	bone-alkaline phosphatase
BUN	blood urine nitrogen
CTR	clinical trial report
DUN	dispensing unit number
ECG	electrocardiogram
FPFV	first patient first visit
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
γ-GTP (GGT)	gamma-glutamyl transpeptidase (gamma-glutamyl transferase)
GH	growth hormone
GHD	growth hormone deficiency
HbA_{1c}	glycosylated haemoglobin A_{1c}
HCM	hypertrophic cardiomyopathy
HDL	high-density lipoprotein
hGH	human growth hormone
IGF-I	insulin like growth factor I
IRB	institutional review board
IV/WRS	interactive voice/web response system
LDL	low-density lipoprotein

LPLV	last patient last visit
MESI	medical event of special interest
NA	not applicable
OGTT	oral glucose tolerance test
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per protocol
RBC	red blood cell
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
TEAE	treatment emergent adverse event
TMM	trial materials manual
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiography
WBC	white blood cell

1 Summary

Objectives:

Primary objective:

- 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.

Secondary objectives:

- To evaluate the safety profile of NN-220 from baseline to 104 weeks of treatment in short stature due to Noonan syndrome.

Endpoints:

Primary endpoint:

- Change in height SDS from baseline to 104 weeks of treatment

Key secondary endpoints:

- Incidence of treatment emergent adverse events (AEs) during 104 weeks of treatment
- Change in IGF-I from baseline to 104 weeks of treatment
- Change in HbA_{1c} from baseline to 104 weeks of treatment

Endpoints for the whole trial including the extension phase:

The period of the extension phase is 104 weeks, and the period of the whole trial will be 208 weeks [104 weeks in the pivotal phase and 104 weeks in the extension phase]. However, if the indication has not yet been approved or rejected by the PMDA at 208 weeks for the first subject, the period for the extension phase will be extended for at least 26 weeks (6 months).

The endpoints at 208 weeks for the whole trial including the extension phase are defined in the same way as for the pivotal phase.

Please refer to section 5 regarding the pivotal phase and the extension phase.

Trial design:

This is a multicentre, randomised, parallel-group, double-blind trial investigating the long-term efficacy and safety of two doses of NN-220 in short stature due to Noonan syndrome.

The subjects are Japanese children with Noonan syndrome where epiphyseal fusion has not taken place. The subjects are clinically diagnosed as Noonan syndrome according to van der Burgt score list. A total of 48 subjects (0.033 mg/kg/day group: 24, 0.066 mg/kg/day group: 24) will be enrolled

and randomised in this trial. NN-220 should be administered subcutaneously in a daily regimen in the upper arm, thigh, abdominal wall or gluteal region. The administration should not be repeated at the same injection site in a short period of time.

A placebo-controlled trial design has not been selected in this trial, because it is considered unethical to have children injecting placebo every day for a long period of time.

The subjects enrolled are offered to continue treatment with NN-220 for at least 104 weeks (pivotal phase) and to extend treatment with NN-220 until NN-220 is approved in Japan (extension phase). However, if the NN-220 developmental programme is terminated or if the health authorities reject the marketing application, this extension phase will be stopped and treatment with NN-220 will be ended.

Trial population:

Approximately 53 children with Noonan syndrome will be screened and 48 children will be randomised to allow for a minimum of 42 children to complete the trial.

Key inclusion criteria:

- Japanese children with Noonan syndrome clinically diagnosed in one of the following ways
    - Clinically diagnosed by at least two medical experts using van der Burgt score list
    - Clinically diagnosed by one medical expert using van der Burgt score list and diagnosed by result of genetic testing for Noonan syndrome.
    - Clinically diagnosed by one medical expert using van der Burgt score list and diagnosed by the same medical expert based on the results of centralised evaluation of facial change using van der Burgt score list.

- Height SDS: −2 SDS or below (according to the Japanese reference data)
- Age: boys 3 to < 11 years, girls 3 to < 10 years
- Height records must be available within the period between 40 and 64 weeks prior to Visit 1 (screening)
- Prepubertal children (definition for girls breast and pubes of Tanner stage is I, and none of menses, and for boys testicular volume < 4 mL, and pubes and penis of Tanner stage is I)

Key exclusion criteria:

- Children with known or suspected hypersensitivity against human growth hormone (hGH) or related products (including any components of the trial products).
- Children with diabetic type diagnosed with the Japanese Diabetes Society Classification.
- Children with history or presence of active malignancy.
- Children who have received GH (growth hormone) treatment.

- Children who have received systemic administration of the following medications within two years prior to Visit 1 (screening): Thyroid hormone (except replacement therapy), antithyroid hormone, androgen, oestrogen, progesterone, anabolic steroid, adrenocortical steroid (hydrocortison ≤ 20 mg/day, treatment period ≥ 13 weeks), derivative of gonadotropin releasing hormone and somatomedin C (IGF-I).

Assessments:

Efficacy assessments:

- Height

Safety assessments:

- Adverse events, clinical laboratory tests (haematology, biochemistry, lipid, endocrinology, IGF-I), blood coagulation tests, urinalysis, OGTT, HbA_{1c}, vital signs (blood pressures and pulse), ECG, transthoracic echocardiography and bone age

Other assessments:

- Pubertal sign and body weight

Trial products:

The trial products during the treatment will be as follows:

- NN-220 (somatropin [genetical recombination]) 5 mg/1.5 mL pre-filled pen for 5 mg
- NN-220 (somatropin [genetical recombination]) 10 mg/1.5 mL pre-filled pen for 5 mg

Both the trial products will be indistinguishable from one another.

Please refer to the trial materials manual (TMM) provided by Novo Nordisk for details regarding trial products.

Novo Nordisk A/S, Denmark, will provide the trial products and the sponsor (Novo Nordisk Pharma Ltd.) will supply them.

2 Flow chart

Table 2-1 Schedule of trial procedures

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
	Screening	Start of treatment										Completion of pivotal phase
	Within 4 weeks prior to Visit 2	0 w [a)]	4 w	8 w	12 w	26 w	39 w	52 w	65 w	78 w	91 w	104 w
Visit window (days)	-	0	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14
Need to be fasting	X							X				X
SUBJECT RELATED INFORMATION												
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X [b)]										
Demography	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/ Concomitant illness	X											
Randomisation		X [c)]										
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X
EFFICACY												
Height	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
IGF-I	X [i)]		X		X	X	X	X	X	X	X	X
Vital Signs [d)]	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X [i)]					X		X		X		X
Transthoracic echocardiography (TTE)	X [i)]					X		X		X		X

Visit	Visit 1 Screening	Visit 2 Start of treatment	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 Completion of pivotal phase
	Within 4 weeks prior to Visit 2	0 w [a)]	4 w	8 w	12 w	26 w	39 w	52 w	65 w	78 w	91 w	104 w
Visit window (days)	-	0	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14
Need to be fasting	X							X				X
Clinical laboratory tests [e)]	X [i)]		X		X	X	X	X	X	X	X	X
Bone metabolism marker [f)]	X [i)]					X		X		X		X
Blood coagulation test [g)]	X [i)]					X		X		X		X
Urinalysis [h)]	X [i)]		X		X	X	X	X	X	X	X	X
Oral glucose tolerance test	X [i)]							X				X
HbA1c	X [i)]					X		X		X		X
Bone age		X						X				X
OTHER ASSESSMENT												
Pubertal sign	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X	X
TRIAL PRODUCT												
Dose adjustment		X	X	X	X	X	X	X	X	X	X	X
Subject compliance			X	X	X	X	X	X	X	X	X	X
Hand out/ return of the daily dosage note		X	X	X	X	X	X	X	X	X	X	X
Dispense trial product/ Drug accountability		X	X	X	X	X	X	X	X	X	X	X
REMINDER												
Interactive voice/web response system(IV/WRS) call	X	X	X	X	X	X	X	X	X	X	X	X
End of Trial Form												

Visit	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20 [j]
	Extension phase							End of Treatment
	117 w	130 w	143 w	156 w	169 w	182 w	195 w	208 w
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14
Need to be fasting				X				X
SUBJECT RELATED INFORMATION								
Informed Consent								
Inclusion/Exclusion Criteria								
Demography								
Concomitant medication	X	X	X	X	X	X	X	X
Medical history/ Concomitant illness								
Randomisation								
Withdrawal criteria	X	X	X	X	X	X	X	
EFFICACY								
Height	X	X	X	X	X	X	X	X
SAFETY								
Adverse Events	X	X	X	X	X	X	X	X
IGF-I	X	X	X	X	X	X	X	X
Vital Signs [d]	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X		X		X		X
Transthoracic echocardiography (TTE)		X		X		X		X

Visit	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20 [j]
	Extension phase							End of Treatment
	117 w	130 w	143 w	156 w	169 w	182 w	195 w	208 w
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14
Need to be fasting				X				X
Clinical laboratory tests [e]	X	X	X	X	X	X	X	X
Bone metabolism marker [f]		X		X		X		X
Blood coagulation test [g]		X		X		X		X
Urinalysis [h]	X	X	X	X	X	X	X	X
Oral glucose tolerance test (OGTT)				X				X
$HbA1_C$		X		X		X		X
Bone age				X				X
OTHER ASSESSMENT								
Pubertal sign	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X
TRIAL PRODUCT								
Dose adjustment	X	X	X	X	X	X	X	
Subject compliance	X	X	X	X	X	X	X	X
Hand out/ return of the daily dosage note	X	X	X	X	X	X	X	X
Dispense trial product/ Drug accountability	X	X	X	X	X	X	X	X
REMINDER								
Interactive voice/web response system(IV/WRS) call	X	X	X	X	X	X	X	X
End of Trial Form								X

[a] The date when all assessments for Visit 2 are completed is set as "0 w" and the time of visit from Visit 3 onward will be counted from the date.

[b] Reconfirmation of inclusion/exclusion criteria will be conducted before randomisation.

[c] All subjects will be allocated to one of the two groups (0.033 mg/kg/day group or 0.066 mg/kg/day group) before procedures at Visit 2.

[d] Vital signs are blood pressure (diastolic and systolic) and pulse, both sitting after 5 minutes of rest.

[e] Clinical laboratory tests are haematology, biochemistry, lipid and endocrinology.

- Haematology: red blood cell (RBC), white blood cell (WBC), haemoglobin, haematocrit, platelets, and leukocytes fraction (neutrophil leukocyte, lymphocyte, monocyte, eosinophil leukocyte, and basophilic leukocyte)
- Biochemistry: aspartate aminotransferase/serum glutamino-oxaloacetic-transaminase (ASAT/SGOT), alanine aminotransferase/serum glutamino-pyruvic-transaminase (ALAT/SGPT), gamma-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), total protein, blood urine nitrogen (BUN), creatinine, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), and phosphorus (P)
- Lipid: total cholesterol, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol
- Endocrinology: thyroid-stimulating hormone (TSH), free thyroxine (FT_4), and free triiodothyronine (FT_3)

[f] Bone metabolism markers are bone-alkaline phosphatase (BAP) and osteocalcin.

[g] Blood coagulation test is the measurements of prothrombin time and partial thromboplastin time.

[h] Urinalysis is the measurements of protein, glucose, and occult blood.

[i] These data will be treated as baseline data.

[j] In case that a subject is withdrawn from the trial, all assessments for visit 20 should be taken as soon as possible.

3 Background information and rationale for the trial

3.1 Background information

3.1.1 Swedish pivotal trials

The indication of NN-220 for "short stature due to Noonan syndrome" targeted in Japan has been already approved in the United States, Switzerland, South Korea, the Philippines and Israel. The submission in these countries was based on the Swedish pivotal trials (GHNOO-1658 including a 2-year, prospective, randomised, parallel-dose group trial period [S/GHD/004/NOO]; Table 3-1).

Table 3-1 Clinical data package of Noonan syndrome in overseas submission

Trial ID	Trial design	Duration	Treatment regimen	No. of subjects	Endpoints
S/GHD/004/NOO	Randomised, prospective, open-label, parallel-group trial	2 years	0.033 mg/kg/day 0.066 mg/kg/day	21 (18 were enrolled in GHNOO-1658)	Height velocity
GHNOO-1658	Retrospective data collection and 'follow-up' visit	until final height (up to 11 years)	0.033 mg/kg/day 0.066 mg/kg/day	24 (18 + 6*)	Final height Safety

*: 6 subjects followed the S/GHD/004/NOO protocol without being randomised in the trial – and were included for supportive purposes.

The results of the S/GHD/004/NOO trial showed NN-220 to be efficacious in the treatment of short stature in children with Noonan syndrome. Therefore, Novo Nordisk decided to extend treatment with NN-220 until the attainment of final height continuously after the completion of this trial. In 2005, Novo Nordisk collected retrospective data from the children, who were originally enrolled in the S/GHD/004/NOO trial or who had followed the protocol without randomisation, and evaluated the efficacy and safety of NN-220 on final height (GHNOO-1658).

A final height gain from baseline of 1.5 and 1.6 SDS was estimated according to the Swedish reference and the Noonan reference, respectively. These height gains are statistically significant and clinically relevant. A height gain of 1.5 SDS (Swedish) 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. A final height SDS (Swedish) within the normal range (over –2 SDS) was reached by 12 out of 18 subjects in the two treatment groups. No difference was observed between the two treatment groups with regard to final height. The reason for no difference between the treatment groups might be that the Swedish trial was only a dose-response trial in the first two years. From the third year and onwards the

patients were treated in accordance to the response, so good responders got the low dose and poor responders got 0.066 mg/kg/day.

Adverse events were few considering the exposure period (119 events in 179 treatment years). The frequency of adverse events was similar across treatment groups. The most frequent adverse events were the common infections, including upper respiratory infection (28 events), gastroenteritis (4 events), ear infection (3 events), and influenza (3 events). The second most frequent adverse events were cardiac disorders (9 events experienced by 7 subjects in the two treatment groups; more than 2 events included: pulmonary valve stenosis [3 events], ventricular hypertrophy [2 events]). Congenital heart disease is an inherent component of Noonan syndrome, and there was no evidence of NN-220 induced ventricular hypertrophy or exacerbation of pre-existing ventricular hypertrophy (as judged by echocardiography) during the study.

A total of 14 serious adverse events were reported. The relationship between the serious adverse events and NN-220 was considered unlikely except for one event of abnormal bone development (difference in bone length). No safety concerns were raised with regard to glucose metabolism, serum biochemistry, haematology or hormones.

The results of these clinical trials have shown the growth promoting effect and safety of NN-220 in patients with Noonan syndrome, and demonstrated that NN-220 is a useful product for the treatment of "Short stature due to Noonan syndrome not related to epiphyseal closing".

3.1.2 Noonan syndrome

Noonan syndrome, first described in 1963, is a dimorphic syndrome which may occur sporadically, with autosomal dominant inheritance and a predominance of maternal transmission, or in an autosomal recessive form[1,2]. The frequency is unknown, but may be in the order of 1/1000 to 1/2500 live births; males and females are affected equally and their karyotypes are normal[3].

The cardinal features of Noonan syndrome are short stature, congenital heart defects (pulmonary stenosis, 62%; or hypertrophic cardiomyopathy, 20%), a broad or webbed neck, chest deformity (pectus carinatum or pectus excavatum of the thorax), scoliosis, coagulation defects, cryptorchidism, mild mental retardation, hearing impairment and characteristic faces with hypertelorism, downward slanting palpebral fissures with high arched eyebrows, ptosis, epicanthic folds, depressed nasal root with a wide nasal base, prominent low-set ears, a low posterior hairline, micrognathia and narrow maxilla[3,4].

Short stature affects 83% of patients; weight and length at birth are within the reference range, but during childhood affected children show growth retardation involving height, weight and bone development[3]. Their heights and weights are usually below –2 SDS for the population[5]. Specific growth charts have therefore been developed for Noonan syndrome[5,6].

Many reports about GH therapy for patients with Noonan syndrome have been published[7,8,9,10,11,12,13]. A number of studies have reported improved growth velocity in response to GH therapy, with no significant adverse effects. Recently, there has been an increasing amount of data concerning adult height in patients with Noonan syndrome treated with GH. Results of long-term studies of GH use in patients with Noonan syndrome with short stature demonstrate a significant improvement in adult height. The response in Noonan syndrome was similar to the response in Turner syndrome. The duration of GH treatment and GH dosage may be important contributors to height optimization.

3.1.3 NN-220

NN-220 is a liquid formulation of hGH developed by Novo Nordisk A/S. The hGH (somatropin [genetical recombination]) is synthesised by genetic recombinant technology.

NN-220 is now used in over 90 countries for the indications of "growth failure due to growth hormone deficiency (GHD)", "growth failure in girls due to gonadal dysgenesis (Turner syndrome)", "growth retardation in prepubertal children due to chronic renal disease", "growth disturbance in short children born small-for-gestational age (SGA)" and "adults with growth hormone deficiency (AGHD)".

In Japan, NN-220 was first approved for the indication of "short stature due to GHD" in 1988, followed by approval of Turner syndrome in 1992, achondroplasia in 1997, short children born SGA in 2009 and AGHD in 2009.

NN-220 was approved for Noonan syndrome in the United States in May 2007, in Switzerland, South Korea and the Philippines in 2008, and in Israel in 2011. The international guideline on Noonan syndrome "Noonan Syndrome: Clinical Features, Diagnosis, and Management Guidelines"[14] was published in September 2010 in Pediatrics. The guideline for Noonan syndrome in Japan is under preparation by the two societies. In addition, the Japanese Noonan syndrome growth standards are also being prepared by experts.

The number of patients with Noonan syndrome registered* as treated with NN-220 is 167 in the United States (as of 03-Aug-2012), 91 in European Union countries (as of 02-Jul-2012) and 13 in the other countries (as of 02-Jul-2012). No unexpected safety concerns have been identified.

* This is the number of patients registered in the NordiNet and NovoNet registries. The actual number of patients with Noonan syndrome treated with NN-220 might be higher than the sum (271) of the above numbers since not all patients on NN-220 are included in the registries.

3.2 Rationale for the trial

If adult height falls below −2 SDS (i.e., the lower limit for normal height), it would not only pose a physical problem, but it may lead to various psychological and social issues. Therefore, using the product to improve short stature and bring the adult height closer to normal would be significant. The aim of the product in the treatment for short stature is not merely to simply improve short stature, but treating short stature is expected to improve psychological and social problems at the same time.

NN-220 has been used worldwide since the latter half of 1980s, and the data accumulated in clinical trials have not indicated that there are any significant safety issues.

The results of the Swedish clinical trials have shown the growth promoting effect and safety of NN-220 in patients with Noonan syndrome, and demonstrated that NN-220 is a useful product for the treatment of "Short stature due to Noonan syndrome not related to epiphyseal closing".

This trial will be conducted in accordance with the Declaration of Helsinki[15], the Ministry of Health and Welfare (MHW) Ordinance on good clinical practice (GCP)[16] and the applicable relevant regulations.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

- 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.

4.1.2 Secondary objectives

- To evaluate the safety profile of NN-220 from baseline to 104 weeks of treatment in short stature due to Noonan syndrome.

4.2 Endpoints

4.2.1 Primary endpoint

- Change in height SDS from baseline to 104 weeks of treatment

4.2.2 Secondary safety endpoints

- Incidence of treatment emergent AEs during 104 weeks of treatment
- Change in IGF-I from baseline to 104 weeks of treatment
- Change in HbA_{1c} from baseline to 104 weeks of treatment
- Change in clinical laboratory tests from baseline during 104 weeks of treatment
- Change in glucose tolerance (AUC of glucose and AUC of insulin) based on the OGTT from baseline to 104 weeks of treatment
- Change in bone age and bone age/chronological age from baseline to 104 weeks of treatment, and (yearly [change in bone age / change in chronological age]) (yearly [Δ bone age/Δ chronological age])
- Change in vital signs (blood pressures and pulse) from baseline during 104 weeks of treatment
- Change in urinalysis from baseline during 104 weeks of treatment
- Change in blood coagulation test from baseline during 104 weeks of treatment
- Change in ECG from baseline during 104 weeks of treatment

4.2.3 Endpoints for the whole trial including the extension phase

The period of the extension phase is 104 weeks, and the period of the whole trial will be 208 weeks [104 weeks in the pivotal phase and 104 weeks in the extension phase]. However, if the indication has not yet been approved or rejected by the PMDA at 208 weeks for the first subject, the period for the extension phase will be extended for at least 26 weeks (6 months).

The endpoints at 208 weeks for the whole trial including the extension phase are defined in the same way as for the pivotal phase.

Please refer to section 5 regarding the pivotal phase and the extension phase.

5 Trial design

The trial design and schematic overview of this trial are shown in Table 5-1 and Figure 5-1, respectively.

Table 5-1 Trial design of this trial

Type of trial	Trial design	Treatment period	Dosage	Endpoints
Phase 3	Double-blind	104 weeks (pivotal phase), from 104 weeks to 208 weeks (extension phase)	0.033 mg/kg/day 0.066 mg/kg/day	Height SDS, Safety

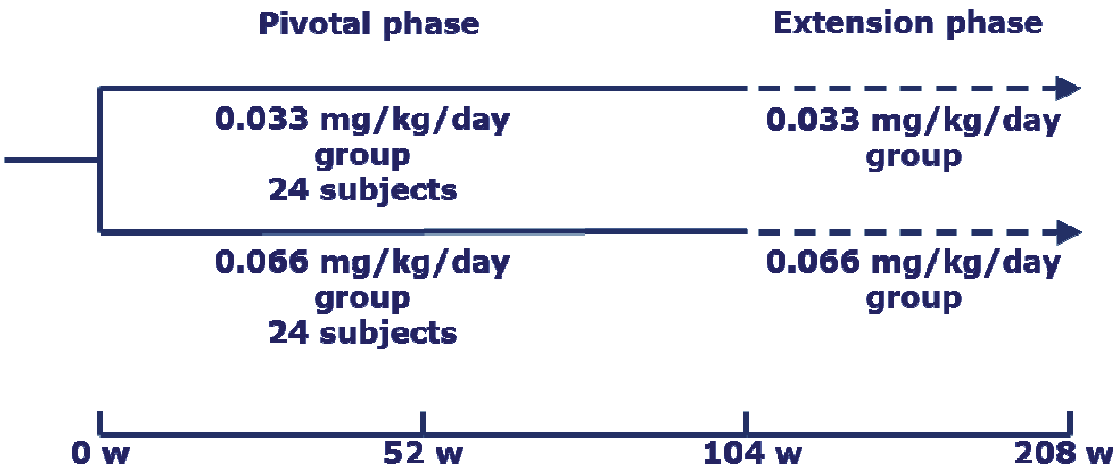

Figure 5-1 Schematic overview of this trial

5.1 Type of trial

This is a multicentre, randomised, parallel-group double-blind trial investigating the long-term efficacy and safety of two doses of NN-220 in short stature due to Noonan syndrome. The pivotal phase is double-blinded as well as the extension phase.

The subjects are Japanese children with Noonan syndrome where epiphyseal fusion has not taken place. The subjects are clinically diagnosed as Noonan syndrome according to van der Burgt score

list (Table 6-1). A total of 48 subjects (0.033 mg/kg/day group: 24, 0.066 mg/kg/day group: 24) will be enrolled and randomised in this trial.

The children enrolled are offered to continue treatment with NN-220 for at least 104 weeks (pivotal phase) and to extend treatment with NN-220 until NN-220 is approved for Noonan syndrome in Japan (extension phase). However, if the NN-220 development programme is terminated or if the health authorities reject the marketing application, this extension phase will be stopped and treatment with NN-220 will be ended.

5.2 Rationale for trial design

The trial uses a parallel design to compare the two different dose levels of NN-220.

The trial is double-blind for the two groups treated with NN-220 to eliminate the risk of the investigator (efficacy and safety endpoints) and subject (reporting of adverse events) bias.

A placebo-controlled trial design has not been selected in this trial, because it is considered unethical to have children injecting placebo every day for a long period of time.

A good response to the treatment with GH in 104 weeks is one of the predictors of further clinical response by the treatment. The trial design including the treatment period of 104 weeks in this trial was accepted by the Pharmaceuticals and Medical Devices Agency (PMDA).

5.3 Treatment of subjects

The pivotal phase of the treatment period is 104 weeks. The extension phase is from 104 weeks to 208 weeks. The subjects will be randomised to one of the two groups (0.033 mg/kg/day group and 0.066 mg/kg/day group).

The trial includes two parallel treatment arms (0.033 mg/kg/day group and 0.066 mg/kg/day group). In the 0.033 mg/kg/day group and the 0.066 mg/kg/day group, the administration of trial products will be started subcutaneously in a daily regimen on the day of Visit 2.

The subjects in the 0.033 mg/kg/day group and in the 0.066 mg/kg/day group will be supplied NN-220 5 mg/1.5 mL pre-filled pen for 5mg and NN-220 10 mg/1.5 mL pre-filled pen for 5mg, respectively.

The dosage scale on pre-filled pen will be selected based on the subject's body weight at each visit. As a reference, listing for the dosage scale is shown in Appendix C. The subjects in the 0.033 mg/kg/day group and in the 0.066 mg/kg/day group will be administered 0.033 mg/kg/day and 0.066 mg/kg/day, respectively, in the same dosage scale to keep the blindness.

NN-220 should be administered subcutaneously in the upper arm, thigh, abdominal wall or gluteal region in an orderly manner. The administration should not be repeated at the same injection site in a short period of time.

5.4 Rationale for treatment

The route of administration and the dosage schedule for subjects randomised to NN-220 at just different doses proposed in this trial are in accordance with the Japanese labelling for other approved indications.

Many reports about GH therapy for patients with Noonan syndrome have been published[7,8,9,10,11,12,13]. A number of studies have reported improved growth velocity in response to GH therapy, with no significant adverse effects. Recently, there has been an increasing amount of data concerning adult height in patients with Noonan syndrome treated with GH.

Japanese and overseas clinical trials investigating the effect of NN-220 on short stature in patients with Noonan syndrome are two trials of the phase 3 trial in Sweden (GHNOO-1658) and the phase 2 trial in Japan (Table 5-2).

Table 5-2 Japanese and overseas clinical trials investigating the effect of NN-220 on short stature in patients with Noonan syndrome

Reference	Patients, N (sex)	Baseline age (years)	Baseline SDS*	Dose	Therapy duration (years)	Adult height SDS*	Height gain
Clinical trials of NN-220							
Osio, 2005 (Sweden)[7]	18 (7:M) (11:F)	8.6 (M) 7.7 (F)	–2.9 (–0.3)	0.23 mg/kg/week (N=10), 0.47 mg/kg/week (N=15) × 2 years then dose titration Estimated mean 0.35 mg/kg/week	7.5	–1.2	13 cm (M) 9.8 cm (F)
Ogawa, 2004 (Japan)[8]	11 (7:M) (4:F)	7.5	–2.8	0.175 mg/kg/week	2	NA	NA

Results are mean values unless specified otherwise.

*: Height standard deviation score (SDS) reported according to population standards and/or (Noonan syndrome standards).

In the Japanese phase 2 trial, the change in height velocity at the investigated dose level of 0.175 mg/kg/week (0.025 mg/kg/day) was 2.2 cm/year. This is smaller compared to the change in height velocity of the approved short stature due to growth hormone deficiency at 5.2 cm/year. In addition, the result of Turner's syndrome using the previously approved dose of 0.175 mg/kg/week (0.025 mg/kg/day) was similar at 2.3 cm/year, but smaller when compared to 3.5 cm/year using the currently approved dose of 0.35 mg/kg/week (0.050 mg/kg/day). This change in height velocity of 3.5 cm/year was the same as that of short stature patients with Noonan syndrome when given a dose

of 0.23 mg/kg/week (0.033 mg/kg/day) in a trial conducted in Sweden. Furthermore, the change in height velocity of 5.4 cm/year for short stature due to Noonan syndrome at a dose of 0.47 mg/kg/week (0.066 mg/kg/day) in Sweden was similar to that of short stature due to growth hormone deficiency at 5.2 cm/year.

Based on the above, if the same dose as the Japanese phase 2 trial is used, it would not be considered high enough to improve short stature due to Noonan syndrome, and in order to achieve the same level of efficacy in the treatment of short stature in children with Turner's syndrome at least 0.23 mg/kg/week (0.033 mg/kg/day) would be necessary, and furthermore in order to achieve the same level of efficacy as short stature due to growth hormone deficiency at least 0.47 mg/kg/week (0.066 mg/kg/day) would be necessary.

From the above reasons, the treatment method and doses for subjects in this trial have been chosen.

6 Trial population

6.1 Number of subjects

Country planned to participate: Japan

Number of sites planned to participate: 34

Number of subjects planned to be screened (i.e., documented informed consent): 53

Number of subjects planned to be randomised: 48

0.033 mg/kg/day group: 24
0.066 mg/kg/day group: 24

Number of subjects expected to complete the trial: 42

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes" at Visit 1 (screening):

1. Informed consent obtained from each subject's parent or the subject's legally acceptable representative before any trial-related activities. Trial-related activities are any procedures that would not have been performed during normal management of the subject.
2. Japanese children with Noonan syndrome clinically diagnosed in one of the following ways
   - Clinically diagnosed by at least two medical experts using van der Burgt score list (Table 6-1)
   - Clinically diagnosed by one medical expert using van der Burgt score list and diagnosed by result of genetic testing for Noonan syndrome.
   - Clinically diagnosed by one medical expert using van der Burgt score list and diagnosed by the same medical expert based on the results of centralised evaluation of facial change using van der Burgt score list.
3. Height SDS: –2 SDS or below (according to the Japanese reference data[17])
4. Age: boys 3 to < 11 years, girls 3 to < 10 years
5. Height records must be available within the period between 40 and 64 weeks prior to Visit 1 (screening)
6. Prepubertal children (definition for girls breast and pubes of Tanner stage[18] is I, and none of menses, and for boys testicular volume < 4 mL, and pubes and penis of Tanner stage is I)

Rationale for the inclusion criteria:

- Criterion 1 is applied through an ethical consideration, in accordance with the GCPs[16].
- Criterion 2 is set in accordance with Noonan Syndrome: Clinical Features, Diagnosis, and Management Guidelines[14] (hereinafter referred to as the "Guideline[14]").

- Criterion 3; According to the consensus guidelines concerning the diagnosis and treatment of child- and adolescence-stage short stature due to GH hyposecretion, short stature is defined as height SDS for chronological age at –2 SDS or below. Since this trial is conducted with the aim of improving short stature, it is necessary to include only children with short stature.
- Criterion 4; Children beyond infancy and 3 years age or older are eligible as subjects. Therefore, the minimum age was set at 3 years old. In addition, it is difficult to judge the efficacy of NN-220 administration in children who have developed secondary sexual characteristics. Puberty is typically delayed for both boys and girls with Noonan syndrome. The mean age of puberty onset is 13.5 to 14.5 years in boys and 13 to 14 years in girls[13]. The upper limit of the subjects is set less than 11 years for boys and less than 10 years for girls taking the treatment period into consideration.
- Criterion 5 is applied because this data is essential to compare the growth promoting effect of NN-220 after administration with that of pre-treatment.
- Criterion 6 is set because it is difficult to evaluate the efficacy of NN-220 in children who have developed secondary sexual characteristics.

Table 6-1 Diagnostic criteria for Noonan syndrome* (van der Burgt score list)

Feature	A = major	B = minor
1 Facial	• Typical face[1)]	• Suggestive face
2 Cardiac	• Pulmonary valve stenosis and / or typical ECG[2)]	• Other defect
3 Height	• < 3rd centile (–1.88 SDS)	• < 10th centile (–1.28 SDS)
4 Chest wall	• Pectus carinatus / excavatum	• Broad thorax
5 Family history	• First degree relative definite Noonan syndrome	• First degree relative suggests Noonan syndrome
6 Other	• All 3 (males): mental retardation, cryptorchidism, lymphatic dysplasia	• One of mental retardation, cryptorchidism, lymphatic dysplasia

* Definite Noonan syndrome: 1A plus one of 2A-6A or two of 2B-6B; 1B plus two of 2A-6A or three of 2B-6B.

[1)] The typical facial anomalies consist of a broad forehead, hypertelorism, ptosis, down-slanting palpebral fissures, micrognathia, apparently lowset, posteriorly angulated ears with a thick helix and a broad short neck.

[2)] The typical ECG is characterized by an abnormal R/S ratio over the left precordial leads, wide QRS complexes, left-axis deviation and a giant Q wave.

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no" at Visit 1 (screening):

1. Children with known or suspected hypersensitivity against hGH or related products (including any component of the trial products).
2. Children with severe cardiac disease, renal disease or hepatic disease (as judged by the investigator).
3. Children with diabetic type diagnosed with the Japanese Diabetes Society Classification[19].
4. Children with history or presence of active malignancy.
5. Children who have received GH treatment.
6. Previous participation in this trial. Participation is defined as screened.
7. The receipt of any investigational medicinal product within 12 weeks prior to screening.
8. Children who have received systemic administration of the following medications within two years prior to screening (Visit 1): Thyroid hormone (except replacement therapy), antithyroid hormone, androgen, oestrogen, progesterone, anabolic steroid, adrenocortical steroid (hydrocortison ≤ 20 mg/day, treatment period ≥ 13 weeks), derivative of gonadotropin releasing hormone and somatomedin C (IGF-I).
9. Children with any condition that the investigator would judge as not appropriate for the trial.

Rationale for the exclusion criteria:

- Criteria 1, 2 and 9 are set for safety reasons.
- Criterion 3 is set because children with diabetic type are excluded because GH has a blood glucose increasing effect and may worsen the blood glucose control therefore diabetes is a contraindication in GH treated patients in Japan.
- Criterion 4 is set because GH is contraindicated for patients with malignant tumours due to the cellular proliferating effects.
- Criterion 5 is set to eliminate the influence of any previous treatment for objective evaluation.
- Criteria 6 and 7 are set to investigate the efficacy and safety of NN-220 objectively.
- Criterion 8 is applied because they may affect height growth of children within one year prior to this trial.

6.4 Withdrawal criteria

The subject may be withdrawn at any time by the subject, the subject's parent or the subject's legally acceptable representative.

The subject may be withdrawn from the trial at the discretion of the investigator or the sponsor, if judged non-compliant with trial procedures or due to safety concern.

A subject must be withdrawn if the following applies:

1. A subject or subject's parent or legally acceptable representative wishes to discontinue treatment.
2. The transfer of a subject to another hospital or moving makes it difficult to continue the trial.
3. A subject is found violation of inclusion or exclusion criteria.
4. A subject proves not to be Noonan syndrome.
5. The occurrence of an adverse event or any other event makes it difficult to continue the trial in the judgement of the investigator.
6. A subject is considered to be withdrawn by the investigator for any other reason.

Further, a subject must be withdrawn if the following applies:

7. The receipt of any prohibited concomitant drugs except for a temporary use for emergent situations (see section 8.3 for prohibited concomitant medication).

In case of withdrawal the premature discontinuation procedures described in sections 8.1.4.3 and 18.3 should be complied with.

Rationale for each withdrawal criterion

- Criterion 1 is applied through an ethical consideration, in accordance with the GCPs.
- Criterion 2 is set to withdraw inappropriate for continuation of the trial
- Criteria 3, 4, 5 and 6 are set for safety concerns and ethical consideration.
- Criterion 7 is selected to investigate the efficacy and safety of NN-220 objectively.

6.5 Subject replacement

A total of 48 subjects are planned to be randomised. No replacement of withdrawn patients will be made in this trial.

6.6 Rationale for trial population

The overseas clinical trial in short stature due to Noonan syndrome was conducted using NN-220 (0.033 mg/kg/day and 0.066 mg/kg/day) (trial ID: GHNOO-1658). The results have shown the growth promoting effect and safety of NN-220 in patients with Noonan syndrome, and demonstrated that NN-220 is a useful product for the treatment of "short stature due to Noonan syndrome not related to epiphyseal closing". Therefore, the patients with Noonan syndrome have been chosen as the trial population in this trial to support marketing authorisation for NN-220 in this population.

The subjects enrolled in this trial are defined as Japanese children with Noonan syndrome who have been clinically diagnosed on the basis of the "Guidelines[14]", published by the American Academy of Pediatrics.

The upper limit of the subject's age is set less than 11 years for boys and less than 10 years for girls, taking the treatment period into consideration because it is difficult to judge the efficacy of NN-220 administration in children who have developed secondary sexual characteristics.

7 Trial schedule

Planned duration of recruitment period (first patient first visit [FPFV] – last patient first visit [LPFV]): 1 year and 4 months

All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the interactive voice/web response system (IV/WRS) will be closed for further screening.

Planned date for FPFV: 30-August-2013

Planned date for LPFV: 26-December-2014

Planned date for last patient last visit (LPLV): 30-June-2018

Information of the trial will be disclosed at www.clinicaltrials.gov and www.novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[20], the Food and Drug Administration Amendment Act (FDAAA)[21]and other relevant recommendations or regulations. In Japan, the trial data will be registered at Clinical Trials Information/JapicCTI (www.clinicaltrials.jp). If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

Procedures for the scheduled visits are described in the section below and in the flow chart (section 2).

It must be stated in the medical record that the subject is participating in the current trial. The subjects enrolled in the trial will be provided with a subject participation card at Visit 2 stating that the subject is participating in the trial and whom to contact (site address, investigator's name and telephone number). The subjects must keep the card with them at all times.

The investigator must keep a subject screening log and a subject enrolment log. The subject screening log and a subject enrolment log may be combined in one list and may be generated from IV/WRS.

8.1.1 Visit schedule

For visit numbers, timing of visits and visit windows during the trial period, please refer to the flow chart (section 2).

8.1.2 Informed consent

Before screening takes place, the subject's parent or the subject's legally acceptable representative will be provided with written information about the trial and the procedures involved, in accordance with Japanese requirements. The subject's parent or the subject's legally acceptable representative will be fully informed, orally and in writing about their responsibilities and rights while participating in the trial, as well as about possible advantages/disadvantages of being dosed with NN-220 and their or their child's rights while participating in the trial. The subject's parent or the subject's legally acceptable representative will have the opportunity to ask questions and have ample time to consider participation. If the subject has the ability to understand (as per the investigator's discretion), an assent form should be obtained from that subject. If the subject's parent or the subject's legally acceptable representative wishes to make her/his child to participate in the trial, they (and the subject in case the subject has the ability to understand) will have to sign, date and record the clock time (if consent and trial procedures except for OGTT occur on the same day the clock time must be recorded. There is no need to record the time point of signatures if the informed consent form is updated during the trial) on the informed consent form for the trial before any trial-related procedures. The informed consent process may take place prior to any trial activities, i.e., procedures that would not have been performed during normal management.

All subject's parent or subject's legally acceptable representative (and the subject in case the subject has the ability to understand) must be provided with a copy of their own signed and dated informed consent form(s).

If the investigator is not the subject's primary physician (the physician, the subject normally attends) the investigator must notify the primary physician about the subject's trial participation. If required, permission should be given by the subject.

The investigator will instruct subjects to attend Visit 1 fasting, having consumed only water from 9 pm in the previous evening for the OGTT after obtaining informed consent.

8.1.3 Visit 1 (screening visit)

It will be confirmed that the subjects must attend Visit 1 fasting, having consumed only water from 9 pm in the previous evening for the OGTT.

At screening, the subjects will be assigned a unique subject identification (ID) which will remain the same throughout the trial. The subject ID will consist of 4 digits (the first 2 digits indicating the site number and the last 2 digits indicating the subject number).

A screening session should be performed in the IV/WRS in order to register the subject in the system.

The following will be performed and/or recorded in the case report form (CRF) in addition to what is described in the flowchart and in the assessment sections (sections 8.2, 8.3 8.4, 8.5 and 8.6).

- Signed informed consent(s)
  - Date
  - Time (if consent and trial procedures occur on the same day the clock time must be recorded)
- Inclusion and exclusion criteria (sections 6.2 and 6.3)
- Demography:
  - Date of birth
  - Sex
- Diagnosis of Noonan syndrome according to van der Burgt score list (Table 6-1), the date of diagnosis and the name of investigators who made diagnosis

- Genotype of Noonan syndrome (In case genetic testing for Noonan syndrome had been performed at the time of diagnosis before Visit 1 and genotype of Noonan syndrome is revealed.)
  - PTPN11
  - KRAS
  - SOS1
  - RAF1
  - BRAF
  - SHOC2
  - NRAS
- Height data within the period between 40 to 64 weeks prior to Visit 1 and the date of measurement
- Medical history of other diseases related to the trial as judged by the investigator

Screening failures

If the subject is ineligible to participate in the trial the subject will be considered a screening failure. Consequently, a screening failure session must be performed using the IV/WRS, a screening failure form must be completed with the reason for not continuing in the trial.

Adverse events from screening failures must be transcribed by the investigator into the case report form (CRF). Follow-up of adverse events should be carried out according to section 12.

When trial-related procedures have been finalised for screening failures, no more AEs should be recorded in the CRF.

8.1.4 Visit 2 to the visit before Visit 20

Randomisation should be performed after subject eligibility is confirmed and before procedures at Visit 2.

Visit 2 will take place within 4 weeks after Visit 1.

Please see the flow chart (section 2) and assessment sections (sections 8.2, 8.3, 8.4, 8.5 and 8.6).

During each visit the subject must be asked about AEs and technical complaints (TCs). This must be documented in the subject's medical record.

In case OGTT is scheduled, the subjects must attend fasting, having consumed only water from 9 pm in the previous evening.

For randomisation and following dispensing of trial products, a randomisation session should be performed in the IV/WRS.

Following randomisation, trial products will be dispensed at each visit. Trial product(s) must not be dispensed to any person not included in the trial. For dispensing of trial products a dispensing session should be performed in the IV/WRS.

The investigator must document that direction for use is given to each subject orally and/or in writing at each dispensing visit. Trial product must not be used if it does not appear clear and colourless.

Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk.

Trial products are allocated via the IV/WRS to the subjects. The subjects are instructed to return all used, partly used and unused trial products at each scheduled site visit. Returned trial products must be stored separately from non-allocated trial products. Trial product accountability will be performed in the IV/WRS drug accountability module.

For the prediction of medication, the investigator must enter the subject's weight into the IV/WRS when trial products are dispensed at each visit.

8.1.4.1 Unscheduled visits

If the subject attends the clinic for an unscheduled visit, the unscheduled visit form must be completed unless the subject's parent or the subject's legally acceptable representative attends the clinic to obtain additional trial products or auxiliary supplies. If additional trial products are required, an additional dispensing session should be made in the IV/WRS and the medical record should be updated accordingly.

8.1.4.2 Re-scheduled visits

If the subject attends a fasting visit in a non-fasting condition, blood sampling must be re-scheduled within visit window.

8.1.4.3 Withdrawn subjects

Subjects randomised in error must be withdrawn from the trial.

If a subject is withdrawn from the trial,

- the investigator must aim to undertake procedures similar to those for Visit 20 as soon as possible.

- although a subject is not obliged to give his/her reasons for withdrawing from the trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the subject's rights. Where the reasons are obtained, the primary reason (AE, non-compliance with the protocol, withdrawal criteria or others) for discontinuation must be specified in the CRF.
- a withdrawal session must be performed using the IV/WRS.
- the end of trial form must be completed, and final drug accountability of trial products must be performed even if the subject is not able to come to the site.

8.1.5 Visit 20

Please see flow chart (section 2) and assessment sections (sections 8.2, 8.3, 8.4, 8.5 and 8.6)

The subjects must attend fasting, having consumed only water from 9 pm the previous evening.

Subjects will be asked to bring all empty, partly used and unused trial products for drug accountability of trial products.

Drug accountability should be performed using the IV/WRS drug accountability module to confirm allocated, returned and lost pen devices.

The subject completion should be registered in the IV/WRS by performing a completion session.

The investigator will complete an end of trial form.

8.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (Visit 1 in this trial). Medical history is an account of medical events that the subject has experienced in the past, and the disease related to the trial as judged by investigator.

The information collected for concomitant illness should include diagnosis, and date of resolution or continuation. The information collected for medical history should include diagnosis. Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

8.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial products, which is taken during the trial period (including the screening period).

Details of any concomitant medication must be recorded at Visit 1 (screening visit). Any changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be recorded and reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

In case of systemic adrenocortical steroid, the information collected for each concomitant medication includes route of administration. If start date is more than one year ago before date of Visit 1, the date of one year ago before Visit 1 can be recorded on the concomitant medication form in the CRF.

Prohibited concomitant medication

Concomitant use of the following drugs, which may effect on growth acceleration, will be prohibited during the trial.

Thyroid hormone (except the replacement treatment), anti-thyroid hormone, androgen, oestrogen, progesterone, anabolic steroid, systemic adrenocortical steroid, derivative of gonadotropin releasing hormone, somatomedin C (IGF-1), and GH preparation except for the trial products.

A use of systemic adrenocortical steroids (hydrocortison ≤ 20 mg/day) for less than 13 weeks may be allowed.

8.4 Assessments for efficacy

8.4.1 Height

Height must be measured three times (without shoes and socks) in total at all visits. Subjects should step away from the height measurer between each measurement. Each measurement will be recorded in centimetre in the CRF and recorded to one decimal place.

A height data within the period between 40 and 64 weeks prior to Visit 1 (screening) is used for assessment for efficacy as a control data. The height had been measured during normal management of subjects.

8.5 Assessments for safety

8.5.1 Adverse events

AEs will be recorded at each visit in accordance with the procedures described in section 12.2. Any clinically significant worsening since baseline of a previous finding must be reported as an AE. For further information, please refer to section 12.

8.5.2 Laboratory assessments for safety

For laboratory analysis of safety parameters, the volumes of blood sampling at each visit are as follows:

- At Visit 1 (screening), Visit 8, Visit 12, Visit 16 and Visit 20, 14.1 mL of blood will be drawn for each visit.
- At Visit 3, Visit 5, Visit 7, Visit 9, Visit 11 Visit 13, Visit 15, Visit 17 and Visit 19, 5.5 mL of blood will be drawn for each visit.
- At Visit 6, Visit 10, Visit 14 and Visit 18, 7.8 mL of blood will be drawn.

The laboratory analyses will be performed by a central laboratory unless otherwise specified. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling and storage of samples and information on who will perform the assessments, will be described in a trial-specific laboratory manual provided by a central laboratory.

Laboratory samples can be drawn at another day than on the day of the actual visit as long as it is within the visit window stated in the flow chart (section 2). For some samples drawn during the trial it is necessary for subjects to visit in fasting state for the sensitivity of the analysis.

The samples will be coded in order to keep subject identity anonymous.

Laboratory printouts except IGF-I will be sent by the central laboratory to the investigator on an on-going basis. All laboratory printouts must be dated and signed by the investigator on the day of evaluation. If a result is outside the normal range, the investigator must judge whether the abnormality is clinically significant. If considered clinically significant the result must be reported as an AE according to section 12.

If any clinically significant abnormalities occur at Visit 1, this must be recorded on the medical history/concomitant illness form. In the case of any clinical significant worsening since Visit 1 the investigator must comment in the medical record and the change must be reported as an AE according to section 12.

Laboratory printouts of IGF-I will be sent by the central laboratory to the investigator after the database lock of the extension phase (hereinafter referred to as 2nd database lock) in this trial to maintain double-blind design in this trial. All the laboratory printouts of IGF-I must be dated and signed by the investigator on the day of evaluation.

Laboratory results of IGF-I of the pivotal phase will be transferred to the sponsor directly for the data management and the analysis after the database lock of the pivotal phase (hereinafter referred to as 1st database lock) to submit the analysis results to the authority.

All laboratory data will be transferred electronically from the central laboratory to the sponsor .

8.5.2.1 Haematology

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20, blood samples will be drawn for the measurement of the following:

- RBC
- WBC
- Haemoglobin
- Haematocrit
- Platelets
- Leukocyte fractions (neutrophil leukocyte, lymphocyte, monocyte, eosinophil leukocyte and basophilic leukocyte)

8.5.2.2 Biochemistry

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20, blood samples will be drawn for the measurement of the following:

- Aspartate aminotransferase (ASAT/SGOT)
- Alanine aminotransferase (ALAT/SGPT)
- γ-glutamyl transpeptidase (γ-GTP)
- Alkaline phosphatase (ALP)
- Total protein
- Blood urea nitrogen (urea) (BUN)
- Creatinine
- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Calcium (Ca)
- Phosphorus (P)

8.5.2.3 Bone metabolism marker

At Visits 1, 6, 8, 10, 12, 14, 16, 18,and 20, blood samples will be drawn for the measurement of the following:

- Bone-alkaline phosphatase (BAP)
- Osteocalcin

8.5.2.4 Lipid

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20the final visit, blood samples will be drawn for the measurement of the following:

- Total-cholesterol
- LDL-cholesterol
- HDL-cholesterol

8.5.2.5 Endocrinology

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20, blood samples will be drawn for the measurement of the following:

- Thyroid-stimulating hormone (TSH)
- Free thyroxine (FT_4)
- Free triiodothyronine (FT_3)

8.5.2.6 IGF-I

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20, blood samples will be drawn for the measurement of IGF-I.

8.5.2.7 Blood coagulation tests

At Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20, blood samples will be drawn for the measurement of the following:

- Prothrombin time
- Partial thromboplastin time

8.5.2.8 Urine samples

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20, urine samples will be drawn for the measurement of the following:

- Protein
- Glucose
- Occult blood

8.5.2.9 OGTT

The OGTT will be performed at Visit 1, 8, 12, 16 and 20. At Visit 1, the OGTT will be performed between Visit 1 and ending the time the subjects are registered (just before Visit 2). After having fasted apart from water from 9 pm in the previous night, the OGTT will be conducted.

1.75 g/kg body weight (maximum: 75 g) glucose will be administered orally after taking blood sample. Blood samples for glucose and insulin will be collected at 30, 60, 90, and 120 min after administration.

The investigator will judge based on the OGTT results whether the subjects are diabetic type or normal type or borderline type according to the classification and diagnosis of diabetes mellitus[19] at Visit 1. The eligibility of the subjects (exclusion criterion 3 [children with diabetic type]) must be confirmed (section 6.3), and recorded in the CRF.

8.5.2.10 HbA_{1c}

At Visits 1, 6, 8, 10, 12, 14, 16, 18, and 20, blood samples will be drawn for the measurement of HbA_{1c}.

8.5.3 Vital signs

At each visit, diastolic blood pressure, systolic blood pressure and pulse will be measured after a 5-minute rest in a sitting position.

Any changes in subsequent visits as compared to Visit 1 which fulfil the criteria for an AE must be recorded as an AE.

8.5.4 ECG

A 12-lead ECG will be recorded after a 3-minute rest in a supine position at Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20. The ECG reader will compute the PR, QT and QTc intervals (QT intervals corrected for heart rate), QRS duration, and RR interval and heart rate. The PR, QT and QTc intervals, QRS duration, and RR interval and heart rate will be recorded in the CRF.

At Visit 1, the investigator will evaluate the findings from the 12-lead ECG examination and classify it as either ‘normal’, ‘abnormal, not clinically significant’ or ‘abnormal, clinically significant’ in the CRFs. An ‘abnormal, clinically significant’ finding at Visit 1 will be recorded as a concomitant illness.

At the subsequent visits, any clinically significant worsening of a pre-existing condition as well as any new clinically significant finding will be recorded in the CRF as an AE (section 12).

Absolute QTc prolongation defined as QTc > 450 ms will be reported as “abnormal, clinical significant” referring to the ICH E14 guideline[22].

In case of “abnormal” ECG, the investigator must comment in the medical record.

If the ECG is performed before the subject has signed the informed consent form, it must be documented in the medical record that performing the procedure was not related to this trial.

8.5.5 Transthoracic echocardiography

A transthoracic echocardiography (TTE) will be performed at Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20.

At Visit 1, the investigator will evaluate the findings from the TTE examination (morphology and dynamic parameters) and classify it as either 'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant' in the CRFs. An 'abnormal, clinically significant' finding at Visit 1 will be recorded as a concomitant illness. Morphology parameters are LV diastolic dimension, LV systolic dimension, interventricular septum, LV posterior wall, LVOT diameter, left atrium, left atrial area, left atrial volume and RV diastolic dimension. Dynamic parameters are cardiac output, ejection fraction and diastolic function. At the subsequent visits, any clinically significant worsening of a pre-existing condition as well as any new clinically significant finding will be recorded in the CRF as an AE (section 12).

In case of "abnormal" TTE, the investigator must comment in the medical record.

If the TTE is performed before the subject has signed the informed consent form, it must be documented in the medical record that performing the procedure was not related to this trial.

8.5.6 Bone age

X-ray picture of carpal bones of left hand will be taken for bone age determination at individual site at Visit 2, 8, 12, 16 and 20. Centralised evaluation of bone age will be done by RUS score method of Tanner-Whitehouse II (TW2) method. Bone age is a first decimal figure.

The analysis result sheet will be obtained from the responsible person of bone age determination. Bone age will be recorded in the CRF.

8.6 Other assessments

8.6.1 Pubertal sign

Pubertal signs will be assessed at all visits. Boys will be observed by pubes and penis according to the method of Tanner[18] (Tanner stages I to V) and testicular volume using an orchidometer[23]. Testicular volume is basically an integer number. In case the measured value is medium, it is recorded in CRFs as a first decimal figure. Girls will be also observed by pubes and breast according to the method of Tanner[18] (Tanner stages I to V) and menses.

Prepubertal children are defined as the result corresponds to all of the following items:

- All of Tanner parameters = stage I
- testicular volume < 4 mL (for boy subjects only)
- none of menses (for girl subjects only)

The investigator will judge whether the subjects are prepubertal children according to the above definition at Visit 1. The eligibility of the subjects (inclusion criterion 6 [prepubertal children]) must be confirmed (section 6.2), and recorded in the CRF.

8.6.2 Body weight

Body weight will be measured (without coat and shoes) and recorded in the CRF at all visits. When body weight is measured with a second decimal figure, the second below decimal figure is rounded up or down to the nearest first decimal.

8.7 Subject compliance

At each visit the investigator will emphasise the necessity for the subject to adhere to trial procedures in order to encourage subject compliance.

Subjects will be asked to record compliance with trial products in the daily dosage note and instructed to be checked it by the investigator at the next visit.

If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial products as directed.

9 Trial supplies

Trial supplies comprise the trial products and auxiliary supplies.

9.1 Trial products

The trial products during the treatment will be as follows:

- NN-220 (somatropin [genetical recombination]) 5 mg/1.5 mL pre-filled pen for 5 mg
- NN-220 (somatropin [genetical recombination]) 10 mg/1.5 mL pre-filled pen for 5 mg

Both the trial products cannot be distinguished from one another.

Please refer to the TMM provided by Novo Nordisk A/S for details regarding trial products.

Novo Nordisk A/S, Denmark, will provide the trial products and the sponsor (Novo Nordisk Pharma Ltd.) will supply them.

9.2 Packaging and labelling of trial products

Trial products will be packaged and labelled by Novo Nordisk A/S, Denmark.

Labelling will be in accordance with Annex 13[24], local law and trial requirements.

Please refer to the TMM provided by Novo Nordisk A/S for details regarding trials products packages.

The investigator will provide each subject with the directions for use (DFU) for NN-220 pre-filled pen.

9.3 Storage, handling, accountability and destruction of trial products

9.3.1 Storage and handling

Storage conditions for NN-220:

- Before use: store in a refrigerator at 2°C to 8°C in the outer carton to protect from light and do not freeze
- Do not store the product directly adjacent to the refrigerator cooling element
- Do not use the product if it has been frozen
- Keep the product away from direct light
- Remove the needle and put the pen cap back on when the pen is not in use
- Do not use the product after the expiration date printed the outer carton and pen

In use time NN-220 may be stored for a maximum of 35 days in a refrigerator. Do not freeze.

Please refer to the TMM provided by Novo Nordisk A/S for further details regarding handling of trial products at sites.

The temperatures during storage should be monitored by a calibrated, stationary and continuously recording system. Minimum requirement is a calibrated minimum/maximum thermometer. The measuring device can be either mechanic or electronic. A temperature log must be kept to document storage within the right temperature interval. The temperature reading must be transferred to the temperature log every working day. Storage facilities should be checked frequently (at least once every working day).

The investigator must ensure the availability of proper storage conditions, and record and evaluate the temperature. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside defined conditions (e.g., outside temperature range)

Returned trial products (used, partly used or unused including empty packaging material) must be stored separately from non-allocated trial products.

The IV/WRS will assign the subject to one of the two treatments groups before the procedures at Visit 2.

NN-220

The correct dispensing unit numbers (DUN) must be dispensed to the subject. The investigator must not dispense trial products to any person not included in the trial.

9.3.2 Drug accountability and destruction of trial products

The responsibility for storage and drug accountability of the trial products at the trial site rests with the head of the trial site. The head of the trial site should assign some or all of the responsibilities for accountability of the trial products at the sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial products in accordance with procedures specified by the sponsor. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

Destruction must not take place until drug accountability has been reconciled by Novo Nordisk. Destruction will be done according to local procedures. Destruction of products must be documented.

The investigator or delegated person will perform drug accountability of trial products using the IV/WRS drug accountability module. The subjects are instructed to return all used, partly used and unused trial products at the next visit. Please refer to the flow chart (section 2).

The monitor will reconcile the drug accountability of trial products using the IV/WRS drug accountability module.

The destruction of trial products will be recorded on a destruction form, which will be signed by the person responsible for the destruction.

9.4 Auxiliary supply

The following will be supplied by Novo Nordisk Pharma Ltd.

- FlexPro® PenMate® injection supportive device
- PenNeedle®
- Other relevant materials required for the trial such as needle containers for used needles and antiseptic cotton

10 Interactive voice/web response system

An interactive voice/web response system (IV/WRS) is used.

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons.

The IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Withdrawal
- Treatment completion
- Emergency code break
- Drug accountability
- Data change

Table 10-1 IV/WRS session in the trial

Trial GHLIQUID-4020	Screen	Rand										Completion of pivotal phase
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Time of visit (weeks)	Within -4 weeks prior to Visit 2	0	4	8	12	26	39	52	65	78	91	104
Visit window (days)		0	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14
Screening	X											
Screening failure	(X)											
Randomisation		X										
Dispensing			X	X	X	X	X	X	X	X	X	X
Data change	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Withdrawal			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Completion												
Drug accountability			X	X	X	X	X	X	X	X	X	X

Trial GHLIQUID-4020	Extension phase							End of Treatment
Visit (V)	V13	V14	V15	V16	V17	V18	V19	V20
Time of visit (weeks)	117	130	143	156	169	182	195	208
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14
Screening								
Screening failure								
Randomisation								
Dispensing	X	X	X	X	X	X	X	
Data change	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Withdrawal	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Completion								X
Drug accountability	X	X	X	X	X	X	X	X

At all times during the trial, only DUNs allocated by the IV/WRS are allowed to be dispensed to a subject. By doing this it will be ensured that:

- needed stock is available at a site for the subjects
- no allocation of trial product that will expire before the next dispensing contact
- drug accountability can be made in IV/WRS

If a subject needs trial product between dispensing visits, the investigator must make an additional dispensing.

The IV/WRS user manual will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

11.1 Randomisation

All subjects will be randomised to one of the two groups (0.033 mg/kg/day or 0.066 mg/kg/day) before procedures at Visit 2. The randomisation will be carried out in a 1:1 manner (0.033 mg/kg/day: 0.066 mg/kg/day) using the IV/WRS.

The trial sites should dispense trial products allocated by the IV/WRS in order to:

- secure available stock at site to cover the drug supply needed for the enrolled subjects
- ensure that no subjects are provided with trial products that will expire in between dispensing visits
- ensure that it will be possible to perform drug accountability of trial products by using the IV/WRS

11.2 Breaking of blinded codes

If the trial site needs to break the code, Novo Nordisk should, if possible, be contacted before the code is broken. The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IV/WRS, record the reason, and sign and date the document.

If the subject is withdrawn after the code has been broken, a withdrawal session should be completed in the IV/WRS.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department, and any other relevant party. If the IV/WRS is not accessible at the time of code break the IV/WRS vendor helpdesk should be contacted. Contact details are listed in attachment II.

Key codes will be disclosed to the sponsor after the 1st database lock in this trial to analyse and submit the data from the pivotal phase to the Authority. Even after the key open, investigators, sub-investigators and the subjects will be kept blinded until the 2nd database lock.

12 Adverse events, and technical complaints

12.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore 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.

AEs include:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): A clinical laboratory abnormality which is clinically significant, i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject's parent or subject's legally acceptable representative (and the subject in case the subject has the ability to understand) has signed the informed consent.

An AE is either a serious AE (SAE) or a non-serious AE.

An SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening [a)] experience
- In-patient hospitalisation [b)] or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity [c)]
- A congenital anomaly or birth defect
- Important medical events [d)] that may not result in death, be life-threatening [a)] or require hospitalisation [b)] may be considered an SAE − when, based on appropriate medical judgement − they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition [d)].
  Suspicion of transmission of infectious agents must always be considered an SAE.

a) The term "life-threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b) The term "hospitalisation" is used when a subject:
   - is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
   - stays at the hospital for treatment or observation for more than 24 hours.

   Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs.

c) A substantial disruption of a subject's ability to conduct normal life functions (e.g., following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

d) For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

A **non-serious AE** is any AE which does not fulfil the definition of an SAE.

In addition to being either an SAE or non-serious AE, some AEs fulfil the below medical event of special interest criteria which must be evaluated by the investigator for each adverse event.

A **medical event of special interest** (MESI) is an event which, in the evaluation of safety, has a special focus.

The following are defined as MESIs in this trial:

Table 12-1 List of MESIs

MESIs	Definitions
Medication errors concerning trial products	The following should be reported: • Administration of wrong drug • Wrong route of administration, such as intramuscular instead of subcutaneous • Administration of a high dose with the intention to cause harm (e.g., suicide attempt) • Administration of an accidental overdose, i.e., a dose which may lead to significant health consequences, as judged by the investigator, irrespective of whether the SAE criterion is fulfilled

Severity assessment definitions:

- **Mild** – No or transient symptoms, no interference with the subject's daily activities
- **Moderate** – Marked symptoms, moderate interference with the subject's daily activities
- **Severe** – Considerable interference with the subject's daily activities, unacceptable.

The following terms and definitions are used in assessing the relationship between each AE and the relevant trial products:

- **Probable** – Good reasons and sufficient documentation to assume a causal relationship
- **Possible** – A causal relationship is conceivable and cannot be dismissed
- **Unlikely** – The event is most likely related to aetiology other than the trial product

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered** – The subject fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent
- **Recovering** – This term is only applicable if the subject has completed the trial or has died from another AE. The condition is improving and the subject is expected to recover from the event.
- **Recovered** with sequelae – The subject has recovered from the conditions, but with lasting effect due to disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered** – The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- **Fatal** – This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered", "recovering", "recovered with sequelae" or "not recovered". An AE with fatal outcome must be reported as an SAE.
- **Unknown** – This term is only applicable if the subject is lost to follow-up.

A **technical complaint** is any communication that alleges defects on trial supplies. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g., discoloration, particles or contamination)
- The packaging material (e.g., leakage, cracks, rubber membrane issues or errors in labelling text)

- Problems related to devices (e.g., to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject's parent or the subject's legally acceptable representative has signed the informed consent until the completion of procedures at Visit 20. The events must be recorded in the applicable forms in a timely manner.

During each visit, the subject and the subject's parent or the subject's legally acceptable representative must be asked about AEs and technical complaints in the following way: "Have you experienced any problems since the last contact?"

All AEs, either observed by the investigator or reported by the subject and the subject's parent or the subject's legally acceptable representative must be reported by the investigator and evaluated. Novo Nordisk' assessment of expectedness is performed according to the following reference documents:

- Current version of company core data sheet (CCDS/version 11.0/29 Feb 2012) and any updates hereof.

The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as an individual AE.

All AEs must be recorded by the investigator on the AE form. A separate AE form should be used for each diagnosis or sign and symptom. For each SAE a safety information form should be completed in addition to the standard AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form may be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form and a MESI form (the medication error form).

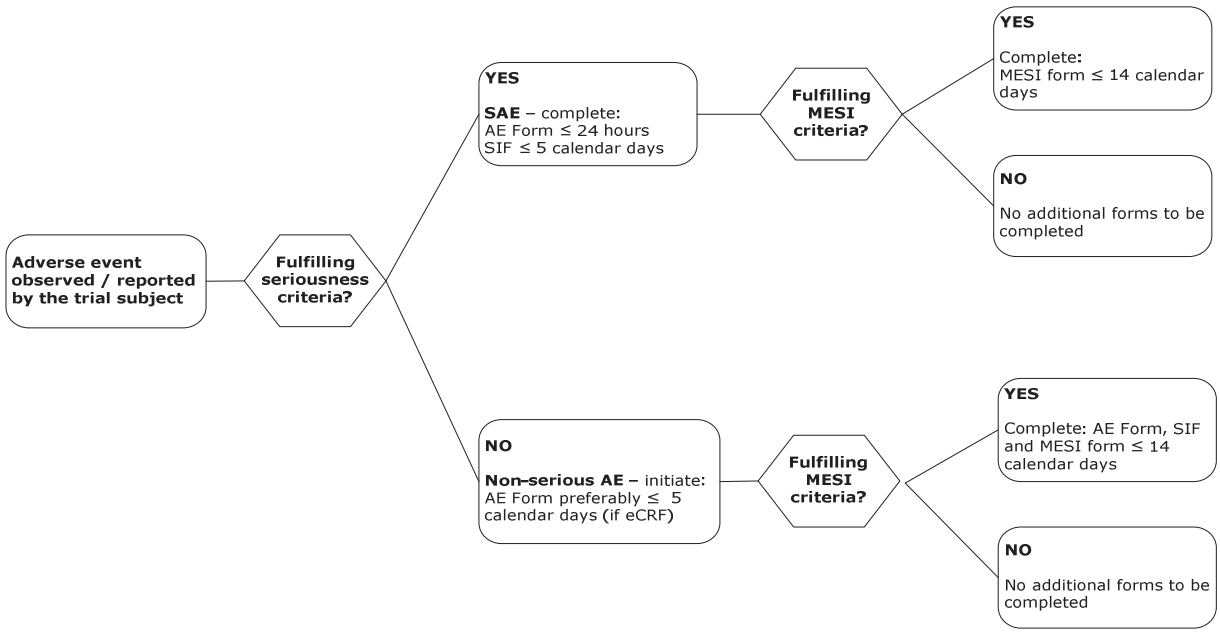

Figure 12-1 Reporting of adverse events

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial.

The investigator must complete and forward the following forms to Novo Nordisk either electronically (e.g., in PDF format) or by fax:

- If the AE fulfils the seriousness criteria: The AE form **within 24 hours** and the safety information form (SIF) **within 5 calendar days** of obtaining knowledge of the SAE.
- If a SAE fulfils the MESI criteria: The MESI form (the medication error form) **within 14 calendar days** of obtaining knowledge of the adverse event.
  If a non-serious AE fulfils the MESI criteria: The AE form, SIF and MESI form (the medication error form) **within 14 calendar days** of obtaining knowledge of the adverse event.

Contact details (fax, telephone, e-mail and address) are provided in attachment I to the protocol.

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with the Japanese requirements and ICH GCP[25]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change to any trial procedure.

Novo Nordisk must inform the institutional review boards (IRBs) in accordance with local requirement and GCP[16], unless locally this is an obligation of the investigator, as for example in the US.

Novo Nordisk must always inform the regulatory authorities in accordance with the Japanese requirements and GCP[16].

12.3 Follow-up of adverse events

All SAEs must be followed up until the outcome of the event is "recovered", "recovered with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering" or "not recovered", when the subject has completed the follow up period.

The follow-up information should only include new (corrections or new or additional) information and should be reported **within 24 hours** of obtaining knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

Follow-up information on MESIs (not also fulfilling the SAE criteria) should only include new (corrections or new or additional) information and should be reported **within 14 calendar days** of obtaining knowledge of the information. This is also the case for previously non-serious AEs which subsequently fulfil the MESI criteria.

Non-serious AEs (not also fulfilling the MESI criteria) must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering" or "not recovered".

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days.

The investigator must forward follow-up information on SAEs to Novo Nordisk within 24 hours of obtaining the follow-up information by using a new AE form and/or a safety information form marked as follow-up.

The investigator must forward follow-up information on MESIs (not fulfilling the SAE criteria) to Novo Nordisk within 14 calendar days of obtaining the follow-up information by using a new AE form and/or a safety information form and/or MESI form marked as follow-up.

The investigator must forward follow-up information on non-serious AEs (not fulfilling the MESI criteria) as corrections to the original AE form, or by using a new AE form marked as follow-up.

12.4 Technical complaints, and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on the pre-filled pen system (pen and/or needle) of the trial products which occur from the time of first usage of trial supplies until the last usage of trial supplies must be collected and reported to Novo Nordisk.

The investigator must assess whether the technical complaint is related to any AE(s), SAE(s) and/or MESI(s).

Technical complaints must be reported on a separate technical complaint form and must be completed for each trial product listed on the technical complaint form. If the technical complaint involves more than one batch number, a technical complaint form for each batch number must be completed.

The investigator must complete and forward the technical complaint form by fax, e-mail or courier to Novo Nordisk, within the same timelines as for reporting AEs and SAEs as follows:

- Technical complaint assessed as related to an SAE within 24 hours of the trial site obtaining knowledge of the complaint
- All other technical complaints within 5 calendar days

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor within 5 calendar days. The monitor must initiate the shipment to Novo Nordisk and ensure the sample is sent in accordance with local regulations as soon as possible to Novo Nordisk complaint centre. A copy or a print of the technical complaint form should be sent with the sample.

The investigator should ensure that the technical complaint sample contains the batch number and, if available, the DUN.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage and shipment of the technical complaint sample must be done in accordance with the conditions prescribed for the product (see section 9 and the TMM). The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage.

12.5 Precautions/over-dosage

In the event of over dosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

12.6 Committee related to safety

12.6.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal safety committee to perform ongoing safety surveillance. The safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

13 Case report forms

Paper CRF is used. CRFs will be provided by the sponsor.

Print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.

If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g., is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information derived from source documentation is consistent with the source information. By signing the affirmation statement, the investigator confirms that the information is complete and correct.

13.1 Correction to CRFs

Corrections to the data in CRFs may only be made by drawing a double straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each correction must be initialled (or sealed), dated and explained (if necessary) by the investigator or the investigator's authorised staff.

If corrections are made by the investigator's authorised staff after the date of the investigator's signature on the affirmation statement, the affirmation statement must be signed and dated again by the investigator.

Corrections necessary after the CRFs have been removed from the investigator's site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his authorised staff. If the affirmation statement for the subject has already been signed, the investigator must approve any correction.

13.2 Case report form flow

The investigator must ensure that data are recorded in the CRF as soon as possible after the visit.

The CRF will consist of two-part NCR (no carbon required) papers. The original is for Novo Nordisk, and the first copy is for the investigator.

The monitor collects the original after the investigator completes the affirmation statement once no further changes are expected.

The investigator will receive three copies of each laboratory report except for IGF-I directly from the laboratory in a timely manner. The report of IGF-I will be sent to investigators after the 2nd database lock. The investigators must review the laboratory reports immediately after receipt, and when no further alterations to the contents are expected, date and sign (or put a seal on) on one copy , and retain it at the study site as source data. One copy will be pasted on the appropriate page of the CRFs. The investigator must sign or seal over the joint appropriately.

Data except laboratory data from the original CRF will be entered in the database by the data management unit of the sponsor. All laboratory data will be transferred electronically from the central laboratory to the sponsor. The original kept until a clean database has been obtained and transfer of data has taken place. The original CRF is kept at the sponsor and the first copy is retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the CRFs are completed correctly and the protocol adhered to, to perform source data verification, monitor drug accountability and collect completed CRF pages. Monitoring visit intervals will not exceed 6 weeks until Visit 5 and18 weeks after Visit 6.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

The monitor will collect CRF pages and other trial related forms containing data from screening failures.

All data must be verifiable in source documentation other than the CRF, except for the following data that may be recorded directly in the paper CRFs, and will be considered source data:

- Existence of subject (subject identifier, date of birth)
- Confirmation of participation in the trial (subject ID, trial ID, and signed and dated informed consent form(s))
- Diagnosis/indication under investigation
- Visit dates
- Data from:
    - AE form(s)
    - safety information form(s)
    - technical complaints form(s)
- Relevant medical history/concomitant illness
- Reason for exclusion or withdrawal

The daily dosage note data will be included as source data.

If source data are entered in a paper CRF, each data entry or clear series of data entry must be signed and dated separately by the trial staff making the entry.

A detailed diagram and description of the transmission of electronic data should be provided. The source data and their respective capture methods should be clearly defined

There must be a source document agreement at each site.

Monitors must review the medical records and other source data to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator must be questioned about these.

14.1 Medical problem

The investigator should assess whether the medical problem entered into the daily dosage note should be considered an AE. If the medical problem is considered an AE, an AE form must be completed in the CRF, according to section 12.2.

15 Data management

Data management is always the responsibility of Novo Nordisk. Data management activities including computer system operations may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk.

Laboratory data will be transferred electronically from the central laboratory performing clinical analyses. In the case where laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer. Details of laboratory data formats and transfer will be specified in a separate written agreement between the laboratories and Novo Nordisk.

The subject and biological material obtained from the subject will be identified by subject ID and trial identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional, and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems which are described in Novo Nordisk standard operating procedures (SOPs) and IT architecture documentation. The use and control of these systems are documented.

The investigators working on the trial may use their own electronic systems to capture source data. Novo Nordisk will collect information on the practical use of these systems within the conduct of this clinical trial.

17 Statistical considerations

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will in that case be finalised before database lock.

Analyses of all efficacy endpoints will be performed based on the full analysis set (FAS). The primary analysis of the primary endpoint will be repeated on the per protocol (PP) analysis set.

Safety endpoints will be summarised using the safety analysis set (SAS).

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses if deemed relevant.

Missing values for endpoints other than OGTT, HbA_{1c} and bone age will be imputed using the last observation carried forward (LOCF) method.

All endpoints will be summarised descriptively at each visit by treatment using observed data. After 104 weeks of treatment, descriptive statistics will be presented based on both observed and LOCF imputed data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are summarised by the geometric mean, coefficient of variation (CV), median, minimum and maximum value.

LOCF imputed data will be used as the basis for plotting data.

A formal statistical test will only be performed at 104 weeks. Presentation of results from a statistical analysis will include the estimated mean treatment effects (LSMeans). Estimated mean treatment differences (or ratios) will be presented together with two-sided 95% confidence intervals and p values for all endpoints analysed statistically.

For endpoints measured over time mean values will be plotted to explore the trajectory over time. Data collected before randomisation will only be summarised descriptively.

Statistical analysis will be performed twice, at 104 weeks and at the end of trial including extension phase.

17.1 Sample size calculation

The primary endpoint is change in height SDS from baseline to 104 weeks of treatment[17]. Since the primary objective of this trial is to evaluate the growth promoting effect of NN-220, the following hypothesis will be statistically tested; $H_0 : \mu_1 = \mu_2$ vs. $H_1 : \mu_1 \neq \mu_2$, where μ_i is the population mean, i

=1, 2 represents the 0.033 mg/kg/day and 0.066 mg/kg/day, respectively. Primary analysis for primary endpoint will be performed based on the analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline height SDS as a covariate.

The sample size is calculated using two sided two sample t-test for $\mu_1 = \mu_2$ with a 5% significance level.

According to Osio D., et al. (2005)[7], the mean (SD) of change in height SDS of treatment with 0.033 mg/kg/day and 0.066 mg/kg/day from baseline was 0.8 (0.4) after 1 year and a further mean gain of 0.4 (0.7) was observed after 2 years (mean and SD for each treatment are not presented in the article). In the GHLiquid-1516 trial (Japanese subjects with short stature born small for gestational age), mean difference of height SDS between 0.033 mg/kg/day and 0.067 mg/kg/day was 0.6 at 104 weeks. The results of the sample size calculations with power 80% can be seen in Table 17-1 for different SDs and mean treatment differences that can be detected.

Table 17-1 Sample size per treatment group with power 80%

	Mean difference of 0.033 mg/kg/day and 0.066 mg/kg/day					
SD	0.35	0.40	0.45	0.50	0.55	0.60
0.40	22	17	14	12	10	9
0.45	27	21	17	14	12	10
0.50	34	26	21	17	15	12
0.55	40	31	25	21	17	15
0.60	48	37	29	24	20	17

With mean difference $\mu_2-\mu_1=0.45$ and SD=0.5, 21 subjects per treatment group give power 80%. In the GHLiquid-1516 trial, withdrawal rates were 6.1% and 5.9% for 0.033 mg/kg/day and 0.067 mg/kg/day, respectively. Assuming 10% of withdrawal rate from this result, sample size was determined as 24 per treatment group in order to ensure the power on PP analysis set. Thus, the sample size of 48 subjects in total is set, assuming exclusion of 6 subjects from PP analysis set.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[26]:

- Full analysis set (FAS): includes all randomised subjects. In exceptional cases subjects from the FAS may be eliminated. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

- The PP analysis set will consist of all subjects in the full analysis set who fulfils the following criteria:
  - Have not violated any inclusion criteria
  - Have not fulfilled any exclusion criteria
  - Have a non-missing height at baseline
  - Have at least 52 weeks of treatment
  - Have at least one non-missing height after 52 weeks of treatment

  Subjects in the PP set will contribute to the evaluation "as treated".

- Safety analysis set: includes all subjects receiving at least one dose of investigational medicinal product (0.033 mg/kg/day and 0.066 mg/kg/day of NN-220). Subjects in the safety analysis set will contribute to the evaluation "as treated".

Randomised subjects who are lost to follow up and where no information on exposure is available after randomisation will be handled as unexposed.

The decision to exclude any subject or observation from the statistical analysis is the joint responsibility of the study group members. The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by all parties, prior to the database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

17.3 Primary endpoint

The primary endpoint is change in height SDS from baseline to 104 weeks of treatment[17].

Statistical analysis

Since the primary objective of this trial is to evaluate the growth promoting effect of NN-220, the following hypothesis will be statistically tested; $H_{0:} \mu_1 = \mu_2$ vs. $H_{1:} \mu_1 \neq \mu_2$, where μ_i is the population mean, i =1, 2 represents 0.033 mg/kg/day and 0.066 mg/kg/day, respectively. Primary analysis for the primary endpoint will be performed based on the ANCOVA model with treatment as a fixed effect and baseline height SDS as a covariate.

Sensitivity analysis

The same analysis as for the primary endpoint will be repeated on the PP analysis set.

All height SDS measurements at scheduled time points after randomisation will be analysed in a linear mixed model with treatment, time and interaction between treatment and time as fixed effects, baseline height SDS and interaction between baseline and time as a covariate and subject as a

random effect. This approach assumes that data are missing at random according to the taxonomy defined by Rubin (1976)[27]. Treatment differences at 104 weeks will be estimated using this model.

Any marked difference concerning treatment differences between the sensitivity results and the result from the primary endpoint will be commented upon in the CTR.

17.4 Secondary endpoints

17.4.1 Efficacy parameters

Efficacy parameters are as follows.

- Height velocity SDS from baseline to 52 weeks of treatment[28]
- Height velocity SDS from 52 weeks to 104 weeks of treatment[28]
- Height velocity from baseline to 52 weeks of treatment
- Height velocity from 52 weeks to 104 weeks of treatment

Statistical analysis

Efficacy parameters will be summarised and graphically presented.

17.4.2 Safety endpoints

Secondary safety endpoints during 104 weeks are as follows:

- Incidence of treatment emergent AEs during 104 weeks of treatment
- Change in IGF-I from baseline during 104 weeks of treatment
- Change in HbA_{1c} from baseline to 104 weeks of treatment
- Change in clinical laboratory tests from baseline during 104 weeks of treatment
- Change in glucose tolerance (AUC of glucose and AUC of insulin) based on the OGTT from baseline to 104 weeks of treatmentChange in bone age and bone age/chronological age from baseline to 104 weeks of treatment, and (yearly [change in bone age] / [change in chronological age]) (yearly [Δ bone age/Δ chronological age])
- Change in vital signs (blood pressures and pulse) from baseline during 104 weeks of treatment
- Change in urinalysis from baseline during 104 weeks of treatment
- Change in blood coagulation test from baseline during 104 weeks of treatment
- Change in ECG from baseline during 104 weeks of treatment

Incidence of treatment emergent adverse events during 104 weeks of treatment

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented based on system organ class and preferred terms.

A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of exposure to NN-220 and no later than the date of Visit 12 (104 weeks). For withdrawal subjects, AEs with onset date no later than 7 days after the last day of NN-220 treatment will be included in the TEAE.

TEAEs are summarised descriptively, whereas non-treatment emergent AEs are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, TEAE data are summarised by seriousness, severity, relation to treatment, relation to device, withdrawal due to AEs and outcome.

Furthermore summary tables based on system organ class and preferred term are made for

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe TEAEs
- Cardiac disease TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment arm or by at least 5% of all subjects

IGF-I

IGF-I SDS will be derived using a reference range[29].

The measurements and their change from baseline during 104 weeks of treatment will be summarised descriptively.

Change in IGF-I and IGF-I SDS from baseline to 104 weeks of treatment will be analysed based on the ANCOVA model with treatment as a fixed effect and baseline as a covariate. A 95% confidence interval of the treatment difference will be provided.

HbA_{1c}

The measurements of HbA_{1c} and its change from baseline to 104 weeks of treatment will be summarised descriptively.

Clinical laboratory tests

The measurements and their change from baseline during 104 weeks of treatment will be summarised descriptively.

Glucose tolerance based on the OGTT

The measurements of glucose and insulin will be summarised descriptively.

AUC of glucose and AUC of insulin will be calculated by the usual trapezoidal method. Before statistical analysis, both of AUC at baseline and at 104 weeks will be logarithmically transformed. Change in log-transformed AUC of glucose and AUC of insulin from baseline to 104 weeks will be analysed based on the ANCOVA model with treatment as a fixed effect and log-transformed baseline as a covariate. A 95% confidence interval of the treatment ratio will be provided.Bone age

Change in bone age and bone age/chronological age from baseline to 104 weeks of treatment will be analysed based on ANCOVA model with treatment as a fixed effect and baseline as a covariate. A 95% confidence interval of the treatment difference will be provided. Yearly Δ bone age/Δ chronological age will be summarised and graphically presented.

Vital signs (blood pressures and pulse)

The measurements and their change from baseline during 104 weeks of treatment will be summarised descriptively.

Urinalysis

The measurements and their change from baseline during 104 weeks of treatment will be summarised descriptively.

Blood coagulation

The measurements and their change from baseline during 104 weeks of treatment will be summarised descriptively.

ECG

The measurements and their change from baseline during 104 weeks of treatment will be summarised descriptively.

17.4.3 Endpoints for the whole trial including the extension phase

The period of the extension phase is 104 weeks, and the period of the whole trial will be 208 weeks [104 weeks in the pivotal phase and 104 weeks in the extension phase]. However, if the indication has not yet been approved or rejected by the PMDA at 208 weeks for the first subject, the period for the extension phase will be extended for at least 26 weeks (6 months).

The endpoints at 208 weeks for the whole trial including the extension phase are defined in the same way as for the pivotal phase.

All efficacy and safety endpoints and parameters will be summarised and analysed in the same way as for the 104 weeks.

TEAEs will be defined as an event that has onset date on or after the first day of exposure to NN-220 and no later than 7 days after the last day of NN-220 treatment.

18 Ethics

The trial will be conducted in compliance with ICH GCP[25], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[15].

At the termination of the trial, the subject and investigator will decide on the best available treatment.

18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s), and adhere to the ICH GCP[25] and the requirements in the Declaration of Helsinki[15].

Before any trial-related activity, the investigator must give the subject's parent or the subject's legally acceptable representative oral and written information about the trial in a form that they can read and understand. If the subject has the ability to understand the information about the trial (as per the investigator's discretion), an assent form should be obtained from that subject.

The investigator must ensure the subject's parent or subject's legally acceptable representative has ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated, including time (if consent and trial procedures except for OGTT occur on the same day), informed consent form will be obtained from the subject's parent or subject's legally acceptable representative (and the subject in case the subject has the ability to understand) before any trial-related activity. The subject's parent or subject's legally acceptable representative (and the subject in case the subject has the ability to understand) must be provided with a copy of his/her signed informed consent.

The responsibility for seeking informed consent must remain with the investigator or be delegated by the investigator to a medically qualified person. The written informed consent must be signed and personally dated, including time (if consent and trial procedures occur on the same day), by the person who seeks the informed consent.

If information becomes available that may be relevant to the subject's parent's or subject's legally acceptable representative's (and the subject in case the subject has the ability to understand) willingness to continue participating in the trial, the investigator must inform the subject's parent or subject's legally acceptable representative (and the subject in case the subject has the ability to understand) in a timely manner, and a revised written informed consent must be obtained.

The subject's participation in the trial has ended no additional care different from what is normally provided according to subject's medical condition.

18.2 Data handling

If the subject is withdrawn from the trial or lost to follow up, then the subject's data will be handled as follows:

- Data already collected will be retained by Novo Nordisk, entered into the database and used for the trial report
- Safety events will be reported to the Novo Nordisk and regulatory authorities according to local/national requirements

If data are used, it will always be in accordance with local law and IRBs.

18.3 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, the IRBs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subject's parent or subject's legally acceptable representative (and the subject has the ability to understand) promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk should also promptly inform the IRBs and provide a detailed written explanation. The relevant regulatory authorities should be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation should be provided to the IRBs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it does have an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

The investigator must document and explain protocol deviations by stating the reason, date, and the action(s) taken.

Documentation on all protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs. Audits and inspections may take place during and after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in such audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a site is allowed to start screening subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Curricula vitae of the investigator(s) (current, dated and signed and/or supported by an official regulatory document. Must include documented GCP training or a certificate.)
- Signed and dated receipt of the IB, and any current updates hereof
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any substantial protocol amendment(s), if applicable
- Approval/favourable opinion from IRBs clearly identifying the documents reviewed as follows: the protocol, any substantial protocol amendments, subject information/informed consent form and any other written information to be provided to the subject, subject recruitment materials
- Copy of IRB approved subject information/informed consent form/any other written information/advertisement
- List of IRB members/constitution
- Financial agreement(s)
- Source document agreement
- FDA financial disclosure form or local equivalent as applicable.

A seal is accepted as signature.

Novo Nordisk will analyse and report data from all sites together.

As documented in writing by protocol signature, each investigator will fully comply with ICH GCP[25], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[15].

22 Responsibilities

All staff (Novo Nordisk, site, laboratory, contract research organization [CRO], etc.) will conduct the trial in compliance with ICH GCP[25], applicable regulatory requirements, and the Declaration of Helsinki[15].

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator should ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator must ensure adequate supervision of the conduct of the trial at the trial site. Consider to require a plan for the supervision and oversight of the trial at the site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject ID list should be kept securely and separate from the personal data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law.

The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator should delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role of the investigator (e.g., if he/she retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and site personnel must have sufficient English skills according to their assigned task(s).

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by Novo Nordisk for regulatory purposes and for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk.

The co-ordinating investigator will be appointed to review and sign the CTR (as signatory investigator) on behalf of all participating investigators.

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may invalidate the results of the entire trial.

At the end of the trial, one or more public disclosures may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

The results of this trial will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

In a multi-centre trial based on the collaboration of all trial sites, any publication of results in a journal article must acknowledge all trial sites. Where required by the journal, the principal investigator from each site will be named in the acknowledgement.

Novo Nordisk maintains the right to be informed of any investigator plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk trial manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria[30]).

The investigator(s) offered authorship will be asked to comment and approve the publication. No permission to publish will be granted to any clinical research organisation involved in the trial described in this protocol.

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations, and frequently do not provide meaningful information for healthcare professionals or subjects; and therefore may not be supported by Novo Nordisk. It is Novo Nordisk's policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

23.2 Investigator access to data and review of results

As owners of the trial database, Novo Nordisk has discretion to determine who will have access to the database. Generally, trial databases are only made available to regulatory authorities.

Individual investigators will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation

Subject records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the site. If the Novo Nordisk provided data (e.g., the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy, as a copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by national regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local requirements.

25 Institutional Review Boards and regulatory authorities

Written approval or favourable opinion must be obtained from IRB prior to commencement of the trial.

Prior to commencement of the trial, the protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject, subject recruitment procedures (including advertisement), if any, IB, available safety information, information about payments and compensation available to subjects if not mentioned in the subject information, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and other documents as required by the local IRB should be submitted. The submission letter should clearly identify the trial identification number, version, title and/or the date of the documents that have been submitted to the IRB. Written approval/favourable opinions must be obtained from the IRB prior to commencement of the trial.

During the trial, the investigator or the sponsor, as applicable, must promptly report the following to the IRB, in accordance with local requirements: updates to the IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial protocol amendments, non-substantial protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB.

Substantial protocol amendments must not be implemented before approval or favourable opinion, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB. The records should be filed in the investigator's trial file and copies must be sent to Novo Nordisk.

Regulatory Authorities

Regulatory authorities will receive the clinical trial notification (CTN), notifications of protocol amendments, reports on SAEs, and the CTR according to the Japanese requirements.

26 Indemnity statement

Novo Nordisk accepts liability in accordance with:

To the extent the sponsor is legally liable, the sponsor shall assume such legal liability for any trial-related injuries resulting from the conduct of the clinical trial, and shall pay the total amount required for resolution of the dispute, litigation or settlement.

If a subject suffers any trial-related injuries resulting from the conduct of the clinical trial and the sponsor accepts to assume responsibility subsequently despite the absence of legal liability, the sponsor could decide to provide appropriate treatment to and/or compensate such subject for the damage.

If applicable, compensation shall be made in accordance with the compensation scheme specified in 'The guideline on compensation for harmful effects resulting from participation in clinical trials[31]' issued by the Japanese Pharmaceutical Industry Legal Affairs Association.

The sponsor assumes no liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible, to the extent provided in the relevant Clinical Trial Services Agreement.

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Approval of Final Protocol

Final version 1.0, dated 21 March 2013

Protocol originator:

[redacted] Approved in novoDOCS

Name & title (printed) signature date

[redacted]of originating department:

[redacted] Approved in novoDOCS

Name & title (printed) signature date

Statistician:

[redacted] Approved in novoDOCS

Name & title (printed) signature date

Medical responsible:

[redacted] Approved in novoDOCS

Name & title (printed) signature date

Agreement on Final Protocol

Trial ID: GHLIQUID-4020

The investigator and Novo Nordisk agree to conduct the trial as outlined in the protocol with reference to Good Clinical Practice (GCP), applicable regulatory requirements, and in accordance with the Declaration of Helsinki. Any modification to the protocol must be agreed upon by both the investigator and Novo Nordisk and documented in writing. By written agreement to this protocol, the investigator agrees to allow direct access to all documentation, including source data to authorised individuals representing Novo Nordisk (including monitoring staff and auditors), to Institutional Review Boards (IRBs) and to regulatory authorities.

Investigator:

Name (printed) Signature Date

[redacted]**of medical/clinical research or Designee:**

[redacted]

Name (printed) Signature Date

Appendix C

Reference listing for the dosage scale based on the subject's body weight

The following table shows reference listing for the dosage scale for subjects (body weight: 7.0 ~ 60.0 kg). The dosage scale of the trial products will be determined based on the subject's body weight at each visit.

Body weight (kg)	Dose/day (mg)	Body weight (kg)	Dose/day (mg)
7.0 ~ 8.3	0.25	34.1 ~ 35.6	1.15
8.4 ~ 9.8	0.30	35.7 ~ 37.1	1.20
9.9 ~ 11.3	0.35	37.2 ~ 38.6	1.25
11.4 ~ 12.8	0.40	38.7 ~ 40.1	1.30
12.9 ~ 14.3	0.45	40.2 ~ 41.6	1.35
14.4 ~ 15.9	0.50	41.7 ~ 43.1	1.40
16.0 ~ 17.4	0.55	43.2 ~ 44.6	1.45
17.5 ~ 18.9	0.60	44.7 ~ 46.2	1.50
19.0 ~ 20.4	0.65	46.3 ~ 47.7	1.55
20.5 ~ 21.9	0.70	47.8 ~ 49.2	1.60
22.0 ~ 23.4	0.75	49.3 ~ 50.7	1.65
23.5 ~ 24.9	0.80	50.8 ~ 52.2	1.70
25.0 ~ 26.5	0.85	52.3 ~ 53.7	1.75
26.6 ~ 28.0	0.90	53.8 ~ 55.3	1.80
28.1 ~ 29.5	0.95	55.4 ~ 56.8	1.85
29.6 ~ 31.0	1.00	56.9 ~ 58.3	1.90
31.1 ~ 32.5	1.05	58.4 ~ 59.8	1.95
32.6 ~ 34.0	1.10	59.9 ~ 60.0	2.00

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Protocol Amendment

no. 1
to Protocol, final version 1.0
dated 21 March 2013

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]

[redacted] Novo Nordisk Pharma Ltd.

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Page

1 Introduction including rationale for the protocol amendment

In this protocol amendment:

- Any new text is written in *italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

The rationales for the changes are:

1. Correction in sections 2, 8.1.4, 9.3.1 and 11.1 is made as randomisation will only occur when subject eligibility is confirmed at Visit 2.
2. Correction in section 7 is made as a calculation mistake has been made. The last patient last visit (LPLV) will be planned approximately 4 years after the last patient first visit (LPFV; 26-December-2014), but 30-June-2018 is approximately 3 years and 6 months after the LPFV.
3. Correction in section 8.1 is made as no subject screening log and the subject enrolment log will be prepared from IV/WRS.
4. Correction in section 8.5.4 is made due to a typo error of the Japanese characters in translation, and we will modify the Japanese protocol.
5. Correction in section 14 is made to update where source documentation should be found.

2 Changes

2.1 Section 2 Footnote c) in the flow chart, page 16

All subjects will be allocated to one of the two groups (0.033 mg/kg/day group or 0.066 mg/kg/day group) ~~before procedures~~ at Visit 2.

2.2 Section 7 Trial schedule, page 32

Planned date for last patient last visit (LPLV): ~~30 June~~ *December*-2018

2.3 Section 8.1 Visit procedures, page 33

The investigator must keep a subject screening log and a subject enrolment log. The subject screening log and a subject enrolment log may be combined in one list. ~~and may be generated from IV/WRS.~~

2.4 Section 8.1.4 Visit 2 to the visit before Visit 20, page 35

Randomisation should be performed after subject eligibility is confirmed~~ and before procedures~~ at Visit 2.

2.5 Section 8.5.4 ECG, page 42

The ECG reader will compute the PR, QT and QTc intervals (QT intervals corrected for heart rate), QRS duration, and RR interval and heart rate. The PR, QT and QTc intervals, QRS duration, and RR interval and heart rate will be recorded in the CRF. [Typo in Japanese characters]

2.6 Section 9.3.1 Storage and handling, page 46

The IV/WRS will assign the subject to one of the two treatments groups ~~before the procedures~~ at Visit 2.

2.7 Section 11.1 Randomisation, page 51

All subjects will be randomised to one of the two groups (0.033 mg/kg/day or 0.066 mg/kg/day) ~~before procedures~~ at Visit 2.

2.8 Section 14. Monitoring procedures, page 62

All data must be verifiable in source documentation other than the CRF, except for the *daily dosage note data.* ~~following data that may be recorded directly in the paper CRFs, and will be considered source data:~~

- ~~Existence of subject (subject identifier, date of birth)~~
- ~~Confirmation of participation in the trial (subject ID, trial ID, and signed and dated informed consent form(s))~~
- ~~Diagnosis/indication under investigation~~
- ~~Visit dates~~
- ~~Data from:~~
    - ~~AE form(s)~~
    - ~~safety information form(s)~~
    - ~~technical complaints form(s)~~
- ~~Relevant medical history/concomitant illness~~
- ~~Reason for exclusion or withdrawal~~

~~The daily dosage note data will be included as source data.~~

Protocol Amendment

no. 2
to Protocol, final version 1.0
dated 21 March 2013

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]

[redacted] Novo Nordisk Pharma Ltd.

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Page

1 Introduction including rationale for the protocol amendment

In this protocol amendment:

- Any new text is written in *italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

The rationales for the changes are:

1. Correction in protocol sections 6.3 and 8.5.4 is made due to a typo error of the Japanese characters in translation. The Japanese protocol will be modified accordingly.
2. Protocol section 8.1.3 incorrectly details that subject identification numbers contain 4 digits instead of 6 digits. Correction in SI/IC section 8 is made due to a change in subject identification numbers from 4 digits to 6 digits.

2 Changes

2.1 Protocol, Section 6.3, Exclusion criteria, page 29

For an eligible subject, all exclusion criteria must be answered "no" at Visit 1 (screening). [Typo error of the Japanese characters in translation; "exclusion" was translated as "inclusion".]

2.2 Protocol, Section 8.1.3, Visit 1 (screening visit), page 34

At screening, the subjects will be assigned a unique subject identification (ID) which will remain the same throughout the trial. The subject ID will consist of *6*~~4~~ digits (the first *3*~~2~~ digits indicating the site number and the last *3*~~2~~ digits indicating the subject number).

2.3 Protocol, Section 8.5.4, ECG, page 42

The ECG reader will compute the PR, QT and QTc intervals (QT intervals corrected for heart rate), QRS duration, and RR interval and heart rate. The PR, QT and QTc intervals, QRS duration, and RR interval and heart rate will be recorded in the CRF. [Typo error of the Japanese characters in translation; "interval" and "duration" were translated as "time" and "wave", respectively.]

Absolute QTc prolongation defined as QTc > 450 ms will be reported as "abnormal, clinical significant" referring to the ICH E14 guideline. [Typo error of the Japanese characters in translation; "QTc" was translated as "QTc time".]

2.4 SI/IC, Section 8, Signature, page 20

Current:

Subject number				

New:

Subject number						

Protocol Amendment

no. 3
to Protocol, final version 1.0
dated 21 March 2013

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]

[redacted] Novo Nordisk Pharma Ltd.

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Page

1 Introduction including rationale for the protocol amendment and the subject information

In this protocol amendment:

- Any new text is written in *italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

The rationales for the changes are:

1. Correction in protocol section 2.1 is made due to a typo error of the Japanese characters in translation. The Japanese protocol will be modified accordingly.
2. Correction in protocol sections 2.2, 2.3, 2.4 and 2.5 is made to clarify when the tests must be re-scheduled. The Japanese protocol will be modified accordingly.

2 Changes

2.1 Protocol, Section 6.4, Withdrawal criteria, page 29

6. A subject is considered to be withdrawn by the investigator for any other reason.

Further, a subject must be *withdrawn* if the following applies: [Typo error of the Japanese characters in translation for ”withdrawn” in this sentence; the smilar but different Chinese character was used in the Japanese protocol.]

7. The receipt of any prohibited concomitant drugs except for a temporary use for emergent situations (see section 8.3 for prohibited concomitant medication).

2.2 Protocol, Section 8.5.2.9, OGTT, page 41

The OGTT will be performed at Visit 1, 8, 12, 16 and 20. At Visit 1, the OGTT will be performed between Visit 1 and ending the time the subjects are registered (just before Visit 2). *At Visits 8, 12, 16 and 20, the OGTT will be performed within the visit window stated in the flow chart (section 2).* After having fasted apart from water from 9 pm in the previous night, the OGTT will be conducted.

2.3 Protocol, Section 8.5.4, ECG, page 42

A 12-lead ECG will be recorded after a 3-minute rest in a supine position at Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20. *At Visit 1, the 12-lead ECG will be recorded between Visit 1 and ending the time the subjects are registered (just before Visit 2). At Visits 6, 8, 10, 12, 14, 16, 18 and 20, the 12-lead ECG will be recorded within the visit window stated in the flow chart (section 2).* The ECG reader will compute the PR, QT and QTc intervals (QT intervals corrected for heart rate), QRS duration, and RR interval and heart rate. The PR, QT and QTc intervals, QRS duration, and RR interval and heart rate will be recorded in the CRF.

2.4 Protocol, Section 8.5.5, Transthoracic echocardiography, page 43

A transthoracic echocardiography (TTE) will be performed at Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20. *At Visit 1, the TTE will be performed between Visit 1 and ending the time the subjects are registered (just before Visit 2). At Visits 6, 8, 10, 12, 14, 16, 18 and 20, the TTE will be performed within the visit window stated in the flow chart (section 2).*

2.5 Protocol, Section 8.5.6, Bone age, page 43

The X-ray picture of carpal bones of left hand will be taken for bone age determination at individual site at Visit 2, 8, 12, 16 and 20. *At Visits 2, 8, 12, 16 and 20, the X-ray picture will be taken within the visit window stated in the flow chart (section 2).* Centralised evaluation of bone age will be done by RUS score method of Tanner-Whitehouse II (TW2) method. Bone age is a first decimal figure.

Protocol Amendment

no. 4
to Protocol, final version 1.0
dated 21 March 2013

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]

[redacted] Novo Nordisk Pharma Ltd.

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Page

1 Introduction including rationale for the protocol amendment and the subject information

In this protocol amendment:

- Any new text is written in *italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

The rationales for the changes are:

1. Correction in protocol sections 2.1 and 2.2 are made because children who have received systemic administration of adrenocortical steroid during the treatment period of ≥13 weeks are excluded regardless of the dose level of hydrocortisone. The protocol says that "adrenocortical steroid (hydrocortisone ≤ 20 mg/day, treatment period ≥ 13 weeks)", but it is the unclear text whether hydrocortisone ≥ 20 mg/day is acceptable or not.
2. Correction in protocol section 2.3 is made because the investigator must evaluate and classify the findings from the 12-lead ECG examination, even if QTc > 450 ms was defined as "abnormal" referring to the ICH E14 guideline".

2 Changes

2.1 Protocol, Section 1, Key exclusion criteria, page 11

Children who have received systemic administration of the following medications within two years prior to Visit 1 (screening): Thyroid hormone (except replacement therapy), antithyroid hormone, androgen, oestrogen, progesterone, anabolic steroid, adrenocortical steroid (~~hydrocortison ≤ 20 mg/day,~~ treatment period ≥ 13 weeks), derivative of gonadotropin releasing hormone and somatomedin C (IGF-I).

2.2 Protocol, Section 6.3, Exclusion criteria, no. 8, page 29

Children who have received systemic administration of the following medications within two years prior to screening (Visit 1): Thyroid hormone (except replacement therapy), antithyroid hormone, androgen, oestrogen, progesterone, anabolic steroid, adrenocortical steroid (~~hydrocortison ≤ 20 mg/day,~~ treatment period ≥ 13 weeks), derivative of gonadotropin releasing hormone and somatomedin C (IGF-I).

2.3 Protocol, Section 8.5.4, ECG, page 42

Absolute QTc prolongation defined as QTc > 450 ms ~~will~~ *must* be reported as *'abnormal, not clinically significant' or* 'abnormal, clinically significant' referring to the ICH E14 guideline.

Protocol Amendment

no. 5
to Protocol, final version 1.0
dated 21 March 2013

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]

[redacted] Novo Nordisk Pharma Ltd.

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Page

1 Introduction including rationale for the protocol amendment and the subject information

In this protocol amendment:

- Any new text is written in *italics*.
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This amendment is based on the results from audit held on 16, 19-22 October 2015.

The rationales for the changes are:

1. Correction in protocol section 2.1:
   Obtaining of informed consent should be separated from visit 1 in the Flowchart, because it is not performed at screening visit.
2. Correction in protocol sections 2 and 8.7:
   The protocol did not specify the requirement for documenting investigator evaluation of returned the daily dosage note. Therefore, it has been specified that investigator's signature and evaluated date are mandatory in the note.
3. Correction in protocol section 4.2:
   The secondary efficacy endpoints have been added in section 4.2 as presented in section 17.4.1.
4. Correction in protocol Appendix C:
   Information of the doses was insufficient, therefore explanations of the doses have been added.
5. Correction in Subject Information/Informed Consent form, sections 1.5 and 1.7.3.2:
   Information of the doses was insufficient, therefore explanations of the doses have been added.

2 Changes

2.1 Protocol, Section 2, Flow chart, page 12

Table 2-1 Schedule of trial procedures

Visit	*Visit 0*	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
	Information	Screening	Start of treatment										Completion of pivotal phase
	Visit 1 -1day minimum	Within 4 weeks prior to Visit 2	0 w [a)]	4 w	8 w	12 w	26 w	39 w	52 w	65 w	78 w	91 w	104 w
Visit window (days)	-	-	0	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14
Need to be fasting		X							X				X
SUBJECT RELATED INFORMATION													
Informed Consent	*X*	~~X~~											
Inclusion/Exclusion Criteria		X	X [b)]										
Demography		X											
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Medical history/ Concomitant illness		X											
Randomisation			X [c)]										
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X
EFFICACY													
Height		X	X	X	X	X	X	X	X	X	X	X	X
SAFETY													
Adverse Events			X	X	X	X	X	X	X	X	X	X	X
IGF-I		X [i)]		X		X	X	X	X	X	X	X	X
Vital Signs [d)]		X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X [i)]					X		X		X		X
Transthoracic echocardiography (TTE)		X [i)]					X		X		X		X

Visit	*Visit 0*	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
	Information	Screening	Start of treatment										Completion of pivotal phase
	Visit 1 -1day minimum	Within 4 weeks prior to Visit 2	0 w [a)]	4 w	8 w	12 w	26 w	39 w	52 w	65 w	78 w	91 w	104 w
Visit window (days)	-	-	0	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14
Need to be fasting		X							X				X
Clinical laboratory tests [e)]		X [i)]		X		X	X	X	X	X	X	X	X
Bone metabolism marker [f)]		X [i)]					X		X		X		X
Blood coagulation test [g)]		X [i)]					X		X		X		X
Urinalysis [h)]		X [i)]		X		X	X	X	X	X	X	X	X
Oral glucose tolerance test		X [i)]							X				X
$HbA1_C$		X [i)]					X		X		X		X
Bone age			X						X				X
OTHER ASSESSMENT													
Pubertal sign		X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X	X	X	X	X	X	X	X	X	X	X	X
TRIAL PRODUCT													
Dose adjustment			X	X	X	X	X	X	X	X	X	X	X
Subject compliance				X	X	X	X	X	X	X	X	X	X
Hand out/ return of the daily dosage note			X	X	X	X	X	X	X	X	X	X	X
Dispense trial product/ Drug accountability			X	X	X	X	X	X	X	X	X	X	X
REMINDER													
Interactive voice/web response system(IV/WRS) call		X	X	X	X	X	X	X	X	X	X	X	X
End of Trial Form													

2.2 Protocol, Section 4.2, Endpoints, page 21

4.2.2 Secondary efficacy endpoints

- *Height velocity SDS from baseline to 52 weeks of treatment*
- *Height velocity SDS from 52 weeks to 104 weeks of treatment*
- *Height velocity from baseline to 52 weeks of treatment*
- *Height velocity from 52 weeks to 104 weeks of treatment*

~~4.2.2~~ *4.2.3 Secondary safety endpoints*

2.3 Protocol, Section 8.7, Subject compliance, page 44

Subjects will be asked to record compliance with trial products in the daily dosage note and instructed to be checked it by the investigator at the next visit. *In addition, the investigator will sign and write the evaluated date in the daily dosage note.*

If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial products as directed. *≥80% dosing is compliant between visit and visit.*

2.4 Protocol, Appendix C, Reference listing for the dosage scale based on the subject's body weight

The following table shows reference listing for the dosage scale for subjects (body weight: 7.0 ~ 60.0 kg). The dosage scale of the trial products will be determined based on the subject's body weight at each visit.

"Dose/day (mg)" are actual doses for subjects who were randmised to 0.033 mg/kg/day. Subjects who were randomised to 0.066 mg/kg/day injects double dose of the dose in the table.

Body weight (kg)	Dose/day (mg)	Body weight (kg)	Dose/day (mg)
7.0 ~ 8.3	0.25	34.1 ~ 35.6	1.15
8.4 ~ 9.8	0.30	35.7 ~ 37.1	1.20
9.9 ~ 11.3	0.35	37.2 ~ 38.6	1.25
11.4 ~ 12.8	0.40	38.7 ~ 40.1	1.30
12.9 ~ 14.3	0.45	40.2 ~ 41.6	1.35
14.4 ~ 15.9	0.50	41.7 ~ 43.1	1.40
16.0 ~ 17.4	0.55	43.2 ~ 44.6	1.45
17.5 ~ 18.9	0.60	44.7 ~ 46.2	1.50
19.0 ~ 20.4	0.65	46.3 ~ 47.7	1.55
20.5 ~ 21.9	0.70	47.8 ~ 49.2	1.60
22.0 ~ 23.4	0.75	49.3 ~ 50.7	1.65
23.5 ~ 24.9	0.80	50.8 ~ 52.2	1.70
25.0 ~ 26.5	0.85	52.3 ~ 53.7	1.75
26.6 ~ 28.0	0.90	53.8 ~ 55.3	1.80
28.1 ~ 29.5	0.95	55.4 ~ 56.8	1.85
29.6 ~ 31.0	1.00	56.9 ~ 58.3	1.90
31.1 ~ 32.5	1.05	58.4 ~ 59.8	1.95
32.6 ~ 34.0	1.10	59.9 ~ 60.0	2.00

2.5 Subject Information/Informed Consent form, Section 1.5, Treatment in this trial, page 4

Your child is supposed to be randomly allocated to one of two treatment groups (low dose *(0.033 mg/kg/day)* of the NN-220 group or high dose *(0.066 mg/kg/day)* of the NN-220 group) in a 1:1 manner (this is called “randomization”, and randomization is like "tossing a coin").

2.6 Subject Information/Informed Consent form, Section 1.7.3.2, Visit 2 (start of treatment), page 10

Your trial doctor will instruct you how to take your trial product (NN-220) during the trial. *In addition, they will also be informed that 50% of the subjects are injecting the double dose of the ‘mg’ stated on the pen (All of you, your child and the study doctor will not be allowed to know if your child will be allocated to the low dose group or high dose group until this is completed).*

Protocol Amendment

no. 6
to Protocol, final version 2.0
dated 03 March 2016

Trial ID: GHLIQUID-4020

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

Trial phase: 3b

Applicable to Japan

Amendment originator:

[redacted]
[redacted], Novo Nordisk Pharma Ltd.

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Page

1 Introduction including rationale for the protocol amendment and the subject information

This protocol amendment introduces:

1. Clarification of the 26 weeks extension of treatment period
2. Additional genetic test
3. Other clarifications

1.1 Clarification of the 26 weeks extension of treatment period

It has been clarified that the extension phase can be further extended for 26 weeks (to week 234) for subjects who will 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 consent to receive the trial products during the period. This is an arrangement for ensuring all completers can continue the trial treatment up until they can use Norditropin as a medicine available under health insurance at each local site. All completers will be offered to praticipate a post-marketing surveillance investigating safety and effectiveness of long-term treatment with Norditropin after getting the marketing approval for treatment of 'short stature due to Noonan syndrome' in Japan. This arrangement will prevent the lack of treatment for each subject prior to the initiation of the post-marketing surveillance.

1.2 Additional genetic test

It has been clarified that the genetic test to serach gene mutations that cause to become Noonan syndrome in each subject can be performed once during the extension phase if the subject would like to take the test. Informed consent should be obtained before conducting the genetic test. This is based on a request from the Pharmaceutical and Medical Devices Agency.

1.3 Other clarifications

It has been clarified that the trial will be classified as post marketing clinical trial after getting the marketing approval for treatment of 'short stature due to Noonan syndrome' in Japan, and then the term "clinical trial" will be replaced with "post marketing clinical trial" in the protocol and other related materials/documents.

In this protocol amendment:

- Any new text is written in *italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Protocol, Section 1 Endpoints for the whole trial including the extension phase, page 9

The period of the extension phase is 104 weeks, and the period of the whole trial will be 208 weeks [104 weeks in the pivotal phase and 104 weeks in the extension phase]. However, ~~if the indication has not yet been approved or rejected by the PMDA at 208 weeks for the first subject, the period for the extension phase will be extended for at least 26 weeks (6 months)~~ *the extension phase can be further extended for 26 weeks (to week 234) for subjects who will 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' who consent to receive the trial products during the period*.

The endpoints at 208 weeks for the whole trial including the extension phase are defined in the same way as for the pivotal phase. *Data collected in the further extended extention phase will only be summarised descriptively.*

2.2 Protocol, Section 1 Trial design, page 10

The subjects enrolled are offered to continue treatment with NN-220 for ~~at least~~ 104 weeks (pivotal phase) and to extend treatment with NN-220 until NN-220 is approved in Japan (extension phase*: from week 104 to week 208. However, the extension phase can be further extended for 26 weeks [to week 234] for subjects who will 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' who consent to receive the trial products during the period*). However, if the NN-220 developmental programme is terminated or if the health authorities reject the marketing application, this extension phase will be stopped and treatment with NN-220 will be ended.

2.3 Protocol, Section 2 Flow chart, page 14

Visit	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20 [j]	*Visit 21*	*Visit 22*
	Extension phase									
								End of Treatment [k]		*End of Treatment*
	117 w	130 w	143 w	156 w	169 w	182 w	195 w	208 w	*221 w*	*234 w*
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	*±14*	*±14*
Need to be fasting				X				X		*X*
SUBJECT RELATED INFORMATION										
Informed Consent										
Inclusion/Exclusion Criteria										
Demography										
Concomitant medication	X	X	X	X	X	X	X	X	*X*	*X*
Medical history/ Concomitant illness										
Randomisation										
Withdrawal criteria	X	X	X	X	X	X	X	*(X)* [M]	*X*	
EFFICACY										
Height	X	X	X	X	X	X	X	X	*X*	*X*
SAFETY										
Adverse Events	X	X	X	X	X	X	X	X	*X*	*X*
IGF-I	X	X	X	X	X	X	X	X	*X*	*X*
Vital Signs [d]	X	X	X	X	X	X	X	X	*X*	*X*
Electrocardiogram (ECG)		X		X		X		X		*X*
Transthoracic echocardiography (TTE)		X		X		X		X		*X*

Visit	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20 [i]	*Visit 21*	*Visit 22*
	Extension phase									
								End of Treatment [k]		*End of Treatment*
	117 w	130 w	143 w	156 w	169 w	182 w	195 w	208 w	*221 w*	*234 w*
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	*±14*	*±14*
Need to be fasting				X				X		*X*
Clinical laboratory tests [e]	X	X	X	X	X	X	X	X	*X*	*X*
Bone metabolism marker [f]		X		X		X		X		*X*
Blood coagulation test [g]		X		X		X		X		*X*
Urinalysis [h]	X	X	X	X	X	X	X	X	*X*	*X*
Oral glucose tolerance test (OGTT)				X				X		*X*
$HbA1_C$		X		X		X		X		*X*
Bone age				X				X		
OTHER ASSESSMENT										
Pubertal sign	X	X	X	X	X	X	X	X	*X*	*X*
Body weight	X	X	X	X	X	X	X	X	*X*	*X*
Genetic test [l]	←	—	—	—	—	—	—	—	—	→
TRIAL PRODUCT										
Dose adjustment	X	X	X	X	X	X	X	*(X)* [m]	*X*	
Subject compliance	X	X	X	X	X	X	X	X	*X*	*X*
Hand out/ return of the daily dosage note	X	X	X	X	X	X	X	X	*X*	*X*
Dispense trial product/ Drug accountability	X	X	X	X	X	X	X	X	*X*	*X*
REMINDER										
Interactive voice/web response system(IV/WRS) call	X	X	X	X	X	X	X	X	*X*	*X*
End of Trial Form								X [n]		*X*

[k] The extension phase can be further extended for 26 weeks for subjects who will complete visit 20 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' who consent to receive the trial products during the period. For subjects who will receive trial treatment for further 26 weeks, visits 21 and 22 should be conducted.

[L] Genetic test can be performed once during the extension phase. Informed consent should be obtained before genetic test.

[M] For subjects who will complete the trial treatment at week 208, the assessment will not be performed at visit 20. For subjects who will receive trial treatment for further 26 weeks, the assessment should be performed at visit 20.

[N] For subjects who will complete the trial treatment at week 208, the end of trial form should be completed at visit 20. For subjects who will receive trial treatment for further 26 weeks, the end of trial form should be completed at visit 22.

2.4 Protocol, Section 4.2.4 Endpoints for the whole trial including the extension phase, page 22

The period of the extension phase is 104 weeks, and the period of the whole trial will be 208 weeks [104 weeks in the pivotal phase and 104 weeks in the extension phase]. However, ~~if the indication has not yet been approved or rejected by the PMDA at 208 weeks for the first subject, the period for the extension phase will be extended for at least 26 weeks (6 months)~~ *the extension phase can be further extended for 26 weeks (to week 234) for subjects who will 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' who consent to receive the trial products during the period.*

The endpoints at 208 weeks for the whole trial including the extension phase are defined in the same way as for the pivotal phase. *Data collected in the further extended extention phase will only be summarised descriptively.*

2.5 Protocol, Section 5 Trial design, page 23

Table 5-1 Trial design of this trial

Type of trial	Trial design	Treatment period	Dosage	Endpoints
Phase 3	Double-blind	*From week 0 to week* 104 ~~weeks~~ (pivotal phase), from *week* 104 ~~weeks~~ to *week* 208 ~~weeks~~ *or week 234* (extension phase)	0.033 mg/kg/day 0.066 mg/kg/day	Height SDS, Safety

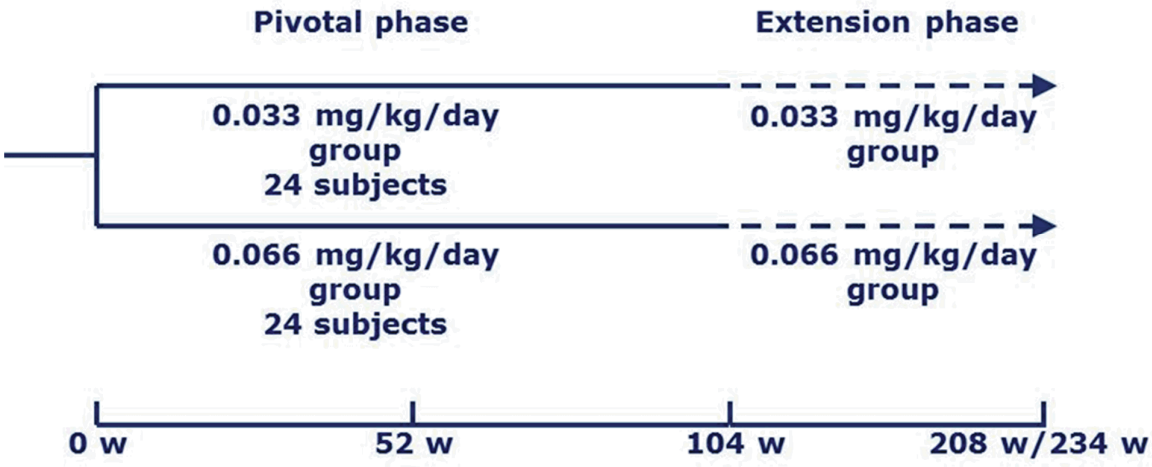

Figure 5-1 Schematic overview of this trial *(updated figure is presented)*

2.6 Protocol, Section 5.1 Type of trial, page 24

The children enrolled are offered to continue treatment with NN-220 for at least 104 weeks (pivotal phase) and to extend treatment with NN-220 until NN-220 is approved for Noonan syndrome in Japan (extension phase*: from week 104 to week 208. However, the extension phase can be further extended for 26 weeks [to week 234] for subjects who will 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' who consent to receive the trial products during the period*). However, if the NN-220 development programme is terminated or if the health authorities reject the marketing application, this extension phase will be stopped and treatment with NN-220 will be ended.

This trial will be classified as post marketing clinical trial after getting the marketing approval for treatment of 'short stature due to Noonan syndrome' in Japan, and then the term "clinical trial" will be replaced with "post marketing clinical trial" in the protocol and other related materials/documents.

2.7 Protocol, Section 5.3 Treatment of subjects, page 24

The pivotal phase of the treatment period is 104 weeks. The extension phase is from 104 weeks to 208 weeks *or 234 weeks*. The subjects will be randomised to one of the two groups (0.033 mg/kg/day group and 0.066 mg/kg/day group).

2.8 Protocol, Section 8.1.4 Visit 2 to the visit before Visit 20, page 35

8.1.4 Visit 2 to ~~the visit before Visit 20~~ *Visit 19, or Visit 21 (if applicable)*

2.9 Protocol, Section 8.1.5 Visit 20, page 37

8.1.5 Visit 20 *or Visit 22 (if applicable)*

2.10 Protocol, Section 8.5.2 Laboratory assessments for safety, page 38

For laboratory analysis of safety parameters, the volumes of blood sampling at each visit are as follows:

- At Visit 1 (screening), Visit 8, Visit 12, Visit 16 ~~and~~ Visit 20 *and Visit 22 (if applicable)*, 14.1 mL of blood will be drawn for each visit.
- At Visit 3, Visit 5, Visit 7, Visit 9, Visit 11 Visit 13, Visit 15, Visit 17 ~~and~~ Visit 19 *and Visit 21 (if applicable)*, 5.5 mL of blood will be drawn for each visit.
- At Visit 6, Visit 10, Visit 14 and Visit 18, 7.8 mL of blood will be drawn.

2.11 Protocol, Section 8.5.2.1 Haematology, page 39

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20*, and Visits 21 and 22 (if applicable)*, blood samples will be drawn for the measurement of the following:

2.12 Protocol, Section 8.5.2.2 Biochemistry, page 40

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20*, and Visits 21 and 22 (if applicable)*, blood samples will be drawn for the measurement of the following:

2.13 Protocol, Section 8.5.2.3 Bone metabolism marker, page 40

At Visits 1, 6, 8, 10, 12, 14, 16, 18,and 20, *and Visit 22 (if applicable)*, blood samples will be drawn for the measurement of the following:

2.14 Protocol, Section 8.5.2.4 Lipid, page 40

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20 ~~the final visit~~*, and Visits 21 and 22 (if applicable)*, blood samples will be drawn for the measurement of the following:

2.15 Protocol, Section 8.5.2.5 Endocrinology, page 41

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20*, and Visits 21 and 22 (if applicable)*, blood samples will be drawn for the measurement of the following:

2.16 Protocol, Section 8.5.2.6 IGF-I, page 41

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20*, and Visits 21 and 22 (if applicable)*, blood samples will be drawn for the measurement of IGF-I.

2.17 Protocol, Section 8.5.2.7 Blood coagulation tests, page 41

At Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20*, and Visit 22 (if applicable)*, blood samples will be drawn for the measurement of the following:

2.18 Protocol, Section 8.5.2.8 Urine samples, page 41

At Visits 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20*, and Visits 21 and 22 (if applicable)*, urine samples will be drawn for the measurement of the following:

2.19 Protocol, Section 8.5.2.9 OGTT, page 41

The OGTT will be performed at Visit 1, 8, 12, 16 and 20*, and Visit 22 (if applicable)*. At Visit 1, the OGTT will be performed between Visit 1 and ending the time the subjects are registered (just before Visit 2). At Visits 8, 12, 16 and 20*, and Visit 22 (if applicable)*, the OGTT will be performed within the visit window stated in the flow chart (section 2). After having fasted apart from water from 9 pm in the previous night, the OGTT will be conducted.

2.20 Protocol, Section 8.5.2.10 HbA_{1c}, page 42

At Visits 1, 6, 8, 10, 12, 14, 16, 18, and 20*, and Visit 22 (if applicable)*, blood samples will be drawn for the measurement of HbA_{1c}.

2.21 Protocol, Section 8.5.4 ECG, page 42

A 12-lead ECG will be recorded after a 3-minute rest in a supine position at Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20*, and Visit 22 (if applicable)*. At Visit 1, the 12-lead ECG will be recorded between Visit 1 and ending the time the subjects are registered (just before Visit 2). At Visits 6, 8, 10, 12, 14, 16, 18 and 20*, and Visit 22 (if applicable)*, the 12-lead ECG will be recorded within the visit window stated in the flow chart (section 2).The ECG reader will compute the PR, QT and QTc intervals (QT intervals corrected for heart rate), QRS duration, and RR interval and heart rate. The PR, QT and QTc intervals, QRS duration, and RR interval and heart rate will be recorded in the CRF.

2.22 Protocol, Section 8.5.5 Transthoracic echocardiography, page 43

A transthoracic echocardiography (TTE) will be performed at Visits 1, 6, 8, 10, 12, 14, 16, 18 and 20*, and Visit 22 (if applicable)*. At Visit 1, the TTE will be performed between Visit 1 and ending the time the subjects are registered (just before Visit 2). At Visits 6, 8, 10, 12, 14, 16, 18 and 20*, and Visit 22 (if applicable)*, the TTE will be performed within the visit window stated in the flow chart (section 2).

2.23 Protocol, Section 8.6.3 Genetic test, page 44

8.6.3 Genetic test

Noonan syndrome is diagnosed by clinical diagnosis score list. The gene mutations that cause to become Noonan syndrome are found in approximately 70% of the patients but not all patients. Therefore, genetic test will be performed for subjects participating in this trial and intending to take the test.

Gene responsible for Noonan syndrome can be tested during the extension phase.

If the subject's parent or the subject's legally acceptable representative wants a genetic test of a gene responsible for Noonan syndrome for her/his child, an informed consent form should be obtained from the subject's parent or the subject's legally acceptable representative. If the subject has the ability to understand (as per the investigator's discretion), an assent form should be obtained from that subject.

The PTPN11, KRAS, SOS1, RAF1, BRAF, SHOC2, NRAS or RIT1 may be identified as the gene responsible for Noonan syndrome by the genetic test. The results are only to be used for statistical analysis. The blood samples are discarded appropriately after the genetic tests.

The genetic tests will be performed by a specific laboratory.

Collection and sending of the samples will be performed by the central laboratory as for other samples. Laboratory supplies and procedures for obtaining samples, handling and storage of samples and information on who will perform the assessments, will be described in a trial-specific laboratory manual provided by the central laboratory.

2.24 Protocol, Section 10 Interactive voice/web response system, page 48

Table 5-1 Trial design of this trial

Trial GHLIQUID-4020	Extension phase									
								End of Treatment [a)]		*End of Treatment*
Visit (V)	V13	V14	V15	V16	V17	V18	V19	V20	*V21*	*V22*
Time of visit (weeks)	117	130	143	156	169	182	195	208	*221*	*234*
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	*±14*	*±14*
Screening										
Screening failure										
Randomisation										
Dispensing	X	X	X	X	X	X	X	*X* [b)]	*X*	
Data change	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	*(X)*	*(X)*
Withdrawal	(X)	(X)	(X)	(X)	(X)	(X)	(X)	*(X)* [b)]	*(X)*	
Completion								X [c)]		*X*
Drug accountability	X	X	X	X	X	X	X	X	*X*	*X*

[a)] *The extension phase can be further extended for 26 weeks for subjects who will complete visit 20 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' who consent to receive the trial products during the period. For subjects who will receive trial treatment for further 26 weeks, visits 21 and 22 should be conducted.*

[b)] *For subjects who will complete the trial treatment at week 208, the assessment will not be performed at visit 20. For subjects who will receive trial treatment for further 26 weeks, the assessment should be performed at visit 20.*

[c)] *For subjects who will complete the trial treatment at week 208, the end of trial form should be completed at visit 20. For subjects who will receive trial treatment for further 26 weeks, the end of trial form should be completed at visit 22.*

2.25 Protocol, Section 12.2 Reporting of adverse events, page 55

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject's parent or the subject's legally acceptable representative has signed the informed consent until the completion of procedures at Visit 20 *or Visit 22 (if applicable)*. The events must be recorded in the applicable forms in a timely manner.

2.26 Protocol, Section 17.4.3 Endpoints for the whole trial including the extension phase, page 70

The period of the extension phase is 104 weeks, and the period of the whole trial will be 208 weeks [104 weeks in the pivotal phase and 104 weeks in the extension phase]. However, ~~if the indication has not yet been approved or rejected by the PMDA at 208 weeks for the first subject, the period for the extension phase will be extended for at least 26 weeks (6 months)~~ *the extension phase can be further extended for 26 weeks (to week 234) for subjects who will 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' who cnsent to receive the trial products during the period.

The endpoints at 208 weeks for the whole trial including the extension phase are defined in the same way as for the pivotal phase. *Data collected in the further extended extention phase will only be summarised descriptively.*

All efficacy and safety endpoints and parameters *after 208 weeks of treatment* will be summarised and analysed in the same way as for the 104 weeks.

2.27 SIIC, Section 1.2 What is a clinical trial?, page 4

This trial will be classified as post marketing clinical trial after getting marketing approval for treatment of 'short stature due to Noonan syndrome' in Japan, and then the term "clinical trial" will be replaced with "post marketing clinical trial". Other implementation is not changed.

2.28 SIIC, Section 1.5 Treatment in this trial, page 4

You will be provided with NN-220 on Visit 2, and please subcutaneously inject it once a day from that day until the previous night of Visit 20 *or Visit 22*.

2.29 SIIC, Section 1.6 Trial period, page 5

The trial period of this trial is 208 weeks. However, ~~if the indication has not been approved by PMDA at 208 weeks for the first subject, the period for the extension phase will be extended. You will be explained before 208 weeks for the first subject whether the period for the extension phase will be extended or not~~ *if the 208 week-treatment is completed by the end of next month of marketing approval date, 26 weeks can be extended for the treatment period (Visit 21 and Visit 22 are added in case of extending the period)*. In case NN-220 is not approved as a "Medicine", specifically, when this developmental program is terminated or if the MHLW rejects the marketing application, this trial will be stopped and the treatment for your child with NN-220 will be ended.

Please continue the treatment until the previous night of Visit 20 *or Visit 22*. At Visit 20 *or Visit 22*, the trial will be completed.

If your child participates in this trial, the number of visiting the hospital/clinic is 20 *or 22*. If your trial doctor needs your child to visit the hospital/clinic at short intervals, more visits may be requested.

2.30 SIIC, Section 1.7.2 Trial schedule, page 6

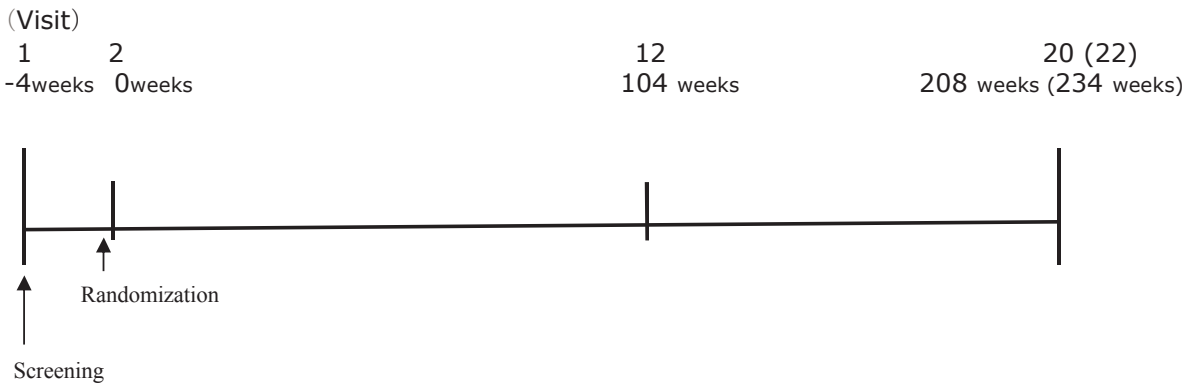

Figure 1-1 Trial diagram *(updated figure is presented)*

2.31 SIIC, Section 1.7.2 Trial schedule, page 8

Table 1-1 Trial schedule

Item \ Period (weeks)	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	*Visit 21*[*2]	*Visit 22*[*2]
	Time (weeks) from Visit 2									
	117	130	143	156	169	182	195	208	*221*	*234*
Need to be fasting				○				○		○
Medical examination/interview[*1], measurement of height, body weight, blood pressure, and pulse	○	○	○	○	○	○	○	○	○	○
Electrocardiogram (ECG)		○		○		○		○		○
Transthoracic echocardiography (TTE)		○		○		○		○		○
Blood examination	○	○	○	○	○	○	○	○	○	○
Urinalysis	○	○	○	○	○	○	○	○	○	○
Oral glucose tolerance test (OGTT)				○				○		○
Measurement of bone age				○				○		
Genetic test[*3]	←									→
Handling out and filling out daily dosage note	○	○	○	○	○	○	○	○	○	○
Receipt of trial product	○	○	○	○	○	○	○	○[*4]	○	
Return of trial product	○	○	○	○	○	○	○	○	○	○

○: To be conducted at the visit.

*[1]: Investigation of the development of the puberty is included in interview.

*[2]: *If the 208 week-treatment is completed by the end of next month of marketing approval date, 26 weeks can be extended for the treatment period. Visit 21 and Visit 22 are added in case of extending the period*

*[3]: *One genetic test is performed during this period, if you want to do.*

*[4]: *If Visit 20 is the last visit, there is no 'Receipt of trial product'.*

Note: In case of any premature discontinuation of this trial, the assessments for Visit 20 should be taken place

2.32 SIIC, Section 1.7.3.3 Visit 3 to Visit 20, page 10

1.7.3.3 Visit 3 to Visit 20 *(Visit 22)*

At Visit 8, Visit 12, Visit 16 and Visit 20 *(Visit 22 if Visit 22 is the last visit)*, your child will be asked to visit the hospital/clinic after having fasted, having consumed only water from 9 pm the previous evening in order to conduct the OGTT.

Examination to be performed on your child:

- Measurement of height and body weight (all visits)
- Measurement of blood pressure and pulse (all visits)
- ECG (Visit 6, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 18and Visit 20 *(Visit 22 if Visit 22 is the last visit)*)
- TTE (Visit 6, Visit 8, Visit 10, Visit 12, Visit 14, Visit 16, Visit 18and Visit 20 *(Visit 22 if Visit 22 is the last visit)*)
- Collection of blood samples for blood examinations (Visit 3, Visit 5 and all visits after Visit 5)
- Collection of a urine sample for urinalysis (Visit 3, Visit 5 and all visits after Visit 5)
- OGTT (Visit 8, Visit 12, visit 16 and Visit 20 *(Visit 22 if Visit 22 is the last visit)*)
  Blood samples will be taken at every 30 minutes during 120 minutes after taking glucose solution.
- X-ray photography of the left hand for the measurement of bone age (Visit 8, Visit 12, visit 16 and Visit 20)
- Assessment of pubertal signs (all visits)
- *Genetic test for Noonan syndrome (One test between Visit 13 and Visit 20 (or Visit 22) if you want to do): A gene responsible for Noonan syndrome for your child can be tested. If you wish the genetic test, the test is carried out after obtaining your consent. Even if you do not want the genetic test, your child can continue this trial.*

2.33 SIIC, Section 1.7.3.4 Other procedures, page 10

A "daily dosage note" will be provided at all visits except Visit 20 *or Visit 22* after Visit 2. You will be asked to record compliance with the drug in the "daily dosage note". Regarding details on how to complete this form, you should follow the study doctor's instruction. You will be asked to hand this "daily dosage note" to your trial doctor at the next visit.

NN-220 will be dispensed to you at all visits except Visit 20 *or Visit 22* after Visit 2. You will be asked to return all the trial products at the next visit.

2.34 SIIC, Section 2.1 Expected benefits, page 12

The trial product (NN-220), which is used in this trial, will be provided by the pharmaceutical company who is a sponsor of this trial. The expenses for all the examinations (such as blood examinations and ECG) required during the period (Visits 2 to ~~Visit 20~~ *the last visit*) will be paid by that company.

2.35 SIIC, Section 4 Financial issues, page 16

~~During the trial period your trial doctor will always monitor your child's condition carefully. In the event of an injury or disease arising directly from this clinical trial, during and after the course of this clinical trial, please inform your trial doctor immediately. An appropriate treatment and/or compensation, which will be determined in accordance with the criteria of the pharmaceutical company who is sponsoring this trial, will be available for your child. However, if the injury or disease is clearly unrelated to the trial product or if the injury or disease is caused by your child's and your negligence or wilful misconduct, your child will either not be entitled to receive compensation and/or treatment or your child's compensation/treatment may be limited.~~

~~Compensation consists of medical expenses, medical allowances and compensation payment, set in accordance with the compensation scheme specified in 'the guideline on compensation for harmful effects resulting from participation in clinical trials' issued by the Japanese Pharmaceutical Industry Legal Affairs Association.~~

During the trial period, the trial doctor will monitor your child's condition carefully. In the event of injury as a direct result of the clinical trial ("trial related injuries"), during and/or after the course of this clinical trial, please inform the trial doctor immediately. The pharmaceutical company sponsoring this trial will ensure that you receive necessary medical care to treat such trial related injuries. The pharmaceutical company sponsoring this trial has appropriate insurance coverage to provide compensation for such trial related injuries in accordance with Japanese laws, rules and regulations including the Japanese Pharmaceutical Affairs Laws and the Standards for the Implementation of Clinical Trials on Pharmaceutical Products. Such compensation shall consist of applicable medical expenses as determined by the pharmaceutical company in accordance with The Guideline on Compensation for Harmful Effects Resulting from Participation in Clinical Trials, as issued by the Japanese Pharmaceutical Industry Legal Affairs Association.

If, however, the injury is not a trial related injury or if the injury is caused by your or a third party's negligence or wilful misconduct, you may not be entitled to compensation.

The trial product (NN-220) will be provided by the pharmaceutical company who is a sponsor of this trial. The expenses for all the examinations (such as the blood examinations and ECG) required during the period (Visits 2 to Visit 20 *(or Visit 22)*) will be paid by that company.

In case your child will be examined and prescribed medications after the procedures required at Visit 20 *or Visit 22* are completed, that expenses will not be paid by that company.

2.36 SIIC, Section 8 Signature page, page 20

~~**Person who conducted the information and discussion about the trial:**~~

~~Date: Time: Signature:~~

~~(yyyy:mm:dd) (hh:mm, 24 hour clock)~~

~~**Subject's parent or subject's legally acceptable representative:**~~

~~Date: Time:~~

~~(yyyy:mm:dd) (hh:mm, 24 hour clock)~~

~~Signature: Relationship to subject:~~

~~**Investigator or appropriately qualified designee seeking the informed consent:**~~

~~(If the information and discussion about the trial is conducted by the investigator, or an appropriately medically qualified person delegated by the investigator, ONLY this signature/date is required)~~

~~Date: Time: Signature:~~

~~(yyyy:mm:dd) (hh:mm, 24 hour clock)~~

~~Time: if consent and trial procedure occur on the same day the clock time must be recorded. There is no need to record time point of signatures if the informed consent form is updated during the trial.~~

ALL INFORMATION IN THIS BOX MUST BE COMPLETED BY THE SUBJECT'S PARENT/LEGALLY ACCEPTABLE REPRESENTATIVE

Subject's parent/legally acceptable representative who has been informed and would like his/her child to participate in the trial:

Date: _____ *Signature:* _____

Name (print): _____

Relationship to subject: _____

Person who conducted the supportive information discussion:
(If the information discussion about the trial was conducted by a person other than the Investigator then this signature/date is required)

Date: _____ *Signature:* _____

Name(print): _____

Investigator conducting the information discussion and seeking the informed consent:

By signing this, I confirm that the entire informed consent process has been conducted before any trial related procedures having taken place.

Date: _____ *Signature:* _____

Name(print): _____

2.37 SIIC, Addendum, page 20

Addendum – Genetic test

The objective for performing the genetic test in this trial is to identify the gene responsible for Noonan syndrome. It is not possible to be identified for all patients, however the genotyping of approximately 70% patients can be identified. Therefore, approximately 30% patients is not identified even if the genetic test is performed to your child. In addition, the genetic test is not covered by health insurance treatment.

PTPN11, KRAS, SOS1, RAF1, BRAF, SHOC2, NRAS or RIT1 may be identified by the genetic test. These genes have been reported as the gene responsible for Noonan syndrome. The genetic tests are carried out by examining the DNA (or deoxyribonucleic acid) from your child's white blood cells. DNA is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA, which is why we can use DNA from white blood cells to identify what is a gene responsible for Noonan syndrome.

What is the procedure for genotyping in this trial?
Your child will have additional blood taken in connection with other planned blood samples at any visits in the trial, if preferred. The extra amount of blood is approximately 4 mL or less than a teaspoon full of blood. The blood sample will only be used for the gene analysis and any leftover blood/DNA will be destroyed after finalisation of the genotype analysis. The genotype analysis and destruction of samples will take place at a special laboratory.

Your child's data will be kept confidential and nobody besides the trial doctor, clinic staff and Novo Nordisk staff quality checking the data will know his identity and have access to the result of the genotyping test.

If you and your child wish, you can get the result of the genotyping from the trial doctor.

Can I say no to have genotyping done?
This extra test is entirely voluntary and it is up to you to decide if this is something you would like to have done or not. If not, your child can still continue in the trial as planned without any penalty.

Is there anything else I need to know?
If you regret and would like to withdraw consent for the genetic test after the genotyping sample has been drawn you just need to say this to the trial doctor and he/she will ensure that the sample is destroyed.

All information regarding conditions for participating in a clinical trial explained in the main information sheet for this trial (Subject Information) are also valid for the Addendum – Genotyping information.

Informed Consent – Signature page for genotype data collection

Title of trial: 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

I hereby confirm I have been given oral and written information about the genetic test to the above trial, and have read and understood the information given.

I understand that my child's participation is voluntary and I can at any time withdraw my consent without it having any consequence for my child's future treatment or participation in the trial.

I have had sufficient time to consider my child's participation and all my questions have been answered satisfactorily.

I understand that the genotype data collected during this trial are entered into a database and analysed, and that these data can be transferred securely to other countries worldwide.

I agree that representatives from Novo Nordisk and the IEC/IRB and international regulatory authorities will have access to my child's data to oversee the trial conduct.

I will receive a copy of this information signed and dated.

ALL INFORMATION IN THIS BOX MUST BE COMPLETED BY THE SUBJECT'S PARENT/LEGALLY ACCEPTABLE REPRESENTATIVE

Subject's parent/legally acceptable representative who has been informed and would like his/her child to participate in the trial:

Date: _____ *Signature:* _____

Name (print): _____

Relationship to subject: _____

Person who conducted the supportive information discussion:
(If the information discussion about the trial was conducted by a person other than the Investigator then this signature/date is required)

Date: _____ *Signature:* _____

Name(print): _____

Investigator conducting the information discussion and seeking the informed consent:

By signing this, I confirm that the entire informed consent process has been conducted before any trial related procedures having taken place.

Date: _____ *Signature:* _____

Name(print): _____