Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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Statistical Analysis Plan

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

Author:

[redacted]

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List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
CI	confidence interval
CTR	clinical trial report
CV	coefficient of variation
IGF-I	insulin like growth factor I
ITT	intention-to-treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
OGTT	oral glucose tolerance test
PMDA	Pharmaceutical and Medical Devices Agency
PP	per protocol
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SDS	standard deviation score
SMQ	Standardised MedDRA Queries
TEAE	treatment emergent adverse event

1 Introduction

1.1 Trial information

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. Primary objective is to evaluate the growth promoting effect of NN-220 from baseline to 104 weeks of treatment in short stature due to Noonan syndrome. Refer to the protocol for further details.

1.2 Scope of the statistical analysis plan

This Statistical Analysis Plan (SAP) is based on the statistical analyses of GHLIQUID-4020 as planned in the trial protocol.

Changes to the statistical methods proposed in this SAP and the reason for the change must be reported in the clinical trial report (CTR).

This SAP is based on the protocol version 2.0 (Dated 03 March 2016).

2 Statistical considerations

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.

2.1 Sample size calculation

Sample size calculations are described in the protocol section 17.1 and will not further be described here.

2.2 Definition of analysis sets

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

- 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.

2.3 Primary endpoint

The primary endpoint is change in height SDS from baseline to 104 weeks of treatment according to the Japanese reference data[ii]. A height SDS will be also calculated according to the Noonan syndrome reference data in Japanese[iii].

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)[iv]. 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.

Exploratory analysis

In order to investigate effects of sex, age at start of treatment and baseline height SDS on the primary endpoint, change in height SDS from baseline to 104 weeks of treatment will be analysed based on the ANCOVA model with treatment and sex as fixed effects and age at start of treatment and baseline height SDS as covariates. Parameter estimates for sex, age at start of treatment and baseline height SDS will be presented together with two-sided 95% CIs and p values.

Height SDS (Noonan syndrome reference data in Japanese)

In addition to height SDS according to the Japanese reference data, height SDS will be also calculated according to the Noonan syndrome reference data in Japanese. The change in height SDS (Noonan syndrome reference data in Japanese) from baseline to 104 weeks of treatment will be

analysed based on the ANCOVA model with treatment as a fixed effect and baseline height SDS (Noonan syndrome reference data in Japanese) as a covariate.

2.4 Secondary endpoints

2.4.1 Efficacy endpoints

Secondary efficacy endpoints are as follows.

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

Statistical analysis

Secondary efficacy endpoints will be summarised and graphically presented.

2.4.2 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 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

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 date of visit 2 (0 week) 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
- Medication errors
    - HLGTs: Medication errors, Device issues and Product Quality Issue
    - HLT: Complications associated with device NEC, Overdoses NEC, Underdoses NEC
    - PTs: Contraindicated drug administered, Drug administered to patient of inappropriate age
- Hyperglycaemia and new-onset diabetes mellitus - pre-defined MedDRA search
    - SMQ code: 20000041, narrow scope
- Malignant tumours - pre-defined MedDRA search
    - SMQ code: 20000194, narrow scope
- Central nervous system vascular
    - HLGT: Central nervous system vascular disorders
- Convulsion - pre-defined MedDRA
    - SMQ code 20000079, narrow scope
- Hyperthyroidism
    - HLT Thyroid hyperfunction disorders (MedDRA HLT code 10043740)
- Nephrotic syndrome
    - HLT Glomerulonephritis and nephrotic syndrome (MedDRA HLT code 10018365)

IGF-I

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

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. Before calculation of AUC, missing data in each individual profile with at least one valid data at screening will be imputed by mean value at each time point for all available data from all subjects. For 52 and 104 weeks, missing data in each individual profile with at least one valid data will be imputed by mean value at each time point for all available data from each treatment.

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.

2.4.3 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.

3 Changes to the statistical analyses planned in the protocol

The following changes from the protocol are implemented in this SAP

Terminology

“Efficacy parameters” is changed to “secondary efficacy endpoints” in section 4.2 in the protocol version 2 but it is not reflected to the section 17. In this SAP, it is changed to “secondary efficacy endpoints” from “efficacy parameters”.

Exploratory analysis on the primary endpoint

In order to investigate effects of sex, age at start of treatment and baseline height SDS on the primary endpoint, change in height SDS from baseline to 104 weeks of treatment is analysed based on the ANCOVA model with treatment and sex as fixed effects and age at start of treatment and baseline height SDS as covariates.

Statistical analysis of height SDS according to the Noonan reference

A statistical analysis on change from height SDS according to the Noonan reference in the protocol is included.

Derivation of AUC

Imputation of missing data for each individual profile is specified.

Definition of treatment emergent adverse event

The date of visit 2 (0 week) instead of the first day of exposure to NN-220 is used for a definition of a treatment emergent adverse event since the first day of exposure to NN-220 is not available in the database by the end of treatment.

Treatment emergent adverse event based on pre-defined MedDRA search

Summary tables based on system organ class and preferred term are made for treatment emergent adverse event based on pre-defined MedDRA search.

4 References

i ICH Harmonised Tripartite Guideline. Statistical principles for clinical trial E9. International Conference on Harmonisation E9 Expert Working Group.
ii Ito Y, Kato N, Tachibana K, Fujieda K. Journal of Pediatric Practice. 2005; 7: 1343-1351.
iii Isojima T, Sakazume S, Hasegawa T, et al. Growth references for Japanese individuals with Noonan syndrome. Pediatr Res. 2016;79(4):543-548.
iv Rubin D.B. Inference and missing data. Biometrika 1976; 63(3): 581-592.
v Suwa S, Tachibana K, Maesaka H, Tanaka T, Yokoya S. Longitudinal standards for height and height velocity for Japanese children from birth to maturity. Clin Pediatr Endocrinol. 1992; 1 (1): 5-13.
vi Isojima T, Shimatsu A, Yokoya S, et al. Standardized centile curves and reference intervals of serum insulin-like growth factor-I (IGF-I) levels in a normal Japanese population using the LMS method. Endocr J. 2012; Advance Publication.