Cover Page for Statistical Analysis Plan

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Official title of study:	A multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of turoctocog alfa pegol (N8-GP) when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with haemophilia A
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*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

NN7088-4595

A multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of turoctocog alfa pegol (N8-GP) when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with haemophilia A

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

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Version history

This Statistical Analysis Plan (SAP) for trial NN7088-4595 is based on the protocol *A multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of turoctocog alfa pegol (N8-GP) when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with haemophilia A*, version 3.0 dated 21Jan2021.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version
2		A few re-wordings in Sections 5.3, 5.4.2 and 5.4.3 Addition of ECG to Section 5.6 Other safety analyses	Clarification of existing text In order to accommodate a request from China Center for Drug Evaluation

1 Introduction

The rationale for this Phase 3b trial is to assess the effect of N8-GP in Chinese patients with severe haemophilia A (FVIII activity <1%) previously treated with other FVIII product(s) (PTPs). The aim is to accumulate sufficient exposure data in order to evaluate efficacy and safety of N8-GP in treatment and prevention of bleeding episodes and to obtain N8-GP PK data in this patient population.

Specifications of tables, figures and listings (TFL) and other specifications not included in this SAP will be described in the mock TFL.

1.1 Objectives and endpoints

Primary objective

- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeding episodes during prophylaxis) in Chinese adolescent and adult patients with severe haemophilia A previously treated with other FVIII products

Secondary objectives

In Chinese adolescent and adult patients with severe haemophilia A previously treated with other FVIII products,

- To evaluate the clinical efficacy of N8-GP when used for treatment of bleeding episodes
- To evaluate the immunogenicity of N8-GP
- To evaluate the general safety of N8-GP
- To evaluate the consumption of N8-GP
- To evaluate the pharmacokinetic properties of N8-GP

1.2 Trial design

This trial is a multi-centre, open-label, non-randomised, single-arm phase 3b trial evaluating the clinical efficacy, safety (including immunogenicity) and PK of N8-GP when used for treatment and prevention (prophylaxis) of bleeding episodes in Chinese patients ≥12 years of age with severe haemophilia A (FVIII activity <1%). This trial design is overall similar to the design of the completed global, pivotal pathfinder™2 trial in adult and adolescent previously treated patients with severe haemophilia A (trial NN7088-3859).

Thirty-six (36) Chinese PTPs with severe haemophilia A, aged ≥12 years and with ≥150 exposure days (EDs) to other FVIII product(s), will receive prophylaxis with 50 IU/kg N8-GP every 4 days (with the possibility of switching to twice-weekly dosing during the treatment period at the discretion of the Investigator). Bleeding episodes will be treated with bolus injection(s) of 20-75 IU/kg N8-GP.

The treatment period in the trial will be at least 28 weeks with N8-GP prophylaxis every 4 days where ≥50 EDs to N8-GP (including treatment of bleeding episodes) must be obtained. The screening period will be 2 weeks and the follow-up period will be 30 days.

At least 30 patients must complete the trial with ≥50 EDs to N8-GP (including treatment of bleeding episodes) and ≥6 months (≥28 weeks) of prophylaxis.

Please refer to the protocol for more details.

2 Statistical hypotheses

No confirmatory hypotheses are planned to be tested due to the low number of patients to be included in this trial.

3 Sample size determination

No formal sample size calculations have been performed. Based on meeting communication with CDE and with the supplement data from the global pivotal trial NN7088-3859 which also included Asian patients, a total number of 30 Chinese patients to complete this trial is considered sufficient to evaluate efficacy and safety in the Chinese population.

Fifteen (15) patients will participate in PK assessments sessions to ensure at least 12 patients with complete single-dose and steady-state PK profiles.

4 Analysis sets

All patients exposed to N8-GP in this trial will be included in the full analysis set (FAS) and the safety analysis set (SAS).

Exceptional outlier pharmacokinetic profiles and/or individual plasma FVIII activities may be excluded when analysing pharmacokinetic endpoints based on the FAS. The rules to exclude data points from analysis of pharmacokinetic endpoints are described in this SAP, and the decision of data exclusion will be made during a review prior to database lock. Any excluded data points will be documented in the database lock minutes and also in the clinical trial report (CTR).

5 Statistical analyses

5.1 General considerations

Novo Nordisk will be responsible for the statistical analyses. The statistical analysis plan (SAP) will be finalised prior to first patient first visit.

Summaries for continuous endpoints will include total number (N), mean (SD), median and min/max, and for pharmacokinetic endpoints also geometric mean and coefficient of variation (CV%). Summaries for categorical endpoints will include N, number (n) and percentages (%) for each outcome category.

In general, all summaries and analyses will also be prepared by age subgroup (12-17 and 18-70 years of age).

FVIII activities below lower limit of quantification (LLOQ) will be set to half the value of the LLOQ.

All bleeding endpoints will be evaluated based on bleeding episodes requiring treatment with N8-GP. Non-treatment requiring bleeding episodes will only be listed. Bleeding episodes in relation to surgery will also only be listed, i.e. not included in the analysis of bleeding endpoints.

Multiple bleeding locations occurring from the same event (e.g. due to a bicycle accident) or at the same time point will be counted as one bleeding episode and only one haemostatic response will be considered for the bleeding episode. In case different responses were registered for different bleeding locations in such a bleeding episode, the worst response will be used in the analysis.

A re-bleed is defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after stopping treatment. If a bleed occurs in the same location later than 72 hours after stopping the treatment it is considered a new bleed. Re-bleeds will only be considered for joint bleeds since the specific location for other bleeds e.g. in subcutaneous are not captured in the database.

In the sub analyses of annualised bleeding rate where there are less than 5 patients in a sub-group, model based estimation will not be done. If no bleedings occur in a sub-group, then the confidence interval will not be calculated.

For patients that discontinue treatment with N8-GP, data after visit P8 will only be included in listings and clearly marked. For secondary safety endpoints separate summary tables for data relating to the period after visit P8 will be prepared if such data is available for 5 or more patients.

5.2 Subject disposition

See mock TFLs.

5.3 Primary endpoint analysis

Endpoint title	Time frame	Unit
Number of bleeding episodes	From start of treatment until visit 7	Count

The primary endpoint will be analysed by a Poisson regression model allowing for over-dispersion (using Pearson's chi-square divided by the degrees of freedom) with the logarithm of duration of actual prophylaxis treatment with N8-GP used as offset. Estimates of the annualised bleeding rate (ABR) will be provided with 95% confidence intervals.

Only the observed bleeding episodes will be counted and the offset will be the duration of actual prophylaxis treatment with N8-GP.

A sensitivity analysis based on negative binomial regression model with the logarithm of duration of actual prophylaxis treatment with N8-GP used as offset will also be performed.

Another sensitivity analysis will be performed imputing the number of bleeding episodes for patients that discontinue treatment. For patients prematurely discontinuing treatment, the number of bleeding episodes counting in the analysis will be imputed up to what they could be expected to have had if they had completed the trial on treatment. If e.g. a patient withdraws after 2 months with 3 bleeding episodes, but the patient should have been in the study for 6 months, then this patient will in the analysis count as having had 9 bleeding episodes in 6 months. This is similar to last observation carried forward (LOCF) and will avoid positive bias occurring from patients with many bleeding episodes withdrawing early. For patients withdrawing within 1 month this method is considered to give too uncertain LOCF values, hence imputation will not be attempted for such patients. Instead only the observed bleeds and the observed duration will be used.

ABRs will be summarised in total, by cause of bleed, and by location of bleed (including ABR in baseline target joints).

Bleeding episodes in relation to surgery will not be included in the analysis.

5.4 Secondary endpoints analysis

5.4.1 Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response	From start of treatment until visit 7	Count

(excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.		
Consumption of N8-GP for treatment of bleeding episodes	From start of treatment until visit 7	IU/kg/bleed
Consumption of N8-GP for prophylaxis	From start of treatment until visit 7	IU/kg/year
FVIII trough activity during prophylaxis	From start of treatment (excluding the first exposure) until visit 7	IU/mL

5.4.1.1 Haemostatic effect of N8-GP

Haemostatic effect of N8-GP when used for treatment of bleeding episodes is assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and none). Excellent and good counts as success and moderate and none as failures. In addition any bleeding episodes with missing response information will be counted as failures.

Specifically this will be done by a logistic regression. The analysis will be performed by use of Proc Genmod in SAS. Correlation within patients will be taken into account using a Generalized Estimation Equations approach with a working correlation matrix with a compound symmetry structure.

Response as measured by the four point scale will also be summarised and listed.

A sensitivity analysis will be performed similar to the primary analysis but only analysing bleeding episodes with recorded responses (i.e. not counting any bleeding episodes with missing response as failures).

The haemostatic effect will be summarised in total, by cause of bleed and by location of bleed (including haemostatic effect in target joints).

Haemostatic effect for bleeding episodes in relation to surgery will not be included in the analysis.

5.4.1.2 Consumption of N8-GP for treatment of bleeding episodes

The number of injections per bleed will be summarised and listed.
The number of IU/Kg per bleed will be summarised and listed.

5.4.1.3 Consumption of N8-GP for prophylaxis

The number of injections for prophylaxis will be summarised and listed.

The number of IU/Kg per month and per year will be summarised and listed.

5.4.1.4 FVIII trough activity during prophylaxis

The trough and recovery levels will be analysed by a mixed model on the log-transformed plasma concentrations with age group as fixed effect and patient as a random effect. The mean trough and recovery levels will be presented back-transformed to the natural scale together with the 95% confidence interval.

The following rules will be implemented for the analysis of trough and recovery levels:

- Pre-dose and post-dose values will be excluded if post-dose activity is ≤ pre-dose activity.
- Pre-dose and post-dose values taken more than ±2 days outside of dosing interval will be excluded.
- Pre-dose and post-dose values taken less than twice the prophylaxis treatment interval after last treatment of a bleeding episode will be excluded.
- Pre-dose and post-dose values taken within 2 weeks after surgery will be excluded.
- Pre-dose and post-dose values taken in relation to the first exposure will be excluded.
- FVIII activity measured in defrosted plasma samples will be excluded.

Furthermore, trough and recovery (30 minutes post-dose) levels measured at scheduled visits will be summarised and listed. Incremental recoveries will be calculated and presented in summary tables and plots.

5.4.2 Secondary safety endpoints

Endpoint title	Time frame	Unit
Incidence rate of confirmed FVIII inhibitors ≥0.6 BU	From start of treatment until visit 7	Rate
Number of adverse events (AEs)	From start of treatment until end of trial	Count
Number of serious adverse events (SAEs)	From start of treatment until end of trial	Count

5.4.2.1 Incidence Rate of Confirmed FVIII-inhibitors ≥0.6 BU

A patient is said to have FVIII-inhibitors if two consecutive tests, preferably within 2 weeks, are positive (≥0.6 BU). The rate of inhibitors will be reported and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the inhibitor rate the numerator will include all patients with neutralising antibodies while the denominator will include all patients with a minimum of 50 exposures plus any patients with less than 50 exposures but with neutralising inhibitors.

5.4.2.2 Adverse Events (AEs) and Serious Adverse Events (SAEs) reported during the trial

Treatment emergent AEs (TEAEs defined as AEs occurring after dosing with trial product) and treatment emergent SAEs (TESAEs) will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity and by causal relation to trial product will be made.

Furthermore, listings will be provided displaying all TEAEs and TESAEs including pertinent clinical information.

5.4.3 Secondary pharmacokinetic endpoints

Table 2 Definition and calculation of PK Parameters

Title	Time frame	Unit	Details
Incremental Recovery	30 min ± 5 min post-injection at visit 2a and visit 7	(IU/mL)/(IU/kg)	The incremental recovery is calculated by subtracting the FVIII activity (IU/mL) measured in plasma at time 0 from that measured at time 30 min after dosing and dividing this difference by the dose injected at time 0 expressed as IU/kg BW
FVIII activity 30 min post-injection (C_{30min})	30 min ± 5 min post-injection at visit 2a and visit 7	IU/mL	The FVIII activity recorded 30 min after end of injection. Expected to be the maximum FVIII activity observed.
FVIII trough activity 96 h post-injection (C_{96h})	96 h ± 8 h post-injection at visit 2a and visit 7	IU/mL	The FVIII activity recorded immediately before next dose is given. Expected to be the minimum FVIII activity observed.
$AUC_{(0\text{-}inf)}$	0−96 h post-injection at visit 2a and visit 7	h*(IU/mL)	Area under the activity versus time profile from time zero to infinity. Measure of total plasma exposure. $AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_{(t)} / \lambda_z$, where $C_{(t)}$ is the last measurable activity.

Title	Time frame	Unit	Details
$AUC_{(0-t)}$	0−96 h post-injection at visit 2a and visit 7	h*(IU/mL)	Area under the plasma activity versus time profile from time zero to the last measurable activity. Measure of plasma exposure in the time interval 0 to last measurable activity. $AUC_{(0-t)}$ is calculated using the linear trapezoidal method from time 0 to the time for the last measurable activity. The activity at time 0 will be estimated by log-linear back extrapolation of the two initial post-administration activities. If the second value is not lower than the first value, the concentration at time 0 will be defined as the highest of these two.
$AUC_{(0-96h)}$	0−96 h post-injection at visit 2a and visit 7	h*(IU/mL)	$AUC_{(0-96h)}$ is calculated using the linear trapezoidal activities. If FVIII activities are not available up to 96 hours post-dose, the area under the missing terminal part of the curve will be determined by interpolation or extrapolation using a similar principle as for $AUC_{(0-inf)}$, where the terminal elimination rate constant, λz, is used given that there are sufficient measurements for the determination of the terminal elimination rate constant.
Accumulation ratio	0−96 h post-injection at visit 7		Accumulation ratio is calculated as $AUC_{(0-96h)}$ at steady state/$AUC_{(0-96h)}$ at single dose.
Terminal half-life ($t_{½}$)	0−96 h post-injection at visit 2a and visit 7	h	$t½ = \ln(2) / \lambda z$, where λz is the terminal elimination rate. The terminal elimination rate will be estimated using linear regression on the terminal part of the log(activity) versus time profile.
Clearance (CL)	0−96 h post-injection at visit 2a and visit 7	mL/h/kg	CL= Dose / AUC. Using $AUC_{(0-inf)}$ for single dose and $AUC_{(0-96h)}$ for steady state.
Vz	0−96 h post-injection at visit 2a and visit 7	mL/kg	Apparent volume of distribution based on the terminal phase. $Vz = CL/\lambda z$
Vss	0−96 h post-injection at visit 7	mL/kg	Apparent volume of distribution at steady-state. Vss = CL*MRT
%extrap	0−96 h post-injection at visit 2a and visit 7	%	Percentage of $AUC_{(0-inf)}$ determined by extrapolation. $AUC_{(t-inf)}/(AUC_{(0-inf)})$

Title	Time frame	Unit	Details
MRT	0−96 h post-injection at visit 2a and visit 7	h	Mean Residence Time. MRT = $AUMC/AUC_{(0\text{-}inf)}$, where AUMC is the area under the first moment curve, i.e. the area under the curve $t \cdot C_{(t)}$, calculated with the same method as $AUC_{(0\text{-}inf)}$ (linear trapezoidal method + extrapolated area)
λz	0−96 h post-injection at visit 2a and visit 7	1/h	Terminal elimination rate constant. The terminal elimination rate constant will be estimated using linear regression on the terminal part of the log(activity) versus time profile

Single dose PK will be based on the PK session at visit 2a, and steady state PK will be based on the PK session at visit 7.

The PK parameters will be calculated using plasma FVIII activity obtained from the FVIII chromogenic assay. The PK parameters will be derived according to a non-compartmental method, as described in Table 2. The actual time points will be used in the calculations.

If any profiles and/or individual plasma FVIII activities are excluded from the primary pharmacokinetic analysis, a sensitivity pharmacokinetic analysis will also be performed and reported based on all observed data. The primary pharmacokinetic analysis is based on the full analysis set excluding outliers.

Specifically which data points and profiles that will be excluded will be defined prior to database lock. It should exclude profiles with pre-dosing activity > 5% (possibly indicating inadequate wash out) at visit 2a and profiles that are not indicative of a normal intravenously injection (i.e. clearly increasing plasma FVIII activities initially). If a patient is treated with an additional dose during the PK session, the plasma FVIII activities after the occurrence will then be excluded. Furthermore, if the profile shows indications of an additional dose (e.g. clearly increased plasma FVIII activity), the plasma FVIII activities after the occurrence will then also be excluded.

All pharmacokinetic endpoints (except MRT, Vss, Vz, percentage of $AUC_{(0\text{-}inf)}$ determined by extrapolation and terminal elimination rate constant) will be analysed using mixed effects model on log-transformed parameters including patient as random effect. Estimates of each endpoint with 95% confidence intervals will be provided back-transformed to the natural scale.

Individual and mean PK profiles will be presented graphically by subject and by visit.

Furthermore, the mean PK endpoints will be summarised and individual PK endpoints will be listed.

5.5 Exploratory endpoints analysis

Not applicable.

5.6 Other safety analyses

Changes in vital signs (blood pressures, pulse, temperature, respiratory rate)

These endpoints will be presented in summary tables and plots.

Other safety parameters

All additional safety parameters such as laboratory parameters, ECG and physical examinations will be presented in summary tables, plots and listings as appropriate.

5.7 Other analyses

Surgery

In relation to surgery the following will be recorded:

- Haemostatic effect evaluated on the four-point scale (excellent, good, moderate and none) and assessed by the investigator/surgeon on the day of surgery (Day 1) and on the last day in the post-operative period the patient is at the trial/surgery site.

- Loss of blood and requirements for transfusion on the day of surgery (Day 1) and during the post-operative period Days 2-7 or until the last day the patient is at the trial/surgery site, whatever comes first.

All records will be summarised and listed.

5.8 Interim analyses

No interim analysis is planned.

5.8.1 Data monitoring committee

Refer to protocol Section 9.6

6 Supporting documentation

6.1 Appendix 1 List of abbreviations

ABR	Annualised bleeding rate
AE	Adverse event
AUC	Area under the curve
BU	Bethesda unit
C_{30min}	FVIII activity at 30 min post injection
CDE	Centre of Drug Evaluation
CI	Confidence interval
CL	Total clearance
CTR	Clinical trial report
ED	Exposure day
FAS	Full analysis set
FVIII	Coagulation factor eight
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MRT	Mean residence time
N8-GP	Glycopegylated recombinant coagulation factor VIII (NCC 0129-0000-1003)
PK	Pharmacokinetics
PTP	Previously treated patient
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set

SD	Standard deviation
t½	Terminal half life
TE	Treatment emergent
TFL	Tables, figures and listings

6.2 Appendix 3: Definition and calculation of endpoints, assessments and derivations

Not applicable

7 References

Not applicable