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: NN7008-4028

Efficacy and safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with haemophilia A

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List of abbreviations

AE	adverse event
$AUC_{0\text{-}inf}$	area under the curve
BU	Bethesda unit
CTR	clinical trial report
CL	clearance
C_{max}	highest measured FVIII activity in the profile
FAS	full analysis set
FVIII	Factor VIII
HLA	human leucocyte antigen
ICH	International Conference on Harmonisation
IU	International units
PK	pharmacokinetic
PRO	patient reported outcome
SAE	serious adverse event
$T_{½}$	half life

1 Introduction

Trial information

The primary objective is to evaluate the clinical efficacy of turoctocog alfa in treatment of bleeding episodes in Chinese patients with severe haemophilia A (FVIII≤1%)

The key secondary objective is

- To assess the safety of turoctocog alfa in terms of immunogenicity
- To evaluate the clinical efficacy of turoctocog alfa during prophylaxis treatment
- To evaluate the consumption of turoctocog alfa during prophylaxis treatment and treatment of bleeding episodes

At least 65 previous treated patients with severe haemophilia A will be given a prophylactic regimen or an on-demand regimen of turoctocog alfa. It is not possible to switch between these 2 treatments regimens in the main phase of the trial, but the dose and frequency of dosing can though be changed. At least 10 patients on the on-demand and 20 patients on the prophylaxis regimen will complete the main phase of the trial, which will last for approximately 6 months.

An extension phase (from visit 8 until LPLV, see section 7) is added to assess long term safety and efficacy, see section 7, and either prophylaxis or on demand treatment can be chosen also in this phase, but it is possible to switch between these treatments regimens during the extension phase and also to change the dose and frequency of dosing.

Of the 65 dosed patients, a minimum of 12 and a maximum of 18 patients will be enrolled in the PK session to characterise the PK profile of turoctocog alfa in a Chinese population with severe haemophilia A.

Enrolled patients who need to undergo surgical procedures will remain in the trial provided that turoctocog alfa is used for the prevention and treatment of the surgical bleeding. All surgical procedures (e.g. minor, major, elective, and emergency) may be performed using turoctocog alfa at he investigators discretion.

Please refer to the protocol for further details.

Scope of the statistical analysis plan

This SAP is based on the protocol *Efficacy and safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with haemophilia A*

Final protocol version 5 (21-Jul-2017) is based on protocol amendment 3 (and protocol version 1(13 February 2014), protocol version 2 (10 May 2016) and protocol version 3 (19-Aug-2016) including protocol amendment 1 and 2).

The statistical analysis is already pre-specified in the protocol but in order to fulfil a requirement from the Chinese authorities this SAP is written.

2 Statistical considerations

Evaluation of data will be based mainly upon descriptive statistics, i.e. summary tables, listings, and figures. Categorical data will be summarised by frequency tables while continuous data will be summarised by mean, standard deviation, minimum and maximum value.

All efficacy endpoints will be reported only for patients without inhibitors (<0.6 BU) and using bleeds with turoctocog alfa treatment. Base on the full analysis set (FAS), but if a patient develops an inhibitor only the time before the positive inhibitor test will be used to evaluate the efficacy endpoints. The following sensitivity analyses will be performed:

- The annualised bleeding rate will be calculated for both treatment-requiring bleeds and non-treatment requiring bleeds
- The annualised bleeding rate will be calculated excluding data from low titer periods
- Treatment success will be summarised excluding data from low titer periods

The main CTR will be written when at least 60 patients have completed the main phase of the trial (completed visit 8 and data is available, including PK data).The patients that have not completed the main phase at the cut off time for the main CTR will also be reported as part of the main phase.

These patients will be included with data until their last scheduled visit prior to the cut-off date. The extension phase data at this time will also be included in the main CTR. The main CTR will present data separately (when relevant) for the above mentioned main and extension phase and this data will also be presented combined.

The primary conclusion will be based on the main CTR and only on the above mentioned main phase data. An updated CTR will be conducted when all patients have completed the extension phase of the trial. The updated CTR will present data separately (when relevant) for the main and extension phase and the combined main and extension phase data. The definition of the main phase will be the same in the main and updated reports. See Figure 16–1.

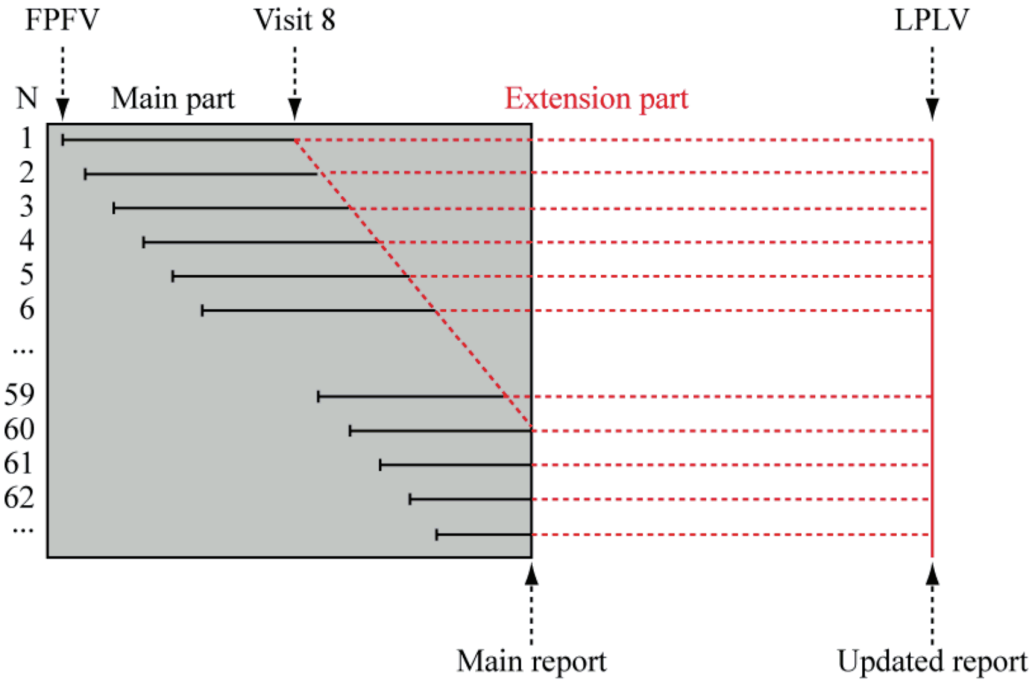

Figure 16–1 in the CTR

Sample size calculation

No formal sample size calculations have been performed. A sample size of 60 patients is considered a sufficient number of patients to evaluate safety and efficacy of turoctocog alfa. The results of this study will supplement results from a corresponding study in non -Chinese patients.

Definition of analysis sets

All main descriptions and analyses of safety and efficacy data will be based on the FAS, as defined in ICH E9 Guidelines (Statistical Principles for Clinical Trials). The FAS includes all dosed patients with data after dosing.

The ABR will also be summarised by the following subgroups:

Cause of bleed (Spontaneous, Traumatic, Re-bleed), Site of bleeding (Central nervous system, Haemarthrosis (Joint), Gastrointestinal, Subcutaneous, Muscular or other), Classification of bleeding (Mild/Moderate or Severe)

Handling of exceptional pharmacokinetic outlier data

Exceptional outlier PK profiles and/or individual plasma concentrations may be excluded when analysing PK endpoints based on the FAS. If exceptional outlier data are identified, a sensitivity analysis including the outlier data will be conducted.

Unless otherwise stated, analysis results obtained from FAS excluding exceptional outliers will be presented with reference to the "full analysis set excluding outliers". The results of the sensitivity analysis including the exceptional outliers will refer to "full analysis set incl. all data".

Documentation of analysis sets

The decision to exclude data points from analysis of PK endpoints based on the FAS will be made from a review prior to database lock. It will be the joint responsibility of the clinical pharmacology scientist and the trial statistician.

The profiles or observations to be excluded from the FAS and the reason for their exclusion will be documented and signed by the clinical pharmacology scientist and the trial statistician as part of the database lock minutes. The documentation will be stored together with the remaining trial documentation. This will also be described in the CTR.

Primary endpoint

Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four point scale for haemostatic response (excellent, good, moderate and none) during the main phase (6 months duration per patient).

In addition treatment success will be summarised by counting haemostatic responses rated as good or excellent as success and responses rated as moderate and none as failure. If the haemostatic response is missing, the response will be counted as failure in the primary analysis, but a sensitivity analysis will be performed excluding bleeding episodes with missing response. Treatment success will also be summarised excluding data from low titer periods as a sensitivity analysis to the primary analysis.

The haemostatic effect of turoctocog alfa will also be summarised by the following subgroups:

Cause of bleed (Spontaneous, Traumatic, Re-bleed), Site of bleeding (Central nervous system, Haemarthrosis (Joint), Gastrointestinal, Subcutaneous, Muscular or other), Classification of bleeding (Mild/Moderate or Severe)

Analyses and presentations will be made by age groups, type of regimen, trial phase and total.

Supportive secondary endpoints

All the following endpoints will be analysed for the main and extension phase and the combined main and extension phase data.

Efficacy endpoints

The primary endpoint will be repeated for the extension phase and the combined main and extension phase (total trial period of 24 months) . The analysis is similar to the primary analysis

Number of bleeds (total bleeds assessed as annual bleeding rate) per patient during both the main phase of 6 months and the trial period of 24 months. This endpoint will only be presented for patients on prophylaxis regimen and will be reported using only treatment requiring bleeds. The following sensitivity analyses will be performed:

- The annualised bleeding rate will be calculated for both treatment-requiring bleeds and non-treatment requiring bleeds
- The annualised bleeding rate will be calculated excluding data from low titer periods

The annualised bleeding rate will be analysed by a negative binomial model and estimated annualised bleeding rate with confidence interval will be presented by trial phase and treatment regimen. As a sensitivity analysis, a Poisson model with over-dispersion will also be applied. Analyses and presentations will be made for the preventative regimen by age groups, trial phase and total.

When turoctocog alfa is administered via a butterfly, the dead space is subtracted from the total volume of the dose to account for the compound left in the butterfly device after injection.

- Consumption of turoctocog alfa for bleeding treatment (average dose to treat a bleed, number of injections and IU/kg per bleed) during both the main phase of 6 months and the trial period of 24 months

This endpoint will be summarised and listed. The presentations will be made by age groups, type of regimen, trial phase and total.

- Consumption of turoctocog alfa during prophylaxis treatment (average prophylaxis dose, number of injections and IU/kg per month and per year) per patient during both the main of 6 months and the trial period of 24 months

This endpoint will be summarised and listed. The presentation will be made for the preventative regimen by trial phase, age groups and total.

- Total consumption of turoctocog alfa (IU/kg per month and per year) per patient during both the main phase of 6 months and the trial period of 24 months. This endpoint will be summarised and listed. The presentation will be made by type of regimen, trial phase, age groups and total

- Surgery-related endpoints where applicable:

– Haemostatic effect evaluated on the four-point scale (excellent, good, moderate and none) and assessed by the investigator/surgeon at 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

Surgery-related endpoints will be summarised by trial phase and listed.

Safety endpoints

- Incidence rate of inhibitory antibodies against factor VIII (≥0.6 BU) during both the main phase of 6 months and the trial period of 24 months

The incidence rate of inhibitors (≥0.6 BU) represented as the percentage of patients developing inhibitors will be calculated 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 incidence rate the numerator will include all patients with inhibitors while the denominator will include all patients in the trial exposed to turoctocog alfa.

FVIII activity (trough) at baseline will be compared graphically between patients with and without inhibitors. HLA genotype will be cross tabulated against the presence of inhibitors

- Frequency of Adverse Events (AEs) and serious adverse events (SAEs) reported during both the main phase of 6 months and the trial period of 24 months. AEs and SAEs reported during the study will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity will also be made. The summary tables will be made by patient with and without inhibitors (<0.6 BU), trial phase, age groups, type of regimen and total.

Furthermore, listings will be provided displaying all AEs and SAEs reported during the study including pertinent clinical information. For patients exposed to both vial strengths the strongest causality will be used in summary tables. In listings both causalities will be displayed for relevant events in these patients.

- Adverse Events/Serious Adverse Events occurred 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

AEs and SAEs at the day of surgery (Day 1) and during the post-operative period Days 2-7 will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity will also be made.

Pharmacokinetic endpoints

- PK endpoints after a single dose of turoctocog alfa:
  - Incremental recovery of FVIII
  - Area under the curve ($AUC_{0\text{-}inf}$)
  - Half-life ($t_{½}$)
  - Clearance (CL)
  - Highest measured FVIII activity in the profile (C_{max})

The PK endpoints will be presented by the mean, standard deviation, minimum and maximum value, the geometric mean and 95% confidence interval for the geometric mean.

Interim reporting

The main CTR will be conducted when at least 60 patients have completed the main phase of the trial (visit 8) and this data is available, including the PK data. The report will also include the full PK evaluation. An updated CTR will be written when all patients have completed the extension phase of the trial. The updated CTR will present separately the main and extension phase data and also the combined main and extension phase of the trial.

Patient reported outcomes

The main PRO endpoints will be total scores from each type of the questionnaires. Changes to scores over time of the main endpoints will be explored and presented graphically from:

- Baseline at visit 2 in the main phase until end of trial in the main phase (visit 8)
- Visit 11 until end of trial in the extension trial

Evaluation of PRO data will be done alone based on descriptive statistics, i.e. summary tables, listings and figures.

3 Changes to the statistical analyses planned in the protocol

There are no changes to the planned analyses described in the protocol.

4 References

No references.