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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LFG316

Study CLFG316X2201 / NCT02534909

An open-label proof of concept study to assess the efficacy, safety and pharmacokinetics of LFG316, an anti-C5 monoclonal antibody in patients with paroxysmal nocturnal hemoglobinuria (PNH)

RAP Module 3: Detailed Statistical Methodology

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List of tables

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1 Introduction to RAP documentation

1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"CLFG316X2201".**

Module 3 (M3) provides the description of the statistical methodology used to analyze the data, **Module 7** (M7) details the presentation of the data, including shells of summary tables, figures and listings, and **Module 8 (**M8) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Changes to RAP documentation (M3)

Refer to corresponding guidances and NIBR RAP Addendum template for detailed information on the requirements of documenting changes to RAP documentation.

For the statistical methodology (M3), any major changes to the statistical methodology should be reflected in the RAP M3 documentation via version control (M3 amendment) (new document version to be approved by the trial team as the original module).

Such major changes could include (but are not limited to):

- change in statistical methodology
- substantial change in (derivation of) main endpoint
- substantial change in study design (e.g. protocol amendment introducing new multiple-dose cohorts in a so far single-dose trial)

Such changes may also require a protocol amendment to ensure consistency. In addition they need to be mentioned (high-level) in the CSR (section for changes to planned analysis).

Minor changes to the RAP M3 documentation can be captured e.g. by a study note to file / note in RAP Addendum or within the CSR itself. Minor changes include, but are not limited to, changes related to exploratory endpoints, addition of further exploratory analyses, changes to the extended scope of interim analyses. Corrections of typographical errors or modification of spelling (from English to American, for example) do not need to be incorporated into the RAP M3 documentation.

Analyses and outputs related to additional exploratory ad-hoc requests used for reporting are regarded minor changes and should be documented in the RAP addendum (no RAP amendment necessary).

2 Study objectives and design

2.1 Study objectives

2.1.1 Primary objective

- To assess the effect of LFG316 on the reduction of intravascular hemolysis in PNH patients

2.1.2 Secondary objective

- To assess the tolerability and pharmacokinetics of LFG316 in patients with PNH

2.1.3 Exploratory objectives

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2.2 Study design and treatment

This is an open-label, non-controlled study in patients with PNH. Approximately 10 patients will be enrolled in the study. Commercially Confidential Information

The study drug will be administered via i.v. infusion at the dose level of 20 mg/kg every 14 days. Patients participating in study will have an option to either complete period 3 Follow up and Study Completion evaluation or continue in study period 4 that is pre-requisite to join the long-term extension study CLNP023C12001B, that is separate to this study protocol. Patients who are potentially eligible and willing to participate in the LNP023 long-term extension study will join period 4, where treatment will be converted from LFG316 to LNP023 200 mg b.i.d.

The study will consist of a 60-day screening period to assess eligibility and conduct vaccinations if required (for all patients not previously vaccinated at least 2 weeks prior to first dosing or if prior vaccination cannot be confirmed). An extensive screening window (up to 60 days) is planned in order to comply with local vaccination requirements, if available and deemed necessary at the investigator's discretion. Safety evaluation assessments requiring blood and urine samplings, pregnancy test, pulmonary function test, ECG, patient reported outcomes, and assessment of number of blood transfusions should be performed no longer than 4 weeks prior to the planned dosing day. Subjects who meet the eligibility criteria at screening will be admitted to baseline (Day 1) evaluations. The patients will enter treatment period 1, and will receive infusions of LFG316 every 14 days, days 1, 15 and 29 (3 administrations).

At the end of period 1, efficacy on hemolytic activity by serum LDH will be assessed. All patients will then be allowed to enter the optional treatment period 2, and will receive infusions of LFG316 every 14 days, and undergo the efficacy, PK, CCI and safety assessments for additional 48 weeks.

Following the 48-week treatment period 2, LFG316-responsive patients (assessed based on investigator's judgment) will be allowed to enter an additional third extension period of up to 260 weeks (extension period 3).

The LFG316 treatment for all patients will be completed by end of 2021 regardless of each individual treatment period.

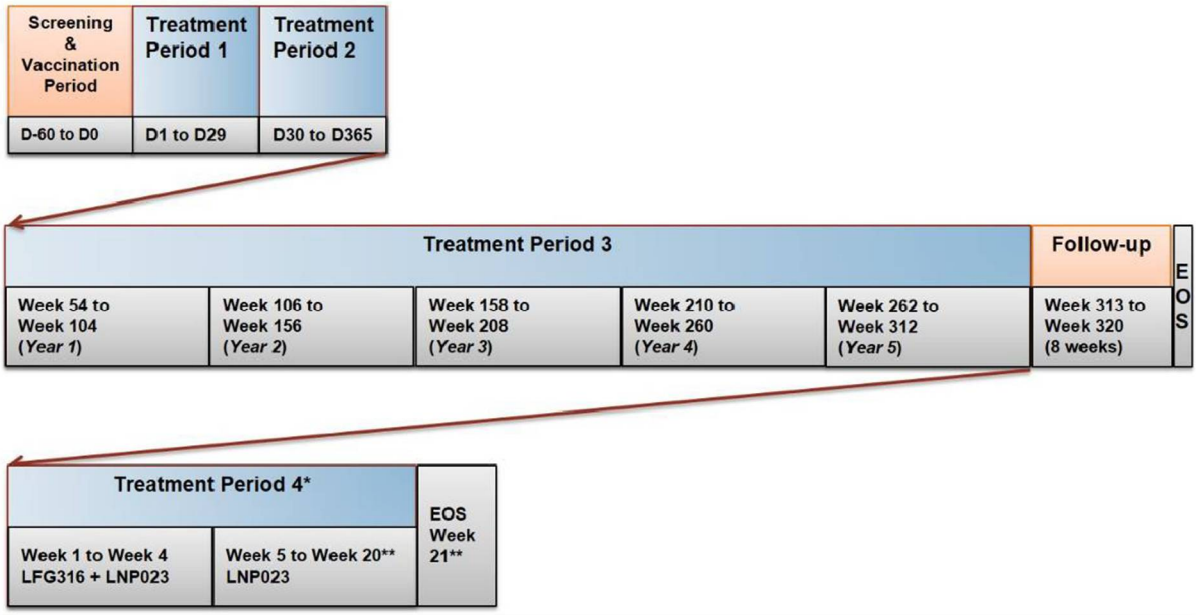
Patients participating in extension period 3 will roll over from the last dosing visit of period 2 to the first visit (which includes drug administration) of period 3. The same dosing interval applied in Period 1 and 2 will be applied between the last dosing visit of Period 2 and the first visit of Period 3.

Period 4 can be initiated as directed by Sponsor and will last approximately 21 weeks. During the first 4 weeks patients will continue to receive LFG316 20 mg/kg every two weeks (total of two administrations) in addition to oral administration of LNP023 200 mg b.i.d. After 4 weeks, patients will discontinue LFG316 and will proceed with LNP023 200 mg b.i.d. monotherapy for approximately 16 weeks (+/- 28 days). Patients who participate in period 4 can join the long-term extension study CLNP023C12001B as soon as their eligibility is confirmed and study CLNP023C12001B is open to receive patients. There should be no LNP023 treatment gap between the studies. Please refer to Section 7.1 of the protocol for guidance regarding safety monitoring and LNP023 down-titration in case of LNP023 treatment discontinuation.

For patients not participating in the period 4, the extension period 3 will be followed by a Study Completion evaluation approximately 8 weeks after the last drug administration. Patients who discontinue treatment prematurely during any of the study periods will be followed for 8 weeks after discontinuation, and will similarly undergo a study completion visit. The 8 weeks follow- up period will start the day after the last drug administration (both for patients completing treatment and patients prematurely discontinuing), and will comprise one visit after approximately 4 weeks, and a study completion visit after approximately 8 weeks from the last drug administration. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis) and adverse event monitoring.

Patients participating in period 4, will complete their Study Completion evaluation approximately one week after last LNP023 treatment administered as a part of this study.

Figure 2-1 Study design



*Period 4 is applicable only for the patients who are potentially eligible and wish to participate in the long-term extension study CLNP023C12001B

**+/-28 days

3 First interpretable results (FIR)

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4 Interim analyses

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5 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the planned treatment the treatment actually received will be used for the analysis. The study has four parts, the safety and efficacy analysis will be presented for period 1, period 2 and period 3 combined, and separately for period 4 unless otherwise stated below/in the output shell.

All subjects that received study drug will be included in the safety analysis set.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

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6 Statistical methods for Pharmacokinetic (PK) parameters

6.1.1 Variables

The following pharmacokinetic parameters will be determined (if feasible) using non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): AUC(0-tlast), AUC(0-t), Cmax, tmax, Cmax/D, AUC/D. The linear trapezoidal rule will be used for AUC calculation. For LNP023 only pre-dose and 2 hour concentrations will be determined in period 4.

6.1.2 Descriptive analyses

Total LFG316 concentration data will be listed by patient, and visit/sampling time point while pharmacokinetic parameters will be listed by patient. Commercially Confidential Information

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Commercially Confidential Information

6.1.3 Model checking procedures

Not applicable.

6.1.4 Graphical presentation of results

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Overlaying individual plasma concentration-time profiles will also be generated.

6.1.5 Pharmacokinetic / pharmacodynamic interactions

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7 Statistical methods for Pharmacodynamic (PD) parameters

7.1 Primary objective

7.1.1 Variables

The primary efficacy variable is response rate where a patient will be considered a responder if the percentage reduction from baseline in serum LDH is at least 60% at any time up to and including week 4 for that patient.

The primary efficacy variable for assessing the effect of LFG316 over the entire treatment period is the actual serum LDH value measured at multiple time points during the study.

7.1.2 Descriptive analyses

Unless stated otherwise, summary statistics for PD variables will include sample size (N), mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information

For serum LDH baseline will be the average of all pre-dose measurements.

7.1.3 Statistical model, assumptions and hypotheses

Proof of concept will be based on LDH levels during the first four weeks. A positive sign of efficacy is when:

- The estimated median response rate is at least 50%

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7.1.4 Graphical presentation of results

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7.1.5 Handling of missing values/censoring/discontinuations

The study aims to replace patients who discontinue before the end of period 1 for reasons other than safety and the primary responder analysis will be based on period 1 completers only, in a per protocol fashion. However further analyses will be performed to assess the effect of including patients with incomplete data on the conclusions drawn from the primary analysis. Lack of efficacy will not be considered a missing value. Even if treatment is discontinued, LDH values should still be assessed in the eight-week follow-up period.

7.1.6 Supportive analyses

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Longitudinal analysis will firstly include individual and average graphical presentations over time incorporating any historical LDH data collected so as to better put post-treatment changes in context. If deemed potentially useful, longitudinal statistical modelling will be used to look at changes within subjects as well as across subjects.

Additionally serum LDH at each timepoint will also be summarized in terms of the number and percentage of patients achieving a reduction in LDH to within the normal limits.

7.2 Secondary objectives

The analysis of the two secondary endpoints of standard safety monitoring with increased vigilance for infections and measurement of serum concentrations of LFG316 are covered in Section 8.1.2 (adverse events) and Section 6 (pharmacokinetics) respectively. There will be no adjustment for multiplicity over the three main analyses of efficacy (primary), safety and PK (both secondary).

7.3 Exploratory objectives

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8 Statistical methods for safety and tolerability data

8.1.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics and baseline characteristics will be listed, summarized and plotted.

8.1.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by ethnicity, C5 variant status and patient. Summary statistics will be provided.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by ethnicity and C5 variant status and summarized.

Treatment

Data for study drug administration, and concomitant therapies will be listed by ethnicity and C5 variant status and summarized.

Vital signs

All vital signs data will be listed by ethnicity, C5 variant status and patient and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided over visit/time.

ECG evaluations

All ECG data will be listed by ethnicity, C5 variant status and patient and visit/time, and abnormalities will be flagged. Summary statistics will be provided over visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by ethnicity, C5 variant status and patient and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a patient with any abnormal values. Summary statistics will be provided over visit/time.

Adverse events

All information obtained on adverse events will be listed by ethnicity and C5 variant status and displayed summarized as per the secondary objective.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

As this study has four treatment periods an adverse event starting in one period and continuing into another is counted only in the first period grouping in which it occurs. A patient with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment period. There will be three types of summaries of AEs, starting in periods 1 to 3, starting in period 4, and overall throughout the study.

Pregnancy test

All pregnancy test results for women will be listed by ethnicity, C5 variant status, patient and visit.

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Other safety evaluations

All other safety evaluations e.g. physical examination will be listed by ethnicity, C5 variant status, patient and visit.

Meningococcal vaccination data will be listed by ethnicity, C5 variant status and patient.

8.1.3 Graphical presentation of results

Plots of individual data across time to visualize trends in longitudinal safety data (vitals, ECG, lab parameters) will be created similarly to those proposed for plots of individual LDH data.

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