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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LFG316

CLFG316X2202

A randomized, open label, controlled, multiple dose study to evaluate the clinical efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of LFG316 in patients with transplant associated microangiopathy after hematopoietic precursor cell transplantation

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The SAP (Statistical Analysis Plan) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial *"CLFG316X2202"*.

The SAP describes the implementation of the statistical analysis planned following study termination which is reduced in scope compared to the original protocol. Objectives and other text remain as in the protocol.

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v05 (incorporating Amendment 05) dated 16 AUG 2016.

1.3 Study objectives

1.3.1 Primary Objective

To assess the hematological response rate in patients with TAM receiving LFG316 compared to standard of care (SoC).

1.3.2 Secondary Objectives

- To assess the safety and tolerability of LFG316 in patients with TAM
- To describe the pharmacokinetics of total LFG316
- To evaluate non-relapse mortality in TAM patients treated with LFG316 as compared to patients on SoC
- To assess complete response rate at 17 weeks in TAM patients treated with LFG316 compared to patients receiving standard of care

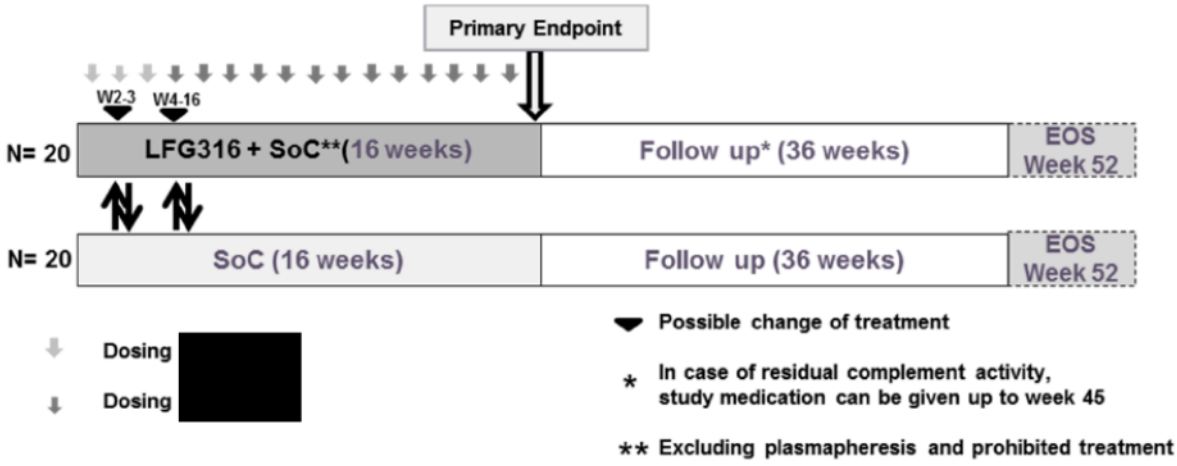
1.3.3 Exploratory Objectives

1.4 Study design and treatment

This is a randomized, SoC-controlled, open-label, multi-center study in patients with TAM after hematopoietic precursor cell transplantation (HPCT) from a related or unrelated donor for malignant and nonmalignant disease after myeloablative or non-myeloablative conditioning.

The study will consist of up to 28 days of screening period, 16 weeks treatment period that can be extended to 45 weeks (in case of ongoing symptoms of TAM), 36 weeks follow up, and end of study visit (EOS) at week 52 (Figure 1-1). Duration of follow up will depend on duration of treatment. Patients who are treated for more than 41 weeks will proceed directly to EOS visit.

Figure 1-1



Approximately 40 patients were to be randomized to receive SoC alone or LFG316 plus SoC (excluding plasmapheresis and prohibited treatment). Patients would be included in the study if they have diagnosis of TAM and poor prognostic markers. Corporate Confidential Information

Patients randomized to LFG316 received [redacted] on study days 1, 8, and 15, followed by weekly doses of [redacted] for remaining treatment duration of total 16 weeks.

[redacted] [redacted]

Patients showing worsening disease (definition below) after two weeks of treatment (day 15) or later until visit at week 3, will be considered failures and could be switched to receive the alternative treatment (SoC or LFG316).

- increasing schistocyte count (+50% or more as compared to baseline),

- and/or increase in erythrocyte or platelet transfusion need (increase of 50% or more in number of transfusions during 2 weeks prior to study visit as compared to number of transfusions needed two weeks before treatment initiation),
- and/or increasing proteinuria (+50% or more as compared to baseline)

Patients showing no response (definition below) between visit at week 4 (day 29) and visit at week 16 were considered to be treatment failures and could be switched to the other treatment arm. Switching the treatment could occur immediately after data is available.

- no decrease in schistocyte count (as compared to baseline)
- and/or continued erythrocyte or platelet transfusion need (less than 25% improvement in number of transfusions during 2 weeks prior to study visit as compared to number of transfusions needed two weeks before treatment initiation)
- and/or non-responding proteinuria (less than 25% reduction in proteinuria compared to baseline)

Patients can only switch study treatment arms once.

2 First interpretable results (FIR)

First interpretable results (FIR) will not be provided for this trial.

3 Interim analyses

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4 Statistical methods: Analysis sets

For patients for which the actual first treatment received does not match the randomized treatment then the treatment actually first received will be used for grouping by treatments received.

All patients who receive study drug or SoC and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

The PK analysis set will include all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received study drug or SoC and who experienced no protocol deviations with relevant impact on PK data.

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Patients who switch treatments according to the protocol defined rules will be indicated as having received two treatments in the listings, and data from the period after switching will in general be summarized separately if required. Thus in general there may be up to 6 treatment groups in the summary tables:

- LFG316
- SoC
- LFG316 then SoC (in case of switch in treatment)
- SoC then LFG316 (in case of switch in treatment)
- All LFG316 first
- All SoC first

with the first four, mutually exclusive, used in listings, 'by treatment'.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Patients are excluded from all *(safety)* analysis in case of these PDs:		Exclude patient completely from all ***(safety)*** analysis sets
I01	*ICF not obtained*	
Patients are excluded from PK analysis in case of these Protocol Deviations:		Exclude patient from PK analysis set
E11	*Patients previously treated with eculizumab for TAM*	*Unless sufficiently long ago to not affect PK.*
Patients are excluded from PD analysis in case of these Protocol Deviations:		Exclude patient from PD analysis set
E01	*Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or even longer if required by local regulations. Investigational drug does not include off label use of drugs. Non-marketed drugs used in expanded access programs that are used as local standard of care may be acceptable but have to be agreed with the sponsor on a case by case basis.*	

Category Deviation code	Text description of deviation	Data exclusion
E11	*Patients previously treated with eculizumab for TAM*	*Unless sufficiently long ago to not affect PD.*

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for pharmacokinetic (PK) parameters

5.1 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.

5.2 Descriptive analyses

Total LFG316 serum concentration data will be listed by treatment (excluding patients receiving SoC alone), patient, and visit/sampling time point. Descriptive summary statistics will be provided by drug treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

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. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be listed by treatment and patient.

5.2.1 Graphical presentation of results

Arithmetic mean (SD) and geometric mean (95% CI) serum concentration data will be plotted across time up to a timepoint where there is sufficient data for calculation of means

Overlaying individual serum concentration-time profiles will be generated along with concentration versus time profiles for individual patients.

6 Statistical methods for Efficacy and Pharmacodynamic (PD) parameters

Summary of key estimands for efficacy

Efficacy estimands are defined for this trial to address the efficacy objectives of the trial and to provide supportive evidence for those objectives. These estimands are defined in detail in the subsequent sections and are summarized in Table 6-1. Although they will be calculated for each patient and treatment they will not be analysed, only listed. The outputs for safety, tolerability, PK, PD and PK/PD relationships are described in other sections of this SAP.

Table 6-1 Summary of key protocol estimands

	Estimand	Variable estimand is based on	Section
P1	Primary	Hematological response at 17 weeks on initially randomized treatment	6.1.1
S1	Secondary - non-relapse mortality	Non-relapse death or switching up to 17 weeks	6.2.1
S2	Secondary - complete response	Complete response at 17 weeks on initially randomized treatment	6.3.1
S3	Secondary for overall survival	All cause death over one year	6.4.1

6.1 Primary estimand

The primary estimand addresses the primary objective:

- To assess the hematological response rate in patients with transplant associated microangiopathy (TAM) receiving LFG316 plus standard of care (SoC) (excluding prohibited treatment) against SoC only.

This estimand addresses the scientific question of whether treatment with LFG316 only increases hematological response rate compared to treatment with SoC only. It is assumed that treatment switching implies that the randomized treatment has failed and that the patient is deteriorating.

6.1.1 Definition of primary estimand: Hematological response (P1)

- Population: TAM patients with high risk of death as per the inclusion/exclusion criteria
- Variable: Hematological response at 17 weeks
- Measure of intervention effect: Difference between response rates for LFG316 versus SoC in the absence of a switch to alternative treatment (considered failure)

A patient is considered to have hematological response at a given timepoint if both of the following criteria are met:

1. Schistocytes <2/microscopic high power field (HPF).
2. Transfusion independent (no need for TAM-related transfusions [platelets and erythrocytes])

Patients meeting the definition of hematological response at week 17 whilst still remaining on their randomized treatment are considered to be responders.

Therefore patients who switch treatments before week 17 are considered to be non-responders.

Patients who do not meet the responder criteria and have missing data are also considered to be non-responders.

6.2 Secondary estimands for non-relapse mortality

This secondary estimand addresses the following secondary objective:

- To evaluate non-relapse-related mortality (any death not considered to be related to a relapse of underlying disease) in TAM patients treated with LFG316 as compared to patients on SoC

6.2.1 Definition of secondary estimand for non-relapse mortality:

- Population: TAM patients with high risk of death as per the inclusion/exclusion criteria
- Variable: Time to non-relapse-related mortality up to 17 weeks on initially randomized treatment.

6.3 Secondary estimand for complete response:

6.3.1 Definition of secondary estimand for complete response:

- Population: TAM patients with high risk of death as per the inclusion/exclusion criteria
- Variable: Complete response at 17 weeks

Complete response is defined as hematological response and no proteinuria as determined by proteinuria <30 mg/dL and eGFR doubled or not less than 0.85 x lower limit of normal

6.4 Secondary estimand for overall survival

6.4.1 Definition of secondary estimand for overall survival (S3):

- Population: TAM patients with high risk of death as per the inclusion/exclusion criteria
- Variable: Time to all cause death up to 1 year on initially randomized treatment.

6.5 Other exploratory secondary variables

The following variables will also be listed and plotted over time to support the assessment of efficacy as they are components of hematological response (first three) and of complete response (all five).

- Schistocytes
- Platelets
- Erythrocytes
- Proteinuria
- eGFR

6.6 Exploratory objectives

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6.6.1 Descriptive analyses

Use in the text below of "treatment group" refers to the initially assigned treatment but, if necessary or useful, allows for use of the four treatment sequences that include switching, as described in Section 4.

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Overlaying plots will be provided over time on study per patient with a colour change to indicate any treatment switch.

7 Statistical methods for safety and tolerability data

7.1.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as patient demographics, baseline characteristics, and treatment information are the relevant variables.

7.1.2 Descriptive analyses

Use in the text below of "treatment group" refers to the initially assigned treatment but, if necessary or useful, allows for use of the four treatment sequences that include switching, as described in Section 4.

Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and patient.

Treatment

Data for study drug administration and concomitant therapies will be listed by treatment group and patient.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged.

ECG evaluations

All ECG data will be listed by treatment group, patient and visit/time; abnormalities will be flagged.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, 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. Overlaying plots will be provided over time on study per patient with a colour change to indicate any treatment switch.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment. Where the duration of an AE spans a switching of treatment, it will only be counted for the treatment in which it initially occurred.

Other safety evaluations

Lansky/Karnofsky scores

Lansky/Karnofsky scores will be listed by treatment group, patient and visit/time along with changes from baseline. Summary statistics (frequency counts) will be provided by treatment group and visit/time. Overlaying plots will be provided over time on study per patient with a colour change to indicate any treatment switch.

ADAMST13

All ADAMST13 results will be listed by patient and visit/time.

Transfusions

Information on transfusions will be listed by patient and visit/time.

8 Statistical methods for Biomarker data

Handling of LLOQ and ULOQ

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two limits: Lower limit of quantification (LLOQ) and Upper limit of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

To ensure that biomarkers only have numerical values, censored values will be imputed as follows

- Values below the LLOQ are replaced by LLOQ/2.
- Values above the ULOQ are replaced by ULOQ.

Imputed values are used for summary statistics, inferential analyses and plots (with a special symbol). Values below LLOQ and values above ULOQ are shown as such in the listings. In the summary table, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

If the proportion of imputed data is more than 20% for any treatment group at any time point, a footnote is added to the summary statistics table stating that the proportion of values outside

the limits of quantification is more than 20% for some treatment groups at some time points and that in such cases summary statistics may be heavily biased.

If the proportion of imputed data for a given biomarker, across all treatment groups and time points, is more than 50%, no summary statistics are provided and the data are only listed.