NOVARTIS

Clinical Development

LFG316

CLFG316A2204

A randomized, active-controlled, open-label, multiple-dose, proof-of concept study of intravitreal LFG316 in patients with active non-infectious intermediate-, posterior-, or panuveitis requiring systemic immunosuppressive therapy

TSc RAP Module 3: Detailed Statistical Methodology

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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 ***"CLFG316A2204".***

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 occurring before database lock to the statistical methodology should be reflected in the RAP M3 documentation via version control (new document version to be approved by the trial team as the original module.

Major changes include, but are not limited to, changes in protocol that affect study design and statistical methodology.

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, change in statistical model. 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.

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2 Study objectives and design

2.1 Study objectives

2.1.1 Primary objective(s)

- To assess the effect of intravitreal LFG316 Corporate Confidential Information on the protocol-defined, Day 85 response rate in the study eye of patients who meet the inclusion criteria.

The above objective applies to the study eye only.

2.2.2 Secondary objective(s)

- To assess the safety and tolerability of intravitreal LFG316 Corporate Confidential Information in patients who meet the inclusion criteria. Corporate Confidential Information

- To assess the effect of intravitreal LFG316 Corporate Confidential Information on vitreous haze as measured on the Nussenblatt scale, ETDRS visual acuity, macular edema, presence or absence of chorioretinal lesions, and anterior chamber cells score in eyes with active NIU, in at least one eye, requiring intensification of systemic immunosuppressive therapy, and compared between Baseline and Days 2, 8, 15, 29, 43, 57, and 85. Corporate Confidential Information

- To evaluate the serum concentrations of total LFG316 and total C5 during the course of the study.

The above objectives apply to the study eye only.

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- Corporate Confidential Information

2.2 Study design and treatment

This is a multi-center, randomized, active-controlled, open-label, proof-of-concept study. The study will be carried out at ocular inflammation specialty clinics in the US and UK. Approximately 24 patients with active NIU in at least one eye, requiring intensification of systemic immunosuppressive therapy will be enrolled and randomized in a 2:1 ratio to receive:

- LFG316 Corporate Confidential Information administered intravitreally (n=16)

Only one eye (designated as the study eye) will be dosed per patient. If either eye would qualify as the study eye, one eye will be selected as the study eye during the screening period based on the following criteria:

- Higher vitreous haze score
- If not determined by vitreous haze score, then by lower visual acuity
- If not determined by visual acuity, investigator preference.

Throughout the study, the fellow eye (i.e., non-study eye) should be examined and treated at the investigator's discretion. Efficacy assessments (visual acuity and eye exams) will be conducted by a clinician masked to treatment condition.

For patients randomized to LFG316, three successive doses will be administered on Days 1 , 29, and 57. First dose (Day 1) may occur within 0-14 days of Screening. After first dose, safety, efficacy, and PK assessments will occur at 6 scheduled visits over a 12-week period. Corporate Confidential Information

However, patients can attend for unscheduled visits as needed and as determined by the investigator. Patients will be monitored for safety and ocular assessments obtained throughout treatment and follow-up periods. Patient eligibility will be assessed as outlined in Figure 2-1 below. An overall study scheme is shown in Figure 2-2 below.

Ocular assessments include:

- Best corrected visual acuity (ETDRS)
- Intraocular pressure (IOP)
- Slit lamp biomicroscopy
- Dilated ophthalmoscopy
- Standardized vitreous haze score (Nussenblatt et al 1985)
- Color fundus photos*
- Spectral domain optical coherence tomography (sd-OCT)*
- Anterior chamber cells
- Chorioretinal lesions (absent/present per PI investigator)
- Vasculitis (absent or present per Investigator)

- Presence of chorioretinal infiltrates due to uveitis
- Macular edema due to uveitis (absent or present per Investigator)

*: sd-OCT images and color fundus photos are only checked for quality and archived.

Figure 2-2 Overall study scheme

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	Screening Period	Treament Period						
Visit	1	2	3	4	5	6	7	8
Day	-14 to -1	1	2	8	15	29	43	57
LFG316 5 mg intravitreal administration (n=16)		X				X		X

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For assessment details, refer to the assessment schedule in protocol.

3 First interpretable results (FIR)

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4 Interim analyses

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5 Statistical methods: Analysis sets

Patients will be analyzed and reported based on the treatment received.

All patients who received study drug Corporate Confidential Information will be included in the safety analysis set.

All patients in the safety analysis set with evaluable PK data and with no major protocol deviations that have an impact on PK data will be included in the PK analysis set.

All patients in the safety analysis set with evaluable PD data (Total C5) with no major protocol deviations that have an impact on PD data will be included in the PD analysis set.

All patients in the safety analysis set who receive any study treatment Corporate Confidential Information with evaluable efficacy data for at least one efficacy endpoint/s (ocular assessments) and with no major protocol deviations that have an impact on efficacy data will be included in the first efficacy (Efficacy 1) analysis set. For the Efficacy 1 analysis set, any patient who discontinues after receiving at least one dose of study drug will be included up to the time of discontinuation or until the time they received rescue medication.

All patients in the safety analysis set who receive any study treatment Corporate Confidential Information with evaluable primary efficacy endpoint (response rate and remission rate on Day 85) and with no major protocol deviations that have an impact on the primary efficacy endpoint will be included in the second efficacy (Efficacy 2) analysis set.

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Table 5-2 Protocol deviation codes and analysis sets (included as reference)

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all *(safety)* analysis in case of these PDs:		Exclude subject completely from all ***(safety)*** analysis sets
I01	*ICF not obtained*	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
I01	*ICF not obtained*	Yes
E07	*Deviation from exclusion criterion 7 (V05)*	Yes
E11	*Deviation from exclusion criterion 11 11(V05)*	Yes
Subjects are excluded from Efficacy 1 analysis in case of these PDs:		Exclude subject from Efficacy 1 analysis set
I01	*ICF not obtained*	Yes

Category Deviation code	Text description of deviation	Data exclusion
E07	*Deviation from exclusion criterion 7 (V05)*	Yes
E11	*Deviation from exclusion criterion 11 11(V05)*	Yes
Subjects are excluded from Efficacy 2 analysis in case of these PDs:		Exclude subject from Efficacy 2 analysis set
I01	*ICF not obtained*	Yes
I02	*Deviation from inclusion criterion 2 (V05)*	Yes
I03	*Deviation from inclusion criterion 3 (V05)*	Yes
I04	*Deviation from inclusion criterion 4 (V05)*	Yes
I10	*Deviation from inclusion criterion 4 (V03-04) and 5 (V05)*	Yes
E01	*Deviation from exclusion criterion 1 (V05)*	Yes
E02	*Deviation from exclusion criterion 2 (V05)*	Yes
E03	*Deviation from exclusion criterion 3 (V05)*	Yes
E04	*Deviation from exclusion criterion 4 (V05)*	Yes
E05	*Deviation from exclusion criterion 5 (V05)*	Yes
E06	*Deviation from exclusion criterion 6 (V05)*	Yes
E07	*Deviation from exclusion criterion 7 (V05)*	Yes
E08	*Deviation from exclusion criterion 8 (V05)*	Yes
E09	*Deviation from exclusion criterion 9 (V05)*	Yes
E11	*Deviation from exclusion criterion 11(V05)*	Yes
E12	*Deviation from exclusion criterion 12 (V05)*	Yes
E13	*Deviation from exclusion criterion 13 (V05)*	Yes
E14	*Deviation from exclusion criterion 14 (V05)*	Yes
E15	*Deviation from exclusion criterion 15 (V05)*	Yes
E16	*Deviation from exclusion criterion 16 (V05)*	Yes
E17	*Deviation from exclusion criterion 17 (V05)*	Yes
E20	*Deviation from exclusion criterion 20 (V05)*	Yes
E21	*Deviation from exclusion criterion 21 (V05)*	Yes
E22	*Deviation from exclusion criterion 22 (V05)*	Yes
E24	*Deviation from exclusion criterion 24 (V05)*	Yes
E25	*Deviation from exclusion criterion 25 (V05)*	Yes
M01	*Use of prohibited medication during the study*	Yes

6 Statistical methods for Pharmacokinetic (PK) parameters

Summary statistics for total LFG316 may be analyzed on the PK analysis set.

Summary statistics of total LFG316 concentrations may be provided by visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and the frequency (n, %) of concentrations below the LLOQ. A geometric mean will not be reported if the dataset includes zero values.

Total LFG316 concentrations may be expressed as μg/mL. All concentrations below the limit of quantification (LLOQ) or missing data may be labeled as such in the concentration data listings. Concentrations below the LLOQ may be treated as zero in summary statistics for concentration data only.

Arithmetic mean (SD) concentration-time plots as well as overlaying individual concentration-time profiles may be provided.

7 Statistical methods for Efficacy and Pharmacodynamic (PD) parameters

7.1 Primary endpoint

The primary endpoints are the response rate (proportion of patients that respond in the study eye) and the remission rate (complete response) at Day 85.

A response will be defined by any one of the following criteria in the study eye:

- An improvement of 2 or more steps in vitreous haze, relative to baseline. For the purpose of "step" calculation, 0.5 shall count as one of the increments. Thus, improvement from a score of 2 to 0.5 or from 1 to 0 would constitute a 2-step improvement or,
- An improvement of 10 or more letters in visual acuity, relative to baseline or,
- An improvement of 2 or more steps in anterior chamber cells, relative to baseline
- Resolution of chorioretinal lesions as determined by the investigator

Remission (complete response) will be defined as

- any patient who has a vitreous haze score of 0 or 0.5 in the study eye, who has an anterior chamber cell score of 0 and no chorioretinal lesions in the study eye and is off all immune modulatory therapy (systemic, corticosteroids and topical), without any worsening of uveitis during the trial.

The analysis of response rate and remission rate at Day 85 will be carried out on the efficacy analysis sets (Efficacy 1 and Efficacy 2) , with the analysis on the Efficacy 1 analysis set being of primary interest.

The baseline value will be defined as Day 1 pre-dose value, or the screening values if the Day 1 pre-dose value does not exist.

The response rates and the 90% exact (Clopper-Pearson) confidence intervals in the LFG316 group Corporate Confidential Information will be reported. Corporate Confidential Information

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The response rates at other time points (Days 2, 8, 15, 29, 43, 57) will be reported and analyzed similarly.

Proportion of responders (90% CI) will be graphically presented at each time point, by treatment group using bar charts.

The same analysis will be performed for remission rates as well.

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At Day 85, the null hypothesis that the response rate of the LFG316 arm (p_{LFG}) is less than Corporate Confidential Information (60%): H_0: $p_{LFG} \leq 0.60$, will be tested against the alternative hypothesis: H_1: $p_{LFG} > 0.60$. The exact (binomial) p-value will be reported. Note that no decision should be made based on this p-value.

No multiplicity adjustments are required for the primary analysis.

Handling of missing values/censoring/discontinuations

If a subject had missing data for any of the parameters needed to derive the responder status, a subject was:

- Considered as a responder if the subject met any of the responder criteria
- Considered as missing if all the parameters for the responder criteria were missing
- Considered as a non-responder, if the subject had at least one non-missing parameter needed for the responder criteria and had met no criteria to be considered a responder.

If a subject had missing data for any of the parameters needed to derive the remission status, a subject was:

- Considered as a remission if the subject met all of the remission criteria.
- Considered as a non-remission, if the subject did not meet at least one of the remission criteria.
- Considered as missing, if the subject met all the available remission criteria but not all the remission criteria were available.

7.2 Secondary Efficacy and PD endpoints

7.2.1 Efficacy endpoints: Ocular assessments

All analyses in this section will be analyzed on the Efficacy 1 analysis set.

For vitreous haze score (VHS), the number and percentage of subjects will be listed by score (0, 0.5/Trace, 1+, 2+, 3+, 4+) for each visit/time and treatment group, separately for the study eye and the fellow eye. The number and percentage of subjects will also be listed by steps of improvement/worsening (change) from baseline in seven categories ("worsening of vitreous

haze score", "no change", and "1 – 5 steps of improvement"). The same analysis will be performed for anterior chamber cells score (ACCS) with the scores being 0, 0.5, 1, 2, 3, 4, and the category of improvement/worsening (change) from baseline being "worsening of anterior chamber cells", "no change", and "1 – 5 steps of improvement". Frequency tables and histograms for both of the original scores and steps of change will be provided for VHS and ACCS by eye (study and fellow), treatment group at each visit/time.

Visual acuity will be listed for each visit/time and treatment group, separately for the study eye and the fellow eye. Summary statistics will be provided for the raw and the change from baseline of best corrected visual acuity by visit/time and treatment group, separately for the study eye and fellow eye. Arithmetic mean (SE) will be plotted across time by treatment (overlaying) for study eyes and fellow eyes separately. Overlaying individual profiles will be plotted across time by treatment (separate) for study eyes and fellow eyes separately.

A longitudinal analysis of best corrected visual acuity will be performed for the study eye. Absolute change from baseline will be analyzed by a mixed model with repeated measurements. The independent variables will be treatment, time (categorical, i.e. visits until Day 85), and treatment-by-time interaction, with baseline and baseline-by-time interaction as covariates, and subject as a random effect. Within treatment arm estimates and 90% confidence interval will be reported. A time plot for least square means and 90% CI by treatment (overlaying) will be provided.

Proportion of patients with presence or absence of macular edema, chorioretinal lesions, will be tabulated using frequency tables, and graphically represented using bar charts, at each visit, by eye (separate).

Percentage of patients that respond per response criterion (for criterion involving central retinal thickness, only if applicable) will be reported in each treatment group.

A separate set of summary tables will be produced for those subjects who participate in the LFG316 treatment extension, if deemed necessary.

7.2.2 PD endpoint: Total C5 Concentrations

Total C5 will be analyzed on the PD analysis set. Summary statistics of total C5 concentrations will be provided by treatment and visit/time. Total C5 concentrations will be expressed as µg/mL. All concentrations below the limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics for concentration data only.

Arithmetic mean (SD) concentration-time plots as well as overlaying individual concentration-time profiles will be provided.

7.4 Handling of Missing values/censoring/discontinuations

Missing values will not be imputed, but treated as “missing at random” in the primary and secondary analyses.

8 Statistical methods for safety and tolerability data

All subjects in the safety analysis set will be included in the safety data analysis.

Subject demographics and other baseline characteristics

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

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

Adverse events

All information obtained on adverse events will be listed by treatment group and subject, separately for ocular and non-ocular adverse events. For ocular adverse events, the eye(s) involved (study/fellow/both eyes) will be reported in the listings. Time since start of IVT injection will be indicated in the listing.

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

Ocular adverse events will be tabulated and summarized separately for the study eye and for the fellow (non-study) eye. An adverse event reported in both eyes will be counted in both study and fellow eyes presentations.

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Concomitant medications / Significant non-drug therapies

All concomitant therapies will be listed by treatment group and subject per visit. For systemic steroids doses of the therapy needs to be captured.

Vital signs

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

ECG evaluations

All ECG data will be listed by treatment, subject and visit, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Standard clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit and abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Special clinical laboratory evaluations

Not applicable.

Ocular assessments

Results from ocular assessments can be used for primary safety analysis
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Ocular assessments will be listed by treatment group, and subject, with specification of the eye involved (study/fellow).

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Results of other ocular assessments (Slit lamp biomicroscopy, Dilated ophthalmoscopy, Color fundus photography and sd-OCT) will be listed and could be summarized if appropriate.

9 Statistical methods for Immunogenicity data

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