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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LKA651

CLKA651X2202
Clinical Trials.gov Identifier: NCT03927690

A randomized, active-controlled, patient and investigator-masked, multiple dose proof-of-concept study of intravitreal LKA651 in patients with diabetic macular edema

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLKA651X2202".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol for the final analysis, as well as the outputs planned for the interim analyses.

1.2 Study reference documentation

Final study protocol amendment (v05) is available at the time of finalization of the Statistical Analysis Plan.

1.3 Study objectives

1.3.1 Primary Objective(s)

Primary objective(s)	Endpoints related to primary objective(s)

• To evaluate the safety/tolerability of three q4w IVT doses of LKA651 alone or in combination with Lucentis® in patients with DME.	• Ocular and systemic AEs
	• Vital signs (blood pressure, heart rate) and ECG intervals.
	• Safety laboratory measures (including reticulocyte count)
	• Complete ophthalmic exam, including:
	  • Intraocular Pressure (IOP)
	  • BCVA
	  • Macular thickness by spectral domain optical coherence tomography (SD-OCT)
	  • FA

• To evaluate the efficacy, in reference to Lucentis® monotherapy, of three q4w IVT doses of LKA651 in treating DME when administered as monotherapy or in combination with Lucentis®.	• Best Corrected Visual Acuity (BCVA) as assessed by ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity charts at week 12. • Central subfield retinal thickness as measured by SD-OCT at week 12

1.3.2 Secondary Objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)

• To evaluate duration of effect of three q4w IVT doses of LKA651 in patients with DME.	• Time to retreatment with anti-VEGF (as determined by PI) after week 12 during an additional 12-week extension phase
• To evaluate the serum pharmacokinetic profile of total LKA651 and Lucentis® following three q4w IVT doses of LKA651 alone or in combination with Lucentis® in patients with DME.	• Serum levels of total LKA651 (Maximum concentration (Cmax) and Area under the curve $(AUC)_{0\text{-}28d}$ in monotherapy or in combination with Lucentis® after the first dose in a subset of patients with sufficient quantifiable serum samples to permit meaningful analysis. • Serum levels of ranibizumab (Cmax and $AUC_{0\text{-}28d}$) when administered in combination with LKA651 after the first dose in a subset of patients with sufficient quantifiable serum samples to permit meaningful analysis.

1.3.3 Exploratory Objective(s)

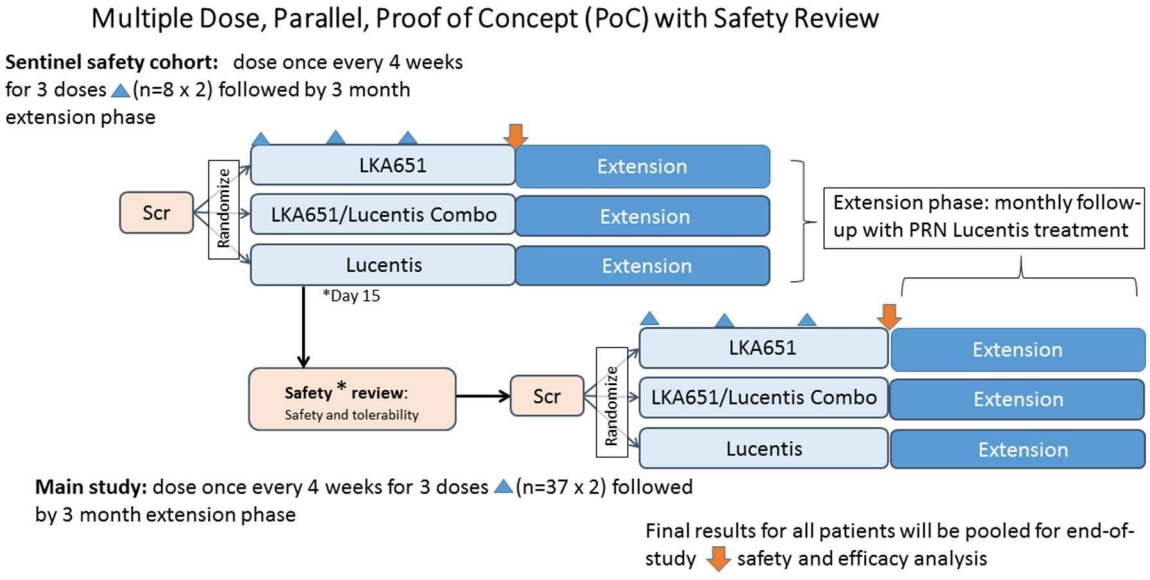
Exploratory objective(s)	Endpoints related to exploratory objective(s)

1.4 Study design and treatment

This study is a 3-arm, parallel group, randomized, patient and investigator-masked phase II trial in 90 patients with DME who are either treatment naïve or who have been treated with anti-VEGF therapy >90 days before baseline. The study will be first stratified in two Sentinel Safety cohorts (n=16; 8 in each geographical region). The Sentinel Safety patients will be randomized 6:1:1 to LKA651 plus Lucentis® (CCI + 0.3 or 0.5 mg), LKA651 monotherapy (CCI) or Lucentis® (0.3 or 0.5 mg). Sentinel Safety cohorts will first be enrolled to test the safety of the combination of LKA651 and Lucentis® by Day 15 before proceeding with further patient randomization. After determination that there are no concerning safety signals, the study will proceed with randomization for the remaining 74 patients who will be randomized 9:14:14 to LKA651 plus Lucentis® (CCI + 0.3 or 0.5 mg), LKA651 monotherapy or Lucentis®. Data from the Safety Sentinel cohorts and main study will be pooled for end of study safety and efficacy analysis.

Figure 1.1: Study Design depicts the design of the study, starting from a screening epoch (60 days) of the Sentinel safety cohort, a treatment period from Visit 1 (Baseline visit) to Day 15. If safety will be determined for the first 8 patients in a region at Day 15, that region can continue. After determination of safety from the two Sentinel Safety cohorts the remaining 74 patients will be randomized. Every patient will be dosed 3 times in 4-week intervals, and then followed for an extension phase of an additional 12 weeks during which PRN Lucentis® may be given.

Figure 1.1: Study Design



2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) they received.

The safety analysis set will include all patients who received any study drug.

The PD and efficacy analysis set will include all patients with available PD and efficacy data and no protocol deviations with relevant impact on PD or efficacy data.

Dose sensitivity analysis set will include patients in the efficacy analysis set who received all 3 doses with 6 injections and dosed correctly.

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 any study drug and experienced no protocol deviations with relevant impact on PK data.

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
Subjects are excluded from safety analysis in case of these PDs:		Exclude subject from safety analysis set
INCL01	Deviation from inclusion criterion 1	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
EXCL01	Deviation from exclusion criterion 1 (anti-VEGF at baseline)	Yes
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EXCL22	Deviation from exclusion criterion 22 (investigational drugs at Screening or during the trial)	Yes
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Deviation from inclusion criterion 1	Yes
INCL03	Deviation from inclusion criterion 3	Yes
EXCL01	Deviation from exclusion criterion 1	Yes
EXCL02	Deviation from exclusion criterion 2	Yes
EXCL03	Deviation from exclusion criterion 3	Yes
EXCL04	Deviation from exclusion criterion 4	Yes
EXCL05	Deviation from exclusion criterion 5	Yes
EXCL08	Deviation from exclusion criterion 8	Yes
EXCL09	Deviation from exclusion criterion 9	Yes
EXCL10	Deviation from exclusion criterion 10	Yes
EXCL11	Deviation from exclusion criterion 11	Yes
EXCL13	Deviation from exclusion criterion 13	Yes
EXCL15	Deviation from exclusion criterion 15	Yes
EXCL22	Deviation from exclusion criterion 22	Yes

Category Deviation code	Text description of deviation	Data exclusion
COMD01	Use of prohibited medication during the study	Yes (from this date onwards)
TRT01	Wrong injection/treatment administered during the study	From dose sensitivity analysis

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

PK analysis will only be performed in a subset of patients where sufficient serum samples have been collected to permit meaningful analysis.

5.1 Variables

The following systemic serum PK parameters for LKA651 and ranibizumab will be determined after the first dose, if feasible, using non-compartmental method(s):

- Area under the curve AUC_{last}, $AUC_{0\text{-}28d}$, maximum concentration (C_{max}), and time to the first occurrence of the maximal concentration (T_{max}).

PK parameters will be determined using non-compartmental methods using the most recent version of WinNonlin Phoenix (Version 8.2).

5.2 Descriptive analyses

Descriptive summaries including mean, coefficient of variation, median, minimum and maximum and including frequency of concentrations below LLOQ, will be presented by treatment and study day/sampling point. Concentrations below LLOQ will be treated as ½ LLOQ in the summary statistics.

A plot of Geometric mean (SE) concentration-time profile of LKA651 from Day 1 0 hour (visit 1) to Day 29 (visit 5) following first LKA651dose will be constructed. Similarly, plot of Geometric mean (SE) concentration-time profile of ranibizumab from Day 1 0 hour (visit 1) to Day 29 (visit 5) following first ranibizumab dose will be constructed. Those Geometric mean concentration by time profile will be plotted on linear-linear and log-linear scale.

6 Statistical methods for Efficacy/Pharmacodynamic (PD) parameters

All patients within the PD analysis set will be included in the PD data analysis.

6.1 Primary objective

The primary objective of this study is to evaluate the efficacy, in reference to Lucentis® monotherapy, of three q4w IVT doses of LKA651 in treating DME when administered as monotherapy or in combination with Lucentis®.

6.1.1 Variables

Best Corrected Visual Acuity (BCVA) at week 12 and central subfield retinal thickness as determined by Spectral Domain-Optical coherence tomography (SD-OCT) at week 12.

6.1.2 Descriptive analyses

The absolute and change from baseline as well as percent change from baseline BCVA and central subfield retinal thickness measurements will be listed by treatment, patient and visit/time and descriptive statistics will be provided by treatment and visit/time. Summary statistics will include number of observations, mean, standard deviation, median, minimum and maximum.

6.1.3 Statistical model, assumptions and hypotheses

BCVA

BCVA for study eye will be analyzed using two repeated measures models. A first model where BCVA will be the dependent variable and a second one where change from baseline of BCVA will be the dependent variable. Independent variables will include treatment, visit, and the treatment by visit interaction. Baseline BCVA for study eye and treatment naïve and treatment experienced variable will be used as covariates. An unstructured residual covariance structure will be used, if possible. If not possible, simpler covariance structures will be considered and the best will be selected using information criteria.

The Kenward-Rodger estimate of denominator degrees of freedom will be used. Least-square means for each treatment by time combination will be presented. Additionally at each time, the difference between the combination treatment and Lucentis® alone, as well as the difference between LKA651 and Lucentis® alone will be presented along with the resulting p-value and 90% confidence interval.

The primary inference will be based on the null hypothesis on no treatment difference for Day 85. A one-sided, alpha=0.05 test will be used for this purpose, with an increase considered as beneficial.

Central subfield retinal thickness

Central subfield retinal thickness will be analyzed in a similar fashion as BCVA, except that central subfield retinal thickness will be log-transformed, thus results will be back-transformed in order to show results as a ratio to baseline and the difference between treatments will be expressed as a ratio of treatments. Similarly, the covariates will be the log-transformed baseline central subfield retinal thickness and treatment naïve and treatment experienced variable.

6.1.4 Supportive and sensitivity analysis

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Dose sensitivity analysis will be performed to exclude patients who did not receive all 3 doses (6 injections) or dosed improperly, including both BCVA (absolute value and change from baseline) and CSFT (change from baseline and ratio to baseline). Analysis will consist of repeating MMRM models and reporting corresponding model estimated means (90% CI) and estimated treatment differences (90% CI). Model estimated mean plots with 90% CI error bars over time may be provided to support the analysis.

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6.2 Secondary objective

The secondary objectives are:

- To evaluate duration of effect of three q4w IVT doses of LKA651 in patients with DME.

6.2.1 Variables

The variables related to the secondary objectives are:

- Time to retreatment with anti-VEGF after week 12 during an additional 12 week extension phase

6.2.2 Descriptive analyses

Time to retreatment with anti-VEGF after week 12 and number of patients with 2 and ≥3 step improvement in the diabetic retinopathy severity scale by color fundus photos at week 12 and week 24 will be listed by treatment group, patient and visit/time, and descriptive statistics will be provided, for raw data, by treatment group (i.e. LKA651 vs Lucentis®, LKA651/Lucentis® combination vs Lucentis®, and LKA/Lucentis® vs LKA651) and visit/time. Summary statistics will include number of observations, mean, standard deviation, median, minimum and maximum.

6.2.3 Statistical model, assumptions and hypotheses

Time to retreatment with anti-VEGF (as determined by PI) after week 12 may be examined with a Kaplan-Meier plot; however, this may be abandoned if the time data are too sparse for accurate model fitting.

6.3 Exploratory objectives

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6.3.1 Descriptive analyses

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7 Statistical methods for safety and tolerability data

The safety analysis set will include all patients that received any study drug.

7.1 Variables

Adverse events, vital signs (blood pressure, heart rate) and ECG intervals, laboratory measurements (including reticulocyte count), complete ophthalmic exam, CCI in patients with DME as well as patient demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject 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

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by treatment group and patient.

Vital signs

Vital sign data such as body temperature, blood pressure and heart rate will be listed by treatment, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

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

Clinical laboratory evaluations

All laboratory evaluations will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting all parameters in a patient with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Reticulocyte count

Reticulocyte count will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting all parameters in a patient with any abnormal values. Summary statistics including mean, standard deviation, median, minimum and maximum will be provided by treatment and visit/time.

Intraocular pressure (IOP)

Intraocular pressure (IOP) will be listed for each eye by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics including mean, standard deviation, median, minimum and maximum will be provided by treatment and visit/time.

Dilated fundus exam

Dilated fundus exam results will be summarized using descriptive statistics. Descriptive statistics including frequency and proportion will be provided. These will be presented by treatment and visit/time.

Slit lamp examination

Slit lamp examination findings will be listed for each eye by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

Separate tables will be provided for ocular events and non-ocular events.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

1. a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
2. more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

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9 Reference list

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