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Novartis Research and Development

LKA651

Clinical Trial Protocol CLKA651X2202
ClinicalTrials.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

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## Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

## Table of contents



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## List of tables



## List of figures

## List of abbreviations

| | |
|---|---|
| A1C | Glycated haemoglobin |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| $AUC_{0-28d}$ | Area under the curve over the dosing interval |
| BCVA | Best Corrected Visual Acuity |
| BMI | Body Mass Index |
| BUN | blood urea nitrogen |
| CBC | Complete Blood Count |
| CDS | Core Data Sheet (for marketed drugs) |
| CFP | Color Fundus Photography |
| CFR | U.S. Code of Federal Regulations |
| CI | Confidence Interval |
| CK | creatinine kinase |
| Cmax | Maximum Concentration |
| CMO&PS | Chief Medical Office & Patient Safety |
| $CO_2$ | carbon dioxide |
| CRA | Clinical Research Associate |
| CRC | Central Reading Center |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| DAR | Dose Administration Record |
| DDE | Direct Data Entry |
| DME | Diabetic Macular Edema |
| DNA | Deoxyribonucleic Acid |
| DR | Diabetic Retinopathy |
| e.g. | For example |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| EMA | European Medicine Agency |
| EPO | Erythropoietin |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| eSource | Electronic Source |
| FA | Fluorescein Angiography |
| Fc | Fragment crystallizable |
| FcRn | Neonatal Fc receptor |
| FDA | Food and Drug Administration |
| FIH | First-in-Human |
| g/dL | Grams/deciliter |
| GCP | Good Clinical Practice |

| | |
|---|---|
| GLP | Good Laboratory Practice |
| GGT | Gamma-glutamyl transferase |
| h | hour |
| Hb | Hemoglobin |
| HbA1C | Glycated haemoglobin |
| hCG | Human chorionic gonadotropin |
| IV | intravenous |
| IA | Interim analysis |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IOP | Intra Ocular Pressure |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IVT | Intravitreal |
| LDH | lactate dehydrogenase |
| LFT | Liver function test |



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|---|---|
| MedDRA | Medical dictionary for regulatory activities |
| mg | milligram(s) |
| mL | milliliter(s) |
| NCDS | Novartis Clinical Data Standards |
| NOAEL | No Observed Adverse Event Level |
| NOVDD | Novartis Data Dictionary |
| NYHA | New York Heart Association |
| PCI | percutaneous coronary intervention |
| PD | pharmacodynamic(s) |
| PoC | Proof of Concept |
| PK | pharmacokinetic(s) |
| PRN | Pro re nata; as needed |
| Q4w | Every 4 weeks |
| QMS | Quality Management System |
| QTcF | Fridericia QT corrected interval |
| RBC | red blood cell(s) |
| RDC | Remote Data Capture |
| SAE | serious adverse event |
| sCR | serum creatinine |
| SD | standard deviation |
| SD-OCT | Spectral domain optical coherence tomography |

| | |
|---|---|
| SMQ | Standardized MedDRA Query |
| SOM | Site Operations Manual |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| Tmax | Time to the first occurrence of the maximal concentration |
| TD | Study Treatment Discontinuation |
| US | United States |
| VEGF | Vascular Endothelial Growth Factor |
| WBC | white blood cell(s) |
| WHO | World Health Organization |
| WoC | Withdrawal of Consent |

## Glossary of terms

| | |
|---|---|
| Assessment | A procedure used to generate data required by the study |
| Cohort | A specific group of patients fulfilling certain criteria |
| Control drug | Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial |
| Dosage | Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 5 mg once a month) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces.<br>EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care. |
| Enrollment | Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Epoch | Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study. |
| eSource | eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate. |
| Investigational drug | The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance” |
| Part | A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease. |
| Patient | An individual with the condition of interest |
| Personal data | Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples. |
| Randomization number | A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Screen Failure | A patient who is screened but is not treated or randomized |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource |
| Study treatment | Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy |
| Study treatment discontinuation | When the patient permanently stops taking study treatment prior to the defined study treatment completion date |
| Patient | A trial participant (can be a healthy volunteer or a patient) |

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|---|---|
| Patient number | A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc. |
| Personal Data | Personal Data: Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples. |
| Variable | A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study |
| Withdrawal of consent (WoC) | Withdrawal of study consent: Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data |

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## Protocol summary

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| **Protocol number** | CLKA651X2202 |
| **Full Title** | A randomized, active-controlled, patient and investigator-masked, multiple dose proof-of-concept study of intravitreal LKA651 in patients with diabetic macular edema |
| **Brief title** | A proof-of concept study of intravitreal LKA651 in patients with macular edema |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II |
| **Investigation type** | Biologic |
| **Study type** | Interventional |
| **Purpose and rationale** | This study will investigate whether LKA651, alone or when co-administered with Lucentis®, displays the clinical safety and efficacy profile to support further development to treat diabetic macular edema (DME) |
| **Primary Objective(s)** | To evaluate the safety, tolerability, and efficacy, in reference to Lucentis® monotherapy, of three q4w intravitreal (IVT) doses of LKA651 in treating DME when administered as monotherapy and in combination with Lucentis®. |
| **Secondary Objectives** | To evaluate the serum pharmacokinetic (PK) profile of total LKA651 and Lucentis® following three q4w IVT doses of LKA651, or a combination of LKA651 and Lucentis,® in patients with DME<br>To evaluate duration of effect of three q4w IVT doses of LKA651 in patients with DME. |
| **Study design** | This study is a 3-arm, parallel group, randomized, patient and investigator-masked trial in 90 patients with DME. The study will be stratified in that Sentinel Safety cohorts will first be enrolled to test the safety of the combination of LKA651 and Lucentis® before proceeding with further patient randomization. After determination of safety from Day 15 data from each sentinel cohort, patients will continue to be enrolled into 1 of 3 arms; LKA651 monotherapy, LKA651 plus Lucentis®, and Lucentis® monotherapy. 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. |
| **Population** | Approximately 90 male or female patients between the ages of 18 and 85 with DME will be randomized. At least 75 patients are expected to complete the study. |

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| **Key Inclusion criteria** | • Male and female patients age 18 to 85 years of age inclusive at screening<br>• Diagnosis of type I or type II diabetes mellitus.<br>• The Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the study eye must be between 24 and 72 letters (approximate Snellen equivalent of 20/40-20/320). The non-study eye (fellow eye) should be ≥34 letters or better (approximate Snellen equivalent of 20/200) at screening<br>• Presence of DME in the study eye, with decrease in vision due to foveal thickening. Central macular thickness of ≥ 320 µm in the central subfield, as assessed on spectral-domain ocular coherence tomography (SD-OCT) and confirmed by the central reading center at screening<br>Commercially Confidential Information |
| **Key Exclusion criteria** | |
| **Study treatment** | LKA651<br>Lucentis® (ranibizumab) |
| **Efficacy assessments** | • Best corrected visual acuity (BCVA)<br>• Central subfield retinal thickness as determined by SD-OCT |
| **Pharmacokinetic assessments** | • Serum levels of total LKA651<br>• Serum levels of total ranibizumab |

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|---|---|
| **Key safety assessments** | • Ocular or systemic adverse events<br>• Vital signs<br>• Electrocardiogram (ECG)<br>• Safety laboratories (including reticulocyte count)<br>• Intraocular pressure<br>• BCVA<br>• Central subfield retinal thickness by SD-OCT |
| **Other assessments** | Commercially Confidential Information |
| **Data analysis** | The primary objective of this study is to assess the safety and tolerability as well as the efficacy of LKA651 alone or in combination with Lucentis® in patients with DME. Descriptive statistics will be provided for all safety variables. Adverse events will be summarized by counts, rates and body system. For efficacy evaluation, BCVA and central subfield retinal thickness at week 12 are the primary endpoints. A repeated measure Analysis of Covariance (ANCOVA) will be performed for BCVA and change from baseline BCVA. Independent variables will include treatment, visit, and the treatment by visit interaction. Baseline BCVA will be used as a covariate. 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. |
| **Key words** | Diabetic Macular Edema (DME) |

# 1 Introduction

## 1.1 Background

Diabetic retinopathy (DR) is the most common visual complication in patients with diabetes. Diabetic macular edema (DME) can occur in any stage of DR and is the main cause of vision loss in patients with DR. The incidence of DME after 10 years of follow-up has been reported to be 20.1% in Type 1 Diabetes Mellitus, 25.4% in Type 2 insulin-dependent diabetes, and 13.9% in Type 2 non-insulin-dependent diabetes (Klein et al 1995). The early treatment diabetic retinopathy (ETDRS) trial, a pioneering study in DR, demonstrated that although laser photocoagulation therapy reduces the risk of moderate visual loss in DME eyes by ~50% at 3 years (ETDRS 1985), only a few eyes gain vision, and some eyes continue to experience vision loss even after intensive treatment (ETDRS 1985). Newer treatment options such as anti-vascular endothelial growth factor (VEGF) therapy have helped, but even in these pivotal trials nearly 50% of eyes are left with visual acuities of 20/40 or worse (Mitchell et al 2011).

LKA651, an anti-erythropoietin (EPO) Fab (antibody fragment), may be an effective treatment for patients with DME. In DME patients, intraocular EPO concentrations are elevated in eyes with DME (for example Lim and Han, 2011).

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The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure (IB).

### 1.1.1 Non Clinical Data

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### 1.1.2 Clinical Data

#### 1.1.2.1 Human Safety and Tolerability Data

Safety and tolerability data from the first-in-human (FIH) trial CLKA651X2104 showed that all doses were safe and well tolerated. This study was a single-ascending dose study with 28 patients who had macular edema from DME, retinal vein occlusion, or neovascular age-related macular degeneration.

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Analyses conducted and detailed in the IB revealed no deaths, discontinuations, or serious adverse events (SAEs) among randomized patients. Eighteen patients had 35 treatment-emergent AEs, all of which were mild or moderate and occurred across all dose groups and sham-injected patients without meaningful differences in numbers. The most common AE related to the procedure was conjunctival hemorrhage, occurring in 4 (16.7%) patients. Two AEs CCI : anterior chamber inflammation in one patient in

Commercially Confidential Information resolved within 24 hours of treatment with topical steroids, and trace vitreous cell in one patient CCI seen within two weeks of injection of drug, that resolved without treatment, and then recurred at the end of study (Day 85). There were no AEs related to red blood cell production or anemia. There were no non-ocular AEs that were related to the study drug.

#### 1.1.2.2 Human pharmacokinetics, pharmacodynamics and immunogenicity data

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## 1.2 Purpose

This study is being conducted to evaluate the safety/tolerability and efficacy of IVT LKA651 for the treatment of macular edema in patients with DME.

# 2 Objectives and endpoints

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for 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<br>• Vital signs (blood pressure, heart rate) and ECG intervals.<br>• Safety laboratory measures (including reticulocyte count)<br>• Complete ophthalmic exam, including :<br>  • Intraocular Pressure (IOP)<br>  • BCVA<br>  • Macular thickness by spectral domain optical coherence tomography (SD-OCT)<br>  • 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.<br>• Central subfield retinal thickness as measured by SD-OCT at week 12. |

| Objective(s) | Endpoint(s) |
|---|---|
| **Secondary objective(s)** | **Endpoint(s) for 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.<br>• 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. |
| **Exploratory objective(s)** | **Endpoint(s) for exploratory objective(s)** |

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# 3 Study design

This study is a 3-arm, parallel group, randomized, patient and investigator masked trial in 90 patients with diabetic macular edema. This study is the first that clinically tests the combination of CCI LKA651 and Lucentis®, therefore the study will be stratified in that Sentinel Safety cohorts will first be enrolled to test the safety of a patient receiving both LKA651 and Lucentis® as separate injections in the same eye before proceeding with further patient enrollment (See Section 4.5). Because the study will be run both in and ex-U.S., different doses of Lucentis® will be used in each region per label. Ex-U.S., the Sentinel Safety cohort will use the maximum dose of Lucentis® globally (0.5 mg). In the U.S., the approved dose for DME is 0.3 mg so this dose will be used. For each Sentinel Safety cohort, 8 patients will be randomized 6:1:1 to LKA651+Lucentis® ( CCI + 0.3 mg or 0.5 mg), LKA651 monotherapy ( CCI ), and Lucentis® monotherapy (0.3 or 0.5 mg). When two injections are required, as in the combination arm, the injections will be given 30 minutes apart. To maintain masking in the

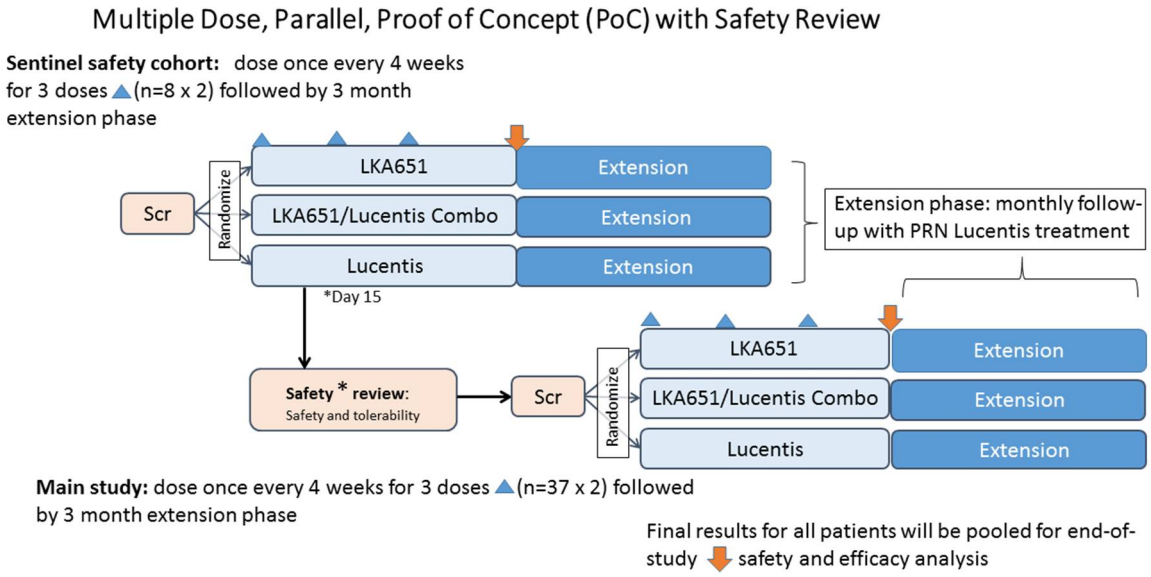
monotherapy arms, a sham injection will be given as a second injection 30 minutes after the first drug injection (A sham injection is a needle-less syringe placed against the globe with pressure simulating that of an injection). Safety assessments through Day 15 will be analyzed for all 8 patients before any other patients from the same geographical region can be randomized; in the FIH study, the two AEs considered related to the study drug occurred within this time frame.

Within each geographical region, masked analysis of Day 15 safety data of the Sentinel Safety cohort will be performed by a joint review by the Sponsor and Investigators who contributed patients to the cohorts. Data review will include the nature of adverse events, vital signs, electrocardiogram, safety laboratories (including reticulocyte count, intraocular pressure, BCVA, CCI , slit lamp examination), and central subfield retinal thickness by SD-OCT.

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 +Lucentis® ( CCI + 0.3 or 0.5 mg), LKA651 monotherapy (CCI ), or Lucentis® monotherapy (0.3 or 0.5 mg). Masking with sham injections will be performed as in the safety sentinel cohorts. Data from the Safety Sentinel cohorts and main study will be pooled for end-of-study safety and efficacy analysis.

For all patients, a screening period of 60 days will be used to assess eligibility and to taper patients off disallowed medications. At Visit 1, the baseline visit, eligible patients will be randomized to one of the treatment arms. Randomized patients will be dosed once q4weeks for a total of 3 doses. The assessment to address the primary objective will be performed at the end of the treatment period (week 12) before the extension phase begins. After 12 weeks, efficacy will be determined based on BCVA criteria. Patients are then followed for an additional 12 weeks in a maintenance/extension phase for further evaluation of secondary endpoints. During the extension phase, patients will be examined every 4 weeks and receive PRN anti-VEGF treatment (Lucentis®) as determined by the Investigator for clinically significant increase in retinal thickness or decrease in BCVA due to DME that warrants anti-VEGF treatment.

**Figure 3-1 Study Design**




In each region, Sentinel Safety cohort is randomized 6:1:1 Combination: LKA651: Lucentis®. Main study is randomized 9:14:14

# 4 Rationale

## 4.1 Rationale for study design

The design of this study addresses the primary objective of improvement of BCVA in patients with DME and takes into account the possible additive effects of LKA651 with anti-VEGF treatment.

- **Sentinel safety cohorts:** The combination of LKA651 CCI and ranibizumab 0.5 mg was shown to be safe in a multiple dose, 13-week GLP toxicology study (see IB). Limiting the initial clinical exposure of the combination of LKA651+Lucentis® to 6 patients in the U.S. and 6 patients outside the U.S., controls the risk associated with potential adverse events that may occur with this combination that has not yet been tested in humans, but has been shown safe in preclinical toxicity studies. Including one patient treated with LKA651 and one patient treated with Lucentis® monotherapy in the Sentinel Safety cohort allows for comparison and control. In addition, because the rest of the patient population will be screened only after Day 15 of the Sentinel Safety cohorts, the Sentinel Safety cohorts will remain ahead of the other patients for the duration of the study, and will provide alerts to potential AEs occurring after multiple doses. Lucentis® alone is an approved treatment for DME, and LKA651 has shown an acceptable safety profile in the FIH study CLKA651X2104, so overall the risk for unanticipated SAEs is considered to be very low. Performing the Sentinel Safety cohort both within and Ex-U.S. will allow the study to begin in the U.S., where the approved dose for Lucentis® for DME is lower but where the study may begin more quickly due to operational reasons.

- **Randomization:** This decreases the chance of an imbalance in patient characteristics between groups, thereby facilitating an unbiased assessment of safety and tolerability.
- **Patient-masked (with selective un-masking of investigators and sponsor staff for operational or safety reasons):** Masking of patients and investigators allows for an unbiased assessment of readouts such as adverse events. Selective un-masking of the investigators and sponsor staff could improve the accuracy of safety-related decisions if necessary.

## 4.2 Rationale for dose/regimen and duration of treatment

Two separate doses of LKA651 will be used in this study, CCI in the monotherapy arm and CCI in combination with Lucentis® in the combination arm.

Because there are no available animal models of DME, the dose/response relationship is unknown for LKA651 alone or in combination with Lucentis®. Thus it is proposed to test the highest safe and tolerable dose of LKA651 as determined by the first-in-human study CLKA651X2104 CCI in the monotherapy arm of this proof-of-concept study. Injection of the maximum deliverable single dose of LKA651 CCI in the monotherapy arm is supported by

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It is possible that a synergistic pharmacological effect between LKA651 and Lucentis® could lead to superior efficacy in the combination arm compared to the monotherapy arm; therefore a combination arm will be tested. The combination (two separate injections given 30 minutes apart) of CCI LKA651 and Lucentis® at the approved dose for DME is supported by the 13 week intravitreal LKA651/ranibizumab combination toxicology study in cynomolgus monkeys. For the combination arm with ranibizumab, the proposal is to evaluate the same dose of LKA651 used in the 13-week IVT LKA651/ranibizumab toxicology study ( CCI LKA651) and the same or lower dose of ranibizumab used (0.5 mg ranibizumab outside the U.S.and 0.3 mg used within the U.S. per label).

Dosing every four weeks is an approved dosing frequency for Lucentis® in treating DME and will be employed in this study. Since macular edema in diseases such as DME is slowly progressive, several months of treatment and observation are required to detect any potential clinical efficacy with LKA651 as a monotherapy or in free combination with Lucentis®. The proposed length of treatment, 12 weeks, is supported by the length of the 13-week GLP-toxicology study, and is consistent with a timeframe by which a clinically significant change in DME can be expected.

## 4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Lucentis® will be used both as a monotherapy comparator and in combination with LKA651 for safety and efficacy measurements. Anti-VEGF therapy is standard of care for patients with DME, and Lucentis® has a well established safety and efficacy profile with approved use per label at doses of 0.3 mg monthly within the U.S. and 0.5 mg monthly outside the U.S. Using Lucentis® as a monotherapy comparator will help establish if any safety or tolerability effects of LKA651 are attributed to the study drug as opposed to an effect of study procedures such as intraocular injection. In addition, because LKA651 has a different mechanism of action than anti-VEGF therapy, the combination of the two may provide additional efficacy benefits not seen with either alone.

## 4.4 Purpose and timing of interim analyses/design adaptations

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## 4.5 Risks and benefits

LKA651 is an anti-EPO antibody that may be effective in treating DME (symptoms or signs), either alone and/or in combination with anti-VEGF therapy. Because the mechanism of LKA651 differs from anti-VEGF standard of care, treatment with LKA651 may offer improved or additional benefits to both patients who respond to anti-VEGF treatment, and those who do not.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Potential human safety concerns include intraocular inflammation. Commercially Confidential Information

Further support is tendered by the FIH study, in which one case of anterior chamber inflammation was seen after one injection of CCI LKA651, and one case of trace vitreal cells was reported 2 weeks after injection of CCI CCI LKA651 (Section 1.1.2.1). Investigators should carefully monitor patients' eyes during the assessments immediately after study drug administration, and any adverse event should be treated according to type and local practice. Other risks not specific to LKA651 include hypersensitivity reactions, or side effects from intraocular injection including endophthalmitis. Refer to the IB for more information.

This study is the first to clinically test the combination of CCI LKA651 and Lucentis®. The low risk to patients is supported by the GLP-compliant 13-week IVT study which found the combination of CCI LKA651 and 0.5 mg ranibizumab safe and well tolerated. Combining another ocular drug with Lucentis® has been shown to be safe in trials investigating other compounds. These include intravitreally-administered anti-platelet derived growth factor aptamer (Jaffe et al 2016), a complement factor C5 inhibitor (Mones 2010), and a topical ocular drug, squalamine (Wroblewski and Hu 2016). Furthermore, LKA651 CCI was safe and well tolerated in the FIH study CLKA651X2104. In addition, the Sentinel Safety cohorts will mitigate risk by limiting exposure of the combination to a few patients whose safety data will be closely monitored, and further randomization will be gated by the review of these data after Day 15.

Some patients in the trial will be assigned to LKA651 without concomitant anti-VEGF therapy. Appropriate eligibility criteria regarding vision and concomitant retinal disease, rescue criteria, and stopping rules will limit disease progression in patients not receiving standard of care therapy. Rescue medication may be given per Section 6.2.3. Furthermore, the study period is only 3 months of duration, with an extension phase of an additional 3 months during which patients may receive PRN Lucentis® treatment.

**Sodium Fluorescein:** Fluorescein angiography is considered a relatively safe procedure, although numerous adverse reactions have been reported in the literature. These are divided into mild (nausea, vomiting, pruritus, sneezing, vaso-vagal disorders, inadvertent arterial injection), moderate (urticaria, other skin eruptions, syncope, thrombophlebitis, pyrexia, local tissue necrosis, muscular paralysis) and severe (bronchospasm, laryngeal edema, circulatory shock, myocardial infarction, tonic-clonic seizure). In a randomized trial, out of 1,500 enrolled patients, 69.3% underwent the test for the first time. Nausea occurred in 71 (6.83%) patients, vomiting in 14 (1.35%), urticaria in 11 (1.06%), bronchospasm in 4 (0.38%) and laryngeal edema in 1 (0.01%). Higher incidences of adverse reactions were observed in diabetic patients [$p<0.002$, RR=1.80 (CI=1.24-2.60)], patients with systemic arterial hypertension [$p<0.002$, RR=1.84 (CI=1.26-2.71)] and patients with allergy history [$p<0.001$, RR=3.90 (CI=2.70-5.63)]. A cumulative incidence of 9.72% adverse reactions was observed in patients who had undergone this test for the first time (Lira et al 2007).

### 4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 6 months from each patient as part of the study. The maximum drawn at any given day is approximately 31 mL. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedule.

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central laboratory manual.

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# 5 Population

Approximately 90 patients with DME, who are either treatment naive or who have been treated with anti-VEGF therapy >90 days before baseline, will be randomized. At least 75 patients are expected to complete the study.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study.

## 5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients age 18 to 85 years of age inclusive at screening
3. Presence of type I or type II diabetes mellitus
4. The ETDRS letter score in the study eye must be between 24 and 72 letters, inclusive (approximate Snellen equivalent of 20/40-20/320). The non-study eye (fellow eye) should be ≥34 letters or better (approximate Snellen equivalent of 20/200) at screening

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6. Sufficiently clear ocular media and adequate pupil dilation in the study eye to permit fundus photographs of adequate clarity to measure diameters of retinal arteries and veins at screening

7. At screening vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least three minutes. The Investigator should be guided by the following ranges for inclusion:
   - Body temperature between 35.0-37.5 °C
   - systolic blood pressure, 90-180 mm Hg
   - diastolic blood pressure, 50-100 mm Hg
   - pulse rate, 40 - 100 bpm
8. Able to communicate well with the investigator, to understand and comply with the requirements of the study

## 5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Patient with history of treatment for DME in the study eye as defined by the following:
   - IVT anti-VEGF treatment CCI in the study eye. History or concurrent treatment with these medications/procedures in the non-study eye is permitted.
   - Patient with history of intraocular corticosteroids in the study eye including dexamethasone intravitreal implants during the 6 month period prior to baseline, Commercially Confidential Information
2. Concomitant conditions or ocular disorders in the study eye which may, in the opinion of the investigator, confound the interpretation of study results, compromise visual acuity or require medical or surgical intervention during the study period
   - High risk proliferative diabetic retinopathy in the study eye, as per investigator assessment at both screening and baseline.
   - Patients with the following conditions in the study eye at screening or baseline must be excluded: CCI , vitreous hemorrhage, retinal detachment, vitreomacular traction, macular hole, retinal vein/arterial occlusion, neovascularization of iris or choroidal neovascularization of any cause.
3. Laser photocoagulation (macular CCI ) in the study eye CCI
4. Patients, with type 1 or type 2 diabetes who have a hemoglobin A1C ≥ 12% at screening.
5. Any progressive disease of the retina (e.g. uveitis, rod-cone dystrophy) or optic nerve in the study eye.
6. Area of retinal ischemia involving the macula (as measured by the foveal avascular zone) ≥ 1000 μm in linear diameter.
7. Active intraocular inflammation (graded as trace or above) in either eye at screening.
8. Any active infection involving the study eye's ocular adnexa including infectious conjunctivitis, keratitis, scleritis, endophthalmitis, as well as idiopathic or autoimmune-associated uveitis in either eye, or intraocular infection in either eye.

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14. Current diagnosis of clinically significant anemia, or hemoglobin <10 g/dL for women and <11 g/dL for men.

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22. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations.
23. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
24. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, *unless* they are using highly effective methods of contraception during duration of the study. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

# 6 Treatment

## 6.1 Study treatment

The investigational drug is LKA651 CCI either alone or in free combination with Lucentis® 0.3 mg (U.S. sites) or 0.5 mg (ex-U.S. sites). Lucentis® (0.3 or 0.5 mg) will also be given in a control arm as monotherapy.

Detailed information regarding the materials/medications supplied to the study clinic(s) can be found in the SOM and pharmacy manual.

### 6.1.1 Investigational and control drugs

The investigational drug, LKA651 20 mg/0.2 ml (Table 6-1) will be provided by Novartis as open label supplies to be dispensed by the unmasked pharmacist at the investigator site according to the randomization schedule as described in the protocol and SOM.

Lucentis® (0.3 or 0.5 mg) is used as active control arm in a monotherapy and in combination with Commercially Confidential Information

**Table 6-1 Investigational drug**

| Investigational (Name and Strength) | Pharmaceutical Dosage Form | Route of Administration | | Sponsor (global or local) |
|---|---|---|---|---|
| LKA651 20 mg/0.2ml | Liquid in Vial | Intravitreal | Open label bulk supply | Novartis |
| LKA651 (vehicle) | NA | NA | Open label bulk supply | Novartis |
| Lucentis® 10 mg/ml solution for injection (used in the combination arm) | Liquid in Vial | Intravitreal | Marketed drug | N/A |

**Table 6-2 Control Drug**

| Control Drug (Name and Strength) | Pharmaceutical Dosage Form | Route of Administration | | Sponsor (global or local) |
|---|---|---|---|---|
| Lucentis® 10 mg/ml solution for injection | Liquid in Vial | Intravitreal | Marketed drug | N/A |

### 6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

### 6.1.3 Treatment arms/group

For each Sentinel Safety cohort, 8 patients will be assigned at visit 1 to one of the following 3 treatment arms/groups in a ratio of 6:1:1: LKA651+ Lucentis® free combination: LKA651:

Lucentis®. The remaining 74 patients will be randomized 9:14:14: LKA651 + Lucentis® free combination: LKA651: Lucentis®.

## 6.2 Other treatment(s)

### 6.2.1 Concomitant therapy

If the fellow eye has DME it may be treated with local (intravitreal or topical) medications per the investigators discretion. The fellow eye may be treated at any time, including on the study day, provided its treatment does not interfere with the timing of the study procedures and assessments.

The investigator must instruct the patient to notify the study site about any new medications he/she takes after enrollment into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

### 6.2.2 Prohibited medication

Use of the treatments displayed in the below Table 6-3 are not allowed.

**Table 6-3 Prohibited medication**

| Medication | Prohibition period | Action taken |
|---|---|---|
| Commercially Confidential Information | | |
| Ozurdex® implant | Prohibited in the study eye at any time <6 months before or during the study | Note protocol deviation |
| Iluvien® implant | Prohibited in the study eye at any time before or during the study | Note protocol deviation |
| Investigational drugs | At Day 1 or any time the patient is still enrolled in the trial. | Discontinue from study treatment |
| Commercially Confidential Information | | |

### 6.2.3 Rescue medication

Rescue of a patient can occur at any time post-LKA651 administration as deemed necessary by the study ophthalmologist. In the case that clinically significant deterioration in a patient's vision or progression of macular edema occurs as determined by the study ophthalmologist, laser photocoagulation can be administered in an attempt to rescue the patient's vision if rescue treatment is needed within 28 days of the last treatment injection. At or after 28 days from the last treatment injection, the patient can be treated as needed with Lucentis® for any further required rescue therapy. After any rescue treatment, the patient should discontinue the experimental treatment. However, unless the investigator feels it is not in the best interest of the patient or their condition, all patients who receive rescue medication should still participate in the scheduled visits and assessments as outlined in the study Assessment Schedule.

Use of rescue medication/treatment must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

### 6.2.4 Restriction for study patients

Not applicable.

## 6.3 Patient numbering, treatment assignment, randomization

### 6.3.1 Patient numbering

The patient number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on patient numbering, please see 'Patient numbering' section in the Site Operations Manual.

### 6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

## 6.4 Treatment masking

Patients, investigator staff, persons performing the assessments, and data analysts will remain masked to the identity of study treatments according to the specifications provided in the SOM. Randomization data are kept strictly confidential until the time of unmasking for the respective person(s). Further information regarding masking (and unmasking) is presented in Table 6-4 and the SOM.

Patients will be randomized to a treatment arm to maintain the mask. Patients will remain masked to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

### 6.4.1 Site staff

With the exception of any unmasked site staff identified below, all site staff (including study investigator and study nurse) will be masked to study treatment during treatment allocation and patient dosing.

Unmasking a single patient at site for safety reasons (necessary for patient management) will occur via an emergency system in place at the site (see Section 6.6.3)

Drug product will be supplied in bulk, so an unmasked pharmacist or study coordinator who is independent of the study team will be required in order to maintain the masking. This unmasked pharmacist or study coordinator will randomize the patient in the IRT system. Appropriate measures must be taken by the unmasked pharmacist or study coordinator to ensure that the treatment assignments are concealed from the rest of the site staff. The injecting physician, different from the investigator performing the assessments, will also be unmasked. The injecting physician will perform the injection and all assessments at 1 minute and 30 minutes post dose. Either the unmasked (injecting) or masked physician may perform the dilated fundus examination on the day of injection (2-4 hours post injection). All other assessments will be completed by the masked investigator.

### 6.4.2 Sponsor staff

The following unmasked sponsor roles are required for this study:

- Unmasked field monitor(s)
- Unmasked clinical staff managing drug re-supply to site
- Unmasked sample analyst(s) (PK blood and urine)

The unmasked field monitors are required to review drug accountability and allocation at site. The unmasked monitors are not provided with a randomization list directly but will be unmasked through review of source documentation compiled by the unmasked pharmacist, which details treatment allocation to individual patients. The unmasked monitors will also be able to review the treatment allocation cards/randomization list provided to the unmasked pharmacist. The names of the unmasked monitor(s) are detailed in the Monitoring Plan.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unmasked through communication of drug re-supply needs via the unmasked site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under unmasked conditions unless otherwise allowed.

The study statistician will be able to access the full randomization list from the start of the study and is allowed to share unmasked information with the rest of the clinical trial team as appropriate for internal decision purposes, as outlined in Table 6-4. For example, unmasked summaries and unmasked individual data can be shared with the team whenever necessary.

Study programmers and other personnel involved in study data analysis CCI are allowed to access treatment assignment information from the start of the study for the purpose of data analysis.

The clinical trial team is allowed to share unmasked results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

All unmasked personnel will otherwise keep randomization lists and data or information that could unmask other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unmasked.

**Table 6-4 Masking levels**

| Role | Time or Event | | | |
|---|---|---|---|---|
| | Randomization list generated | Treatment allocation & dosing | Safety event (single patient unmasked) | CCI dose escalation |
| Patients/Patients | M | M | UI | M |
| Site staff | M | M | UI | UI |
| Unmasked site staff (see text for details) | M | UI | UI | UI |
| Drug Supply and Randomization Office | UI | UI | UI | UI |
| Unmasked sponsor staff (see text for details) | UI | UI | UI | UI |
| Unmasked Pharmacovigilance sponsor staff | UI | UI | UI | UI |
| Statistician/statistical programmer/data analysts | M | M | UI | UI |
| Independent committees used for assessing interim results | NA | NA | NA | NA |
| All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions) | M | M | UI | UI |

M Remains masked

NA Not applicable

UI Allowed to be unmasked on individual patient level

## 6.5 Dose escalation and dose modification

Study drug dose adjustments and/or interruptions are not permitted.

In case of notable adverse events or safety concerns, termination of any further doses may be considered as per Section 9.

These changes must be recorded on the Dosage Administration Record CRF.

### 6.5.1 Dose escalation guidelines

Not applicable.

## 6.6 Additional treatment guidance

### 6.6.1 Treatment compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with LKA651 and Lucentis®, as detailed in pharmacokinetics section.

### 6.6.2 Recommended treatment of adverse events

Ocular adverse events should be treated according to the type of adverse event. For clinically significant acute elevation of IOP following LKA651, anterior chamber paracentesis should be performed and normalization of IOP verified. For subacute or persistent elevation in IOP, aqueous suppressants may be indicated.

Iritis or vitritis should be treated with steroidal or non-steroidal anti-inflammatory medications; other medications such as cycloplegics may be indicated; endophthalmitis should be ruled out.

Endophthalmitis should be treated with vitreous tap and culture and/or vitrectomy, as indicated, plus appropriate IVT antibiotics.

In case of an adverse event attributed to LKA651, such as clinically significant inflammation or signs of retinal toxicity not responsive to standard of care treatment, the investigator may wish to remove the LKA651 by pars plana vitrectomy.

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Systemic hypersensitivity reactions are theoretically possible. These can manifest with itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema. Assess and treat for anaphylaxis if indicated, and initiate supportive care. Fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, and oxygen should be on hand.

Patients should remain in the study even after receiving treatments for adverse events until the PI feels that patient discharge is warranted.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

### 6.6.3 Emergency breaking of assigned treatment code

Emergency unmasking should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Details will be provided in the SOM.

**The unmasked treatment code should not be recorded on the eCRF.**

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to IRT (Interactive Response Technology) or code break cards in case of emergency. If appropriate, the investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable.

## 6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

LKA651 and Lucentis® will be administered to the patient via intraocular injection at the study site. When administered in combination, they will be given as separate injections 30 minutes apart. If a patient is randomized to a monotherapy arm, a sham injection will be done 30 minutes after the first injection. See the SOM for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

# 7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB and/CDS for marketed drugs. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

# 8 Visit schedule and assessments

Assessment Schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Patients should be seen for all visits/assessments as outlined in the Assessment Schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

## Table 8-1 Assessment Schedule

| Epoch | Screening | Baseline | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Follow-up | Follow-up | Follow-up | Study Completion[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Visit 1 | Visit 1 [2] | Visit 1[2] | Visit 4 – Telephone visit | Visit 5 | Visit 5 [2] | Visit 5[2] | Visit 6 – Telephone Visit | Visit 7 | Visit 7 [2] | Visit 7[2] | Visit 8 | Visit 9 | Visit 10 | Visit 11 |
| Visit Numbers[1] | 10 | 1010 | 1010 | 1010 | 1040 | 1050 | 1050 | 1050 | 1060 | 1070 | 1070 | 1070 | 1080 | 1090 | 1100 | 1999 |
| Days | Screen -60 to-1 | 1 | 1 | 1 | 15 | 29 | 29 | 29 | 43 | 57 | 57 | 57 | 85 | 113 | 141 | 169 |
| Visit Window (Days) | | | | | +/- 1 | +/- 1 | | | +/- 2 | +/- 3 | | | +/- 3 | +/- 3 | +/- 3 | +/- 3 |
| Inclusion / Exclusion criteria | X | X | | | | | | | | | | | | | | |
| Hematology[3] | X | X | | | | X | | | | X | | | X | | | X |
| Clinical Chemistry | X | X | | | | X | | | | | | | X | | | X |
| Pulse rate | X | X | | | | X | | | | X | | | X | X | X | X |
| Demography | X | | | | | | | | | | | | | | | |
| Physical Examination | X | | | | | | | | | | | | | | | X |
| Body Height | X | | | | | | | | | | | | | | | |
| Body Weight | X | X | | | | X | | | | X | | | | | | X |
| Study completion information | | | | | | | | | | | | | | | | X |
| Concomitant therapies | X | X | | | X | X | | | X | X | | | X | X | X | X |
| Blood Pressure | X | X | | | | X | | | | X | | | X | X | X | X |
| Informed consent | X | | | | | | | | | | | | | | | |
| Body Temperature | X | X | | | | X | | | | X | | | X | X | X | X |
| Adverse Events | X | X | | X | X | X | | X | X | X | | X | X | X | X | X |
| ECG evaluation | X | X | | | | | | | | | | | | | | X |
| Urinalysis | X | X | | | | | | | | | | | X | | | X |
| Medical history/current medical conditions | X | X | | | | | | | | | | | | | | |
| Ocular history | X | | | | | | | | | | | | | | | |
| DME history | X | | | | | | | | | | | | | | | |
| Pregnancy and assessments of fertility | X[4] | X[4] | | | | X[4] | | | | X[4] | | | | | | X[4] |

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| Epoch | Screening | Baseline | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Treatment | Follow-up | Follow-up | Follow-up | Study Completion[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Visit 1 | Visit 1 [2] | Visit 1[2] | Visit 4 – Telephone visit | Visit 5 | Visit 5 [2] | Visit 5[2] | Visit 6 – Telephone Visit | Visit 7 | Visit 7 [2] | Visit 7[2] | Visit 8 | Visit 9 | Visit 10 | Visit 11 |
| Visit Numbers[1] | 10 | 1010 | 1010 | 1010 | 1040 | 1050 | 1050 | 1050 | 1060 | 1070 | 1070 | 1070 | 1080 | 1090 | 1100 | 1999 |
| Days | Screen -60 to-1 | 1 | 1 | 1 | 15 | 29 | 29 | 29 | 43 | 57 | 57 | 57 | 85 | 113 | 141 | 169 |
| Visit Window (Days) | | | | | +/- 1 | +/- 1 | | | +/- 2 | +/- 3 | | | +/- 3 | +/- 3 | +/- 3 | +/- 3 |



| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Best corrected visual acuity (BCVA) | X | X | X[6] | | | X | X[6] | | | X | X[6] | | X | X | X | X |
| Intraocular Pressure (IOP) | X | X | | X | | X | | X | | X | | X | X | X | X | X |
| Slit lamp biomicroscopy | X | X | | X | | X | | X | | X | | X | X | X | X | X |
| Dilated fundus exam | X | X | X[7] | | | X | X[7] | | | X | X[7] | | X | X | X | X |
| Optical coherence tomography[8] | X | X | | | | X | | | | X | | | X | X | X | X |
| Fluorescein angiography | X | | | | | | | | | | | | X | | | X |
| Color fundus photo | X | X | | | | X | | | | | | | X | | | X |
| HbA1C | X | | | | | | | | | | | | X | | | X |
| PK blood collection | | X[5] | | | | X[5] | | | | X[5] | | | X[5] | | | X |
| Study drug administration | | X | | | | X | | | | X | | | | | | |

[1] Visit structure given for internal programming purpose only

## 8.1 Screening

### 8.1.1 Eligibility Screening

Rescreening is only allowed by permission of the Sponsor.

In the case where a safety laboratory assessment at screening and/or initial baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the patient must be excluded from the study.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

### 8.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during the screening phase (see SAE section for reporting details).

## 8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data as outlined in the SOM will be collected on all patients.

Relevant medical history/current medical conditions data includes data until signature of informed consent.

## 8.3 Efficacy

### 8.3.1 Efficacy assessment 1

#### 8.3.1.1 Best-Corrected Visual Acuity (BCVA)

ETDRS BCVA will be obtained in each eye separately. This assessment is to be performed prior to pupil dilation. The number of letters read correctly (for each eye) will be recorded in the appropriate eCRF page.

### 8.3.2 Efficacy assessment 2

#### 8.3.2.1 Spectral-Domain Optical coherence tomography (SD-OCT)

SD-OCT will be performed on the designated eye(s) for each patient according to the Assessment Schedule (Table 8-1) and the imaging manual provided by the Central Reading Center (CRC). SD-OCT images will be transferred to the CRC. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study patients.

### 8.3.3 Appropriateness of efficacy assessments

BCVA is an FDA accepted endpoint for efficacy trials in DME and will be performed using standardized ETDRS charts. Central subfield retinal thickness will be measured to evaluate changes in retinal anatomy. Although an anatomical response can correspond with improvements in vision, the two do not always correlate (DRCRnet 2007), and thus BCVA will be the primary efficacy readout.

## 8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment schedule (Section 8) detailing when each assessment is to be performed.

### 8.4.1 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

### 8.4.2 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated as (Body weight (kg) / [Height (m)]$^2$)

### 8.4.3 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at screening and/or at the initial baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the patient is excluded from the study.

In the case where a laboratory range is not specified by the protocol, but is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. This includes laboratory evaluations obtained at Baseline visit V1, if the results are not received until after study drug has been administered. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### 8.4.3.1 Hematology

CBC (Hemoglobin, hematocrit, red blood cell count, white blood count, platelet count) white blood cell differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and reticulocyte count will be measured.

Additional measurements of hemoglobin A1c, CBC, and reticulocytes will be measured as outlined in the Assessment Schedules. Sample handling will be as outlined in the laboratory manual.

#### 8.4.3.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/$CO_2$, calcium, cholesterol, chloride, creatinine, creatinine kinase (CK), gamma-glutamyl transferase (g-GT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, triglycerides, urea/ blood urea nitrogen (BUN) and uric acid will be measured.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Sample handling will be outlined in the laboratory manual.

#### 8.4.3.3 Urinalysis

A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of white blood cells (WBC), red blood cells (RBC) and casts.

### 8.4.4 Electrocardiogram (ECG)

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs and copy on non-heat sensitive paper, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, patient initials, patient number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with patient safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.

### 8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule, Table 8-1, for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum beta-human chorionic gonadotropin β-hCG is performed and found to be negative.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

### 8.4.6 Other safety evaluations

#### 8.4.6.1 Best-Corrected Visual Acuity (BCVA)

ETDRS BCVA will be obtained in each eye separately. This assessment is to be performed prior to pupil dilation. The number of letters read correctly (for each eye) will be recorded in the appropriate eCRF page.

#### 8.4.6.2 Intraocular Pressure (IOP)

Intraocular pressures will be measured per the study site's regular practice.

#### 8.4.6.3 Fluorescein angiography (FA)

FA using a standardized technique (with transit views of the study eye) will be performed on the designated eye(s) for each patient according to the Assessment schedule (Table 8-1) and the imaging manual.

#### 8.4.6.4 Slit lamp biomicroscopy

Slit lamp exam of the adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, and lens will be obtained on both eye(s) for each patient according to the Assessment Schedule (Table 8-1). Results from the slit lamp biomicroscopy exam for both eyes will be recorded in the appropriate eCRF page.

#### 8.4.6.5 Dilated fundus exam

Dilated exam of the vitreous, optic nerve, choroid, macula, peripheral retina will be obtained on the designated eye(s) for each patient according to the Assessment schedule (Table 8-1). The process will be outlined in the SOM.

##### 8.4.6.5.1 Vitreous haze and hemorrhage

During the above examination, additional attention should be directed to scoring the evaluation for retinal tear/detachment, retinal hemorrhage, vitreous hemorrhage, density and vitreous haze. Results from the dilated fundus exam (for each eye) will be recorded on the appropriate eCRF page. Vitreous Haze grade will be outlined in the SOM.

#### 8.4.6.6 Spectral-Domain Optical coherence tomography (SD-OCT)

SD-OCT will be performed on the designated eye(s) for each patient according to the Assessment Schedule (Table 8-1) and the imaging manual provided by the Central Reading Center (CRC). SD-OCT images will be transferred to the CRC. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study patients.

#### 8.4.6.7 Color Fundus Photo

Color fundus photography will be performed on the designated eye(s) for each patient according to the Assessment schedule (Table 8-1) and the imaging manual. Fundus photograph will be performed according to a standardized procedure for the collection of fundus photographic images as outlined in a separate manual provided by the CRC. Training of examiners at each investigative site will occur prior to evaluation of study patients.

## 8.5 Additional assessments

### 8.5.1 Pharmacokinetics, Commercially Confidential Information

Quantitation of total LKA651, free ranibizumab, CCI will be performed.

For a detailed PK, CCI sampling schedule, please refer to the Assessment schedule (Table 8-1), SOM, and the lab manual. All samples will be given a unique sample number and a collection number as outlined in the SOM. Additional collection, processing and shipping details for samples collected for the quantitation of serum total LKA651 and ranibizumab are available in the SOM. Additional collection, processing and shipping details for samples collected for analysis for anti-LKA651 antibodies and anti-ranibizumab antibodies are available in the SOM.

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### 8.5.5 Other Assessments

Not applicable.

# 9 Study discontinuation and completion

## 9.1 Discontinuation

### 9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the patient or the investigator.

Study treatment must be discontinued under the following circumstances:

- An SAE or severe AE that in the opinion of the Investigator is related to the study treatment.
- Patient/guardian decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 8.4 (Safety) and Section 10.1.4 (Pregnancy reporting))
- Use of prohibited treatment as outlined in Table 6-3.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study.
- Emergence of the following adverse events:
    - Acute, marked, reduction in visual acuity, defined as either of the following: At least a 3-line (15-letter) decrease within the first 8 days that persists until day 15, or at least a 5-line (25-letter) decrease as assessed on any post injection day through Day 15.
    - Presence of persistent grade 2 or more anterior chamber inflammation (cells ± flare) for 14 days or more following IVT injection of study drug.
    - An increase in vitreous inflammation of 2 units on a Vitreous Haze Scale sustained over 14 days or more following IVT injection of study drug.

  - Sustained elevation of intraocular pressure characterized by an increase of 15 mmHg over pre-dose value for >60 minutes, or an intraocular pressure >30 mmHg maintained for an hour after the injection.
- The following deviations from the protocol treatment:
  - Treatment with LKA651 and/or Lucentis® within less than 28 days from the previous treatment.

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2, Withdraw of Informed Consent). Where possible, they should return for the assessments indicated by an asterisk (*) in the Assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 9.1.3 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

#### 9.1.1.1 Replacement policy

Not applicable.

### 9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the Assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the Assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

### 9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed.

### 9.1.4 Study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs during any part of the study:

- One (1) or more patients presenting with acute or delayed hypersensitivity of study drug administration.
- One (1) or more patients presenting with a serious adverse event (SAE) that, in the opinion of the investigator, is related to the study drug, at any time during the trial.
- Patient(s) presenting with dose-limiting toxicity defined as any one of the following suspected to be related to study drug administration:
  - Two (2) or more patients presenting with:
    - Acute, marked, reduction in visual acuity, defined as either of the following: At least a 3-line (15-letter) decrease within the first 8 days that persists until

day 15, or at least a 5-line (25-letter) decrease as assessed on any post injection day through Day 15.

- Presence of persistent grade 2 anterior chamber inflammation (cells ± flare) for 14 days or more following IVT injection of study drug.
- An increase in vitreous inflammation of 2 units on a Vitreous Haze Scale for 14 days or more following IVT injection of study drug.
- Sustained elevation of intraocular pressure characterized by an increase of 15 mmHg over pre-dose value for >60 minutes, or an intraocular pressure >30 mmHg maintained for an hour after the injection.

- The aggregate severity, frequency, and/or drug relatedness of adverse events, in the opinion of the investigator, merit placing the study on hold; or
- Other clinically significant changes or effects that, in the opinion of the Investigator or Sponsor, are deemed unsafe to continue dosing

The study may resume following the safety review, if the Investigators and Sponsor agree it is safe to proceed.

### 9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the patient, when the patient should stop taking drug, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

## 9.2 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. There are approved medications for the disease under study, and the patient can continue treatment with these medications as per his or her physician's recommendation.

Study completion is defined as when the last patient completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

# 10 Safety monitoring and reporting

## 10.1 Definition of adverse events and reporting requirements

### 10.1.1 Adverse events (AEs)

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded in the AE CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade

   mild: usually transient in nature and generally not interfering with normal activities

   moderate: sufficiently discomforting to interfere with normal activities

   severe: prevents normal activities
2. Its relationship to the study treatment If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased

- Drug interrupted/withdrawn

6. its outcome
   a. not recovered/not resolved;
   b. recovered/resolved;
   c. recovering/resolving,
   d. recovered/resolved with sequelae;
   e. fatal; or unknown

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease.

Follow the instructions found in the SOM for data capture methodology regarding AE collection for patients that fail screening.

### 10.1.2 Serious adverse events (SAEs)

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - *elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study* and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the patient's general condition

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

### 10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after study exit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

### 10.1.4 Pregnancy reporting

#### Pregnancies

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

### 10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. Please see Table 10-1 for details.

**Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse**

| Treatment error type | Document in Dose Administration (DAR) eCRF (Yes/No) | Document in AE eCRF | Complete SAE form |
|---|---|---|---|
| Unintentional study treatment error | Yes | Only if associated with an AE | Only if associated with an SAE |
| Misuse/Abuse | Yes | Yes | Yes, even if not associated with a SAE |

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

## 10.2 Additional Safety Monitoring

Not applicable.

# 11 Data Collection and Database management

## 11.1 Data collection

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into eCRF are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

## 11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unmasked** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.



## 11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

# 12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. Descriptive analyses will be defined as number of observations, mean, standard deviation, median, first quartile and third quartile, minimum and maximum.

## 12.1 Analysis sets

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

The safety analysis set will include all patients that 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.

## 12.2 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.

## 12.3 Treatments

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

## 12.4 Analysis of the primary endpoint(s)

### 12.4.1 Definition of primary endpoint(s)

Primary efficacy endpoints for this study are BCVA as assessed by ETDRS visual acuity charts at week 12 and central retinal thickness as measured by SD-OCT at week 12. Primary safety endpoints include adverse events, vital signs, ECG intervals, safety laboratory measures, and complete ophthalmic exam, including: intraocular pressure, BCVA, dilated fundus exam, slit lamp examination, macular thickness by SD-OCT, and FA.

### 12.4.2 Statistical model, hypothesis, and method of analysis

BCVA will be analyzed with the change from baseline and a repeated measures model. Independent variables will include treatment, visit, and the treatment by visit interaction. Baseline BCVA and treatment naive and treatment experienced variable will be used as a covariate. An unstructured covariance matrix will be used. The mixed model repeated measures technique will be used to account for missing values. 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.

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 naive and treatment experienced variable. Although there appears to be a slight skewness in the distribution of central retinal thickness, making the inferential results of a log-transformed analysis more reliable, it is uncommon for this parameter to be analyzed this way. Thus, analysis will also be done with untransformed data, but with deference given to the inferential results (p-values and confidence intervals) of the log-transformed analysis.

Safety analysis is described in Section 12.5.1.

### 12.4.3 Handling of missing values/censoring/discontinuations

Missing values will be accounted for my using mixed methods repeated measures.

### 12.4.4 Sensitivity and Supportive analyses

## 12.5 Analysis of secondary endpoints

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.

### 12.5.1 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

The on-treatment period lasts from the date of first administration of study treatment to the end of the extension phase.

#### 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 AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

#### Vital signs

All vital signs data 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 data will be listed 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.

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## 12.5.2 Pharmacokinetics

Due to the reduced number of visits for remaining patients to enroll into the study, there will be fewer overall blood draws for PK sampling. Accordingly, the PK analysis will only be performed in a subset of patients where sufficient serum samples have been collected to permit meaningful analysis. 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 $AUC_{last}$, $AUC_{0\text{-}28d}$, Maximal 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).

Descriptive summaries including mean, coefficient of variation, median, minimum and maximum Commercially Confidential Information be presented by treatment and study day/sampling point.

The derivation of PK parameters at the patient level will be based on observed concentrations only, Commercially Confidential Information . A plot of mean concentration-time profile will be constructed. Plots of mean-time concentration profile of total LKA651 concentrations and ranibizumab will also be constructed.

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### 12.5.5 Patient reported outcomes

Not applicable.

## 12.6 Analysis of exploratory endpoints

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## 12.7 Interim analyses

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## 12.8 Sample size calculation

Twenty five patients per arm provide 80% power to detect a 5 letter improvement in BCVA compared to Lucentis®, p=0.05 (one-sided) for the single comparison (after 12 weeks of treatment), assuming a standard deviation (SD) of 7 letters, the SD observed in the Lucentis® DME trials. The software nQuery 7.0 was used to evaluate the power estimation and the sample size.

# 13 Ethical considerations and administrative procedures

## 13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## 13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (*defined as last patient last visit*) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings

## 13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

# 14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

## 14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

# 15 References

References are available upon request

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