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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LKA651

Trial Indication(s)

Diabetic Macular Edema

Protocol Number

CLKA651X2202

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: May 24, 2019 (Actual)
Primary Completion Date: June 17, 2022 (Actual)
Study Completion Date: August 31, 2022 (Actual)

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Reason for Termination (If applicable)

Study Design/Methodology

This study was a 3-arm, parallel group, randomized, patient- and investigator-masked trial planned in 90 patients with diabetic macular edema (DME). The study consisted of a screening period of 60 days, main study (12 weeks), and an extension period (12 weeks). The study was stratified such that sentinel safety cohorts were first 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 were enrolled into 1 of 3 arms: LKA651 monotherapy, LKA651 plus Lucentis, and Lucentis monotherapy. Every patient was dosed 3 times in 4-week intervals in the treatment phase and was then followed up for an extension phase of an additional 12 weeks during which Lucentis was allowed to be administered as rescue / PRN, at the discretion of the Investigator. No predefined rescue criteria were outlined as guidance.

Centers

22 centers in 4 countries: United States(8), Germany(5), Spain(5), Turkey(4)

Objectives:

The primary objectives of this study were to evaluate the safety/tolerability of three q4w Intravitreal (IVT) doses of LKA651 alone or in combination with Lucentis in patients with diabetic macular edema (DME) and 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. For this, the endpoints were ocular and systemic adverse events (AEs), vital signs (blood pressure, heart rate) and Electrocardiogram (ECG) intervals, safety laboratory measures (including reticulocyte count) and complete ophthalmic exam.

The secondary objectives were to evaluate duration of effect of three q4w IVT doses of LKA651 in patients with DME, for which, the endpoints were time to retreatment with anti- Vascular endothelial growth factor (VEGF) (as determined by the Investigator) after Week 12 during an additional 12-week extension phase. Another secondary objective was 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, the endpoints for this was assessment of serum levels of total LKA651 (maximum concentration (Cmax)) and area under curve

over the dosing interval (AUC0-28d) 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. And assessment of serum levels of ranibizumab (Cmax and AUC0-28d) when administered in combination with LKA651 after the first dose in a subset of patients with sufficient quantifiable serum samples to permit meaningful analysis.

Test Product (s), Dose(s), and Mode(s) of Administration

LKA651 monotherapy: 5 mg intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase

LKA651 + Lucentis combination therapy: LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase

Lucentis monotherapy: 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase

Statistical Methods

All efficacy evaluations were based on efficacy analysis set.

Best Corrected Visual Acuity (BCVA) was analyzed using a repeated measures model - a model where BCVA was the dependent variable. An unstructured covariance matrix was used. The mixed model repeated measures technique was used to account for missing values. The Kenword-Rodger estimate of denominator degrees of freedom was used. The Least square means (LSMs) for each treatment by time combination was presented. Additionally at each time, the difference between the combination treatment and Lucentis alone, as well as the difference between LKA651 and Lucentis alone were presented along with the resulting p-value and 90% Confidence interval (CI). The primary inference was based on the null hypothesis on no treatment difference for Day 85. A one-sided, alpha = 0.05 test was used for this purpose.

Central subfield retinal thickness was analyzed similarly as BCVA, with the exception that it was log-transformed, thus results were back-transformed to show results as a ratio to baseline and the difference between treatments was expressed as a ratio of treatments.

All safety evaluations were based on the safety analysis set. All tables were presented by treatment group. Summary tables for Adverse events (AEs) summarized only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). The on-treatment period lasted from the date of first administration of study treatment to the end of the extension phase.

All data obtained on AEs were displayed by treatment group and patient. The number and percentage of patients with treatment-emergent ocular AEs were summarized by treatment, primary System organ class (SOC), and Preferred term (PT). Separate summaries were provided for study medication related AEs, death, Serious adverse events (SAEs), intesities (mild, moderate, or severe), and AEs leading to discontinuation.

Intraocular pressure and slit lamp examination findings were listed by for each eye by treatment, patient, and visit/time. Summary statistics were provided by treatment and visit/time. Descriptive summary statistics for dilated fundus exam were presented by treatment and visit/time.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria
-Written informed consent must be obtained before any assessment is performed.
-Male and female patients age 18 to 85 years of age inclusive at screening
-Presence of type I or type II diabetes mellitus
-The Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the study eye must be between 24 and 70 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
-Presence of Diabetic macular edema (DME) in the study eye, with decrease in vision due to foveal thickening of central macular thickness ≥ 320 µm in the central subfield, as assessed on Spectral domain optical coherence tomography (SD-OCT) and confirmed by the central reading center at screening
-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

Exclusion criteria
-Patient with history of intravitreal (IVT) anti-vascular endothelial growth factor (VEGF) treatment in the study eye <90 days from baseline
-Patient with history of intraocular corticosteroids including dexamethasone intravitreal implants during the 6 month period prior to baseline. Any prior use of fluocinolone acetonide intravitreal implant (Iluvien) is prohibited regardless of timing
- Laser photocoagulation (macular or panretinal) in the study eye during the 3-month period prior to baseline.
- High risk proliferative diabetic retinopathy
-Patients, with type 1 or type 2 diabetes who have a hemoglobin A1C ≥ 12% at screening.
- Any progressive disease of the retina in the study eye (e.g. uveitis,rod-cone dystrophy) or optic nerve
- Area of macular retinal ischemia (as measured by the foveal avascular zone) ≥ 1000 µm.
- Active intraocular inflammation (graded as trace or above) or active
intraocular infection in either eye.
- Current diagnosis of or laboratory evidence for anemia, defined as a hemoglobin <10 g/dL for women and <11 g/dL for men.

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Participant Flow Table

Overall Study

	LKA651	LKA651 + Lucentis	Lucentis	Total
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	
Started	28	30	33	91
Completed	21	27	31	79
Not Completed	7	3	2	12
Withdrawal by Subject	3	1	1	5
Adverse Event	1	0	0	1
Death	1	0	0	1
Lost to Follow-up	2	2	1	5

Baseline Characteristics

	LKA651	LKA651 + Lucentis	Lucentis	Total
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	

Number of Participants [units: participants]	28	30	33	91
Baseline Analysis Population Description				
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation				
	61.6±8.58	63.8±8.18	61.2±9.02	62.2±8.60
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	9	13	10	32
Male	19	17	23	59
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
American Indian or Alaska Native	0	1	1	2
Asian	2	1	0	3
Native Hawaiian or Other Pacific Islander	0	1	0	1
Black or African American	3	0	0	3
White	23	27	32	82
More than one race	0	0	0	0
Unknown or Not Reported	0	0	0	0

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Primary Outcome Result(s)

Number of participants with Adverse Events

Description	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. The severity of the AEs (mild, moderate, severe) was based on the Common Terminology Criteria for Adverse Events (CTCAE). Number of participants in each category is reported in the table. A participant who falls multiple times in one category is counted only once.
Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Analysis Population Description	Safety Set

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	28	30	33
Number of participants with Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
AEs, Patients with AEs	20 (71.43%)	16 (53.33%)	19 (57.58%)
AEs of mild intensity	16 (57.14%)	15 (50%)	19 (57.58%)
AEs of moderate intensity	8 (28.57%)	6 (20%)	3 (9.09%)
AEs of severe intensity	4 (14.29%)	2 (6.67%)	1 (3.03%)

Study drug-related AEs	2 (7.14%)	1 (3.33%)	2 (6.06%)
Serious AEs	3 (10.71%)	4 (13.33%)	1 (3.03%)
AEs leading to discontinuation of study treatment	1 (3.57%)	0 (%)	0 (%)
Study-drug related AEs leading to discontinuation of study treatment	1 (3.57%)	0 (%)	0 (%)
Non-serious AEs	20 (71.43%)	16 (53.33%)	19 (57.58%)

Number of participants with ocular Adverse Events by preferred term in study eye

Description	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.
Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Analysis Population Description	Safety Set

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	28	30	33
Number of participants with ocular Adverse Events by preferred term in study eye (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**

Patients with at least one ocular AE in study eye	11 (39.29%)	7 (23.33%)	9 (27.27%)
Conjunctival haemorrhage	1 (3.57%)	4 (13.33%)	2 (6.06%)
Diabetic retinal oedema	2 (7.14%)	1 (3.33%)	2 (6.06%)
Diabetic retinopathy	1 (3.57%)	1 (3.33%)	1 (3.03%)
Visual acuity reduced	3 (10.71%)	0 (%)	0 (%)
Vitreous haemorrhage	1 (3.57%)	0 (%)	2 (6.06%)
Dry eye	0 (%)	1 (3.33%)	1 (3.03%)
Macular oedema	2 (7.14%)	0 (%)	0 (%)
Ocular hypertension	2 (7.14%)	0 (%)	0 (%)
Abnormal sensation in eye	0 (%)	0 (%)	1 (3.03%)
Anterior chamber flare	0 (%)	1 (3.33%)	0 (%)
Corneal erosion	1 (3.57%)	0 (%)	0 (%)
Cystoid macular oedema	1 (3.57%)	0 (%)	0 (%)
Dacryostenosis acquired	1 (3.57%)	0 (%)	0 (%)
Eye pain	1 (3.57%)	0 (%)	0 (%)
Eyelids pruritus	0 (%)	0 (%)	1 (3.03%)

Lenticular opacities	0 (%)	0 (%)	1 (3.03%)
Punctate keratitis	0 (%)	1 (3.33%)	0 (%)
Retinal cyst	1 (3.57%)	0 (%)	0 (%)
Retinal detachment	1 (3.57%)	0 (%)	0 (%)
Retinal exudates	1 (3.57%)	0 (%)	0 (%)
Retinal haemorrhage	1 (3.57%)	0 (%)	0 (%)
Vitreoretinal traction syndrome	0 (%)	0 (%)	1 (3.03%)

Number of participants with non-ocular Adverse Events (>=2%)

Description	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.
Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Analysis Population Description	Safety Set

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase

Number of Participants Analyzed [units: participants]	28	30	33
Number of participants with non-ocular Adverse Events (>=2%) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Patients with at least one non-ocular AE	16 (57.14%)	15 (50%)	14 (42.42%)

Intraocular pressure (IOP) in study eye

Description	Intraocular pressure was measured per the study site's regular practice.
Time Frame	Screening, and Day 85
Analysis Population Description	Safety analysis set

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	28	30	33
Intraocular pressure (IOP) in study eye (units: mmHg)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Screening	15.1 ± 3.20	14.9 ± 3.44	15.5 ± 2.88
Day 85 (n=24,28,31)	15.5 ± 3.56	15.6 ± 3.67	15.2 ± 3.79

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Best Corrected Visual Acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts in study eye

Description	BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. Visual function of the study eye was assessed using the ETDRS protocol. BCVA in study eye was analyzed with a mixed model for repeated measures. The model included treatment, visit, and the treatment by visit interaction as independent variables. An unstructured residual covariance structure was used. Baseline BCVA value and treatment naïve and treatment experienced variable were used as covariates. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.
Time Frame	Days 2, 8, 15, 29, 43, 57, and 85
Analysis Population Description	Pharmacodynamic analysis set - Participants with a valid measure and without a protocol deviation that would have an impact on the outcome measure.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	25	28	32
Best Corrected Visual Acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts in study eye (units: Scores on a scale)	**Mean (90% Confidence Interval)**	**Mean (90% Confidence Interval)**	**Mean (90% Confidence Interval)**
Day 2 (n=6,17,10)	61.5 (58.6 to 64.4)	64.4 (62.3 to 66.6)	64.1 (61.8 to 66.5)
Day 8 (n=6,16,10)	65.2 (61.7 to 68.7)	68.6 (66.1 to 71.2)	66.2 (63.4 to 69.0)
Day 15 (n=6,16,10)	65.9 (62.4 to 69.4)	68.6 (65.8 to 71.4)	68.4 (65.4 to 71.3)
Day 29 (n=25,28,32)	65.5 (62.6 to 68.4)	68.2 (65.3 to 71.0)	68.5 (65.9 to 71.1)

Day 43 (n=5,16,8)	67.8 (64.4 to 71.1)	70.4 (67.6 to 73.3)	69.1 (66.2 to 71.9)
Day 57 (n=24,27,31)	67.6 (64.7 to 70.5)	71.5 (68.6 to 74.4)	70.0 (67.4 to 72.6)
Day 85 (n=23,27,31)	67.8 (64.8 to 70.9)	72.5 (69.5 to 75.4)	70.5 (67.8 to 73.2)

Statistical Analysis

Groups	LKA651, Lucentis	Day 2
Type of Statistical Test	Superiority	
P Value	0.887	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-2.6	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-6.2 to 1.0	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 2
Type of Statistical Test	Superiority	
P Value	0.431	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	0.3	Comparison of model-based mean estimates.

90 % Confidence Interval 2-Sided	-2.6 to 3.2	

Statistical Analysis

Groups	LKA651, Lucentis	Day 8
Type of Statistical Test	Superiority	
P Value	0.647	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-1.0	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-5.4 to 3.4	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 8
Type of Statistical Test	Superiority	
P Value	0.130	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	2.4	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-1.1 to 6.0	

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Statistical Analysis

Groups	LKA651, Lucentis	Day 15
Type of Statistical Test	Superiority	
P Value	0.818	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-2.5	Comparison of model-based mean estimates
90 % Confidence Interval 2-Sided	-6.9 to 2.0	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 15
Type of Statistical Test	Superiority	
P Value	0.457	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	0.3	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-3.6 to 4.1	

Statistical Analysis

Groups	LKA651, Lucentis	Day 29
Type of Statistical Test	Superiority	

P Value	0.906	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-3.1	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-6.9 to 0.8	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 29
Type of Statistical Test	Superiority	
P Value	0.566	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-0.4	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-4.1 to 3.3	

Statistical Analysis

Groups	LKA651, Lucentis	Day 43
Type of Statistical Test	Superiority	
P Value	0.686	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-1.3	Comparison of model-based mean estimates.

90 % Confidence Interval 2-Sided	-5.6 to 3.1	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 43
Type of Statistical Test	Superiority	
P Value	0.280	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	1.4	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-2.5 to 5.2	

Statistical Analysis

Groups	LKA651, Lucentis	Day 57
Type of Statistical Test	Superiority	
P Value	0.849	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-2.4	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-6.3 to 1.4	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 57
Type of Statistical Test	Superiority	
P Value	0.254	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	1.5	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-2.2 to 5.2	

Statistical Analysis

Groups	LKA651, Lucentis	Day 85
Type of Statistical Test	Superiority	
P Value	0.866	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	-2.7	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-6.6 to 1.3	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 85
Type of Statistical Test	Superiority	

P Value	0.198	
Method	Other Mixed model repeated measures analysis	
Other Difference (Test vs Reference)	2.0	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	-1.9 to 5.8	

Inner Macular Thickness (inferior)

Description	Macular thickness was measured by spectral domain optical coherence tomography (SD-OCT).
Time Frame	Week 12 (Day 85)
Analysis Population Description	Safety analysis set - Participants in the safety analysis set with a valid measurement for the outcome measure.

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	24	28	31
Inner Macular Thickness (inferior) (units: micrometer)	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**
	503.06 ± 137.235	400.82 ± 53.180	390.48 ± 48.097

Inner Macular Thickness (temporal)

Description	Macular thickness was measured by spectral domain optical coherence tomography (SD-OCT).

Time Frame	Week 12 (Day 85)
Analysis Population Description	Safety analysis set - Participants in the safety analysis set with a valid measurement for the outcome measure.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	24	28	31
Inner Macular Thickness (temporal) (units: micrometer)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	505.27 ± 141.410	414.64 ± 67.032	404.93 ± 56.099

Outer Macular Thickness (inferior)

Description	Macular thickness was measured by spectral domain optical coherence tomography (SD-OCT).
Time Frame	Week 12 (Day 85)
Analysis Population Description	Safety analysis set - Participants in the safety analysis set with a valid measurement for the outcome measure.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection,	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4

		every 4 weeks for a total of 3 doses in the treatment phase	weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	23	28	31
Outer Macular Thickness (inferior) (units: micrometer)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	388.66 ± 88.128	349.39 ± 44.538	342.88 ± 50.612

Outer Macular Thickness (temporal)

Description	Macular thickness was measured by spectral domain optical coherence tomography (SD-OCT).
Time Frame	Week 12 (Day 85)
Analysis Population Description	Safety analysis set - Participants in the safety analysis set with a valid measurement for the outcome measure.

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	23	28	31
Outer Macular Thickness (temporal) (units: micrometer)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	404.60 ± 103.616	371.83 ± 70.124	352.24 ± 56.793

NOVARTIS

Number of participants without changes in foveal avascular zone as measured by Fluorescein angiography (FA) in study eye

Description	Foveal avascular zone was assessed by fluorescein angiography (FA).
Time Frame	Days 29, 57, 85, End of Study (Up to Day 140)
Analysis Population Description	Pharmacodynamic analysis set - Participants with a valid measure and without a protocol deviation that would have an impact on the outcome measure.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	21	25	30
Number of participants without changes in foveal avascular zone as measured by Fluorescein angiography (FA) in study eye (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Day 29 - NO CHANGE (n=3,16,11)	3 (100%)	16 (100%)	11 (100%)
Day 57 - NO CHANGE (n=3,16,7)	3 (100%)	16 (100%)	7 (100%)
Day 85 - NO CHANGE (n=21,25,29)	21 (100%)	25 (100%)	29 (100%)
End of Study (Up to Day 140) - NO CHANGE (n=17,23,30)	17 (100%)	22 (95.65%)	30 (100%)
End of Study (Up to Day 140) - CANNOT GRADE (n=0,23,0)	(NaN%)	1 (4.35%)	(NaN%)

NOVARTIS

Mixed model repeated measures analysis of ratio to baseline in central subfield retinal thickness (CSFT) in the study eye

Description	Central subfield thickness was measured by spectral domain optical coherence tomography (SD-OCT). Central subfield retinal thickness was analyzed with a mixed model for repeated measures. The model included treatment, visit, and the treatment by visit interaction as independent variables. An unstructured residual covariance structure was used. Log-transformed baseline central subfield retinal thickness and treatment naïve and treatment experienced variable were used as covariates. Results were back-transformed to show results as a ratio to baseline.
Time Frame	Days 8, 15, 29, 43, 57, 85
Analysis Population Description	Pharmacodynamic analysis set - Participants with a valid measure and without a protocol deviation that would have an impact on the outcome measure.

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	25	28	32
Mixed model repeated measures analysis of ratio to baseline in central subfield retinal thickness (CSFT) in the study eye (units: ratio)	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**
Day 8 (n=6,16,10)	0.99 (0.92 to 1.07)	0.83 (0.78 to 0.88)	0.83 (0.78 to 0.88)
Day 15 (n=6,16,10)	0.97 (0.90 to 1.05)	0.83 (0.78 to 0.88)	0.80 (0.76 to 0.86)
Day 29 (n=25,28,32)	1.00 (0.94 to 1.05)	0.80 (0.76 to 0.85)	0.82 (0.78 to 0.86)
Day 43 (n=5,16,8)	1.04 (0.97 to 1.13)	0.76 (0.71 to 0.81)	0.79 (0.74 to 0.84)

Day 57 (n=24,27,30)	0.95 (0.89 to 1.00)	0.75 (0.70 to 0.80)	0.80 (0.76 to 0.84)
Day 85 (n=23,27,31)	0.97 (0.91 to 1.05)	0.75 (0.70 to 0.80)	0.78 (0.73 to 0.83)

Statistical Analysis

Groups	LKA651, Lucentis	Day 8
Type of Statistical Test	Superiority	
P Value	0.998	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.20	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	1.08 to 1.33	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 8
Type of Statistical Test	Superiority	
P Value	0.527	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.00	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	0.92 to 1.09	

Statistical Analysis

Groups	LKA651, Lucentis	Day 15
Type of Statistical Test	Superiority	
P Value	0.999	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.21	Comparison of model-based mean estimates
90 % Confidence Interval 2-Sided	1.10 to 1.33	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 15
Type of Statistical Test	Superiority	
P Value	0.716	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.03	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	0.95 to 1.12	

Statistical Analysis

Groups	LKA651, Lucentis	Day 29
Type of Statistical Test	Superiority	

P Value	1.000	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.21	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	1.13 to 1.31	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 29
Type of Statistical Test	Superiority	
P Value	0.281	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	0.98	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	0.91 to 1.05	

Statistical Analysis

Groups	LKA651, Lucentis	Day 43
Type of Statistical Test	Superiority	
P Value	1.000	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.32	Comparison of model-based mean estimates.

90 % Confidence Interval 2-Sided	1.20 to 1.46	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 43
Type of Statistical Test	Superiority	
P Value	0.200	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	0.96	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	0.88 to 1.04	

Statistical Analysis

Groups	LKA651, Lucentis	Day 57
Type of Statistical Test	Superiority	
P Value	1.000	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	1.18	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	1.09 to 1.28	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 57
Type of Statistical Test	Superiority	
P Value	0.083	
Method	Other Mixed model repeated measures analysis	
Other Ratio (Test vs Reference)	0.94	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	0.87 to 1.01	

Statistical Analysis

Groups	LKA651, Lucentis	Day 85
Type of Statistical Test	Superiority	
P Value	1.000	
Method	Other Mixed model repeated measures analysis	
Other Ratio(Test vs Reference)	1.26	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	1.14 to 1.38	

Statistical Analysis

Groups	LKA651 + Lucentis, Lucentis	Day 85
Type of Statistical Test	Superiority	

P Value	0.254	
Method	Other Mixed model repeated measures analysis	
Other Ratio(Test vs Reference)	0.96	Comparison of model-based mean estimates.
90 % Confidence Interval 2-Sided	0.88 to 1.06	

Secondary Outcome Result(s)

Number of participants who needed retreatment with anti-VEGF in study eye after week 12

Description

Time Frame: Week 12 (Day 85) up to Day 140

Analysis Population Description: Pharmacodynamic analysis set - Participants with a valid measure and without a protocol deviation that would have an impact on the outcome measure.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	25	29	32
Number of participants who needed retreatment with anti-VEGF in study eye after week 12 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**

Number (%) of subjects who needed retreatment with anti-VEGF in study eye after Week 12	16 (64%)	16 (55.17%)	21 (65.63%)

Time to retreatment in study eye with anti-VEGF after week 12

Description	Time to retreatment with anti VEGF (as determined by the investigator) after Week 12 during the additional 12 week extension phase (that was up to 16 weeks after the last dose) was examined with a Kaplan Meier plot.
Time Frame	Week 12 (Day 85) up to Day 140
Analysis Population Description	Pharmacodynamic analysis set - Participants with a valid measure and without a protocol deviation that would have an impact on the outcome measure.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	25	29	32
Time to retreatment in study eye with anti-VEGF after week 12 (units: Days after Day 85 (Week 12))	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	55.0 (17.0 to NA)[1]	34.0 (12.0 to NA)[1]	31.0 (9.0 to 109.0)

[1] Not estimable due to insufficient number of participants with events.

Summary statistics of Pharmacokinetics - serum concentrations of LKA651

Description	PK parameters were determined using non-compartmental methods using the most recent version of WinNonlin Phoenix (Version 8.2). Concentrations below the lower limit of quantification (LLOQ) were treated as 1/2 LLOQ in summary statistics.

Time Frame	Day 1 (0, 0.5 and 4 hrs post dose), Day 2, Day 8, Day 15, Day 29 (0, 0.5 and 4 hrs post dose), Day 43, Day 57 (0, 0.5 and 4 hrs post dose), Day 85
Analysis Population Description	Pharmacokinetic analysis set. Concentrations below the Lower Limit of Quantification (LLOQ) are reported as zero.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	23	28	0
Summary statistics of Pharmacokinetics - serum concentrations of LKA651 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1 - 0 hrs (n=23,28,0)	0.00 ± 0.00	0.00 ± 0.00	
Day 1 - 0.5 hrs post dose (n=1,8,0)	0.00	0.00 ± 0.00	
Day 1 - 4 hrs post dose (n = 6,15,0)	114 ± 211	4.43 ± 17.1	
Day 2 (n=6,15,0)	36.3 ± 29.2	8.13 ± 21.6	
Day 8 (n=6,15,0)	16.2 ± 27.5	2.08 ± 8.06	
Day 15 (n=5,15,0)	7.24 ± 16.2	0.00 ± 0.00	
Day 29 - 0 hrs (n=22,24,0)	0.00 ± 0.00	0.00 ± 0.00	
Day 29 - 0.5 hrs post dose (n=1,6,0)	0.00	0.00 ± 0.00	
Day 29 - 4 hrs post dose (n=0,6,0)		7.60 ± 18.6	
Day 43 (n=1,6,0)	0.00	0.00 ± 0.00	

Day 57 - 0 hrs (n=21,23,0)	0.00 ± 0.00	0.00 ± 0.00
Day 57 - 0.5 hrs post dose (n=1,6,0)	0.00	0.00 ± 0.00
Day 57 - 4 hrs post dose (n=0,6,0)		0.00 ± 0.00
Day 85 (n=19,23,0)	0.00 ± 0.00	0.00 ± 0.00

Summary statistics of Pharmacokinetics - AUC0-28d of LKA651 (serum)

Description	Area under the curve over the dosing interval 0 to 28 days.
Time Frame	Day 1 - 4 hrs post dose, Day 2, Day 8, Day 15, Day 29 - 4 hrs post dose, Day 43, Day 57 - 4 hrs post dose, Day 85
Analysis Population Description	Pharmacokinetic analysis set. PK parameters could not be derived due to the limited number of LKA651 concentrations above the lower limit of quantification.

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	0	0	0
Summary statistics of Pharmacokinetics - AUC0-28d of LKA651 (serum) (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Summary statistics of Pharmacokinetics - serum concentrations of Lucentis

Description

Time Frame	Day 1 - 4 hrs post dose, Day 2, Day 8, Day 15, Day 29 - 4 hrs post dose, Day 43, Day 57 - 4 hrs post dose, Day 85
Analysis Population Description	Pharmacokinetic analysis set. PK parameters could not be derived due to the limited number of Lucentis concentrations above the lower limit of quantification.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	0	0	0
Summary statistics of Pharmacokinetics - serum concentrations of Lucentis (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Summary statistics of Pharmacokinetics - AUC0-28d of Lucentis (serum)

Description	Area under the curve over the dosing interval 0 to 28 days.
Time Frame	Day 1 - 4 hrs post dose, Day 2, Day 8, Day 15, Day 29 - 4 hrs post dose, Day 43, Day 57 - 4 hrs post dose, Day 85
Analysis Population Description	Pharmacokinetic analysis set. PK parameters could not be derived due to the limited number of Lucentis concentrations above the lower limit of quantification.

	LKA651	LKA651 + Lucentis	Lucentis
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection,	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4

	total of 3 doses in the treatment phase	every 4 weeks for a total of 3 doses in the treatment phase	weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	0	0	0
Summary statistics of Pharmacokinetics - AUC0-28d of Lucentis (serum) (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Post-Hoc Outcome Result(s)

All Collected Deaths

Description	On-treatment deaths are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days). Post-treatment deaths are reported for the timeframe of greater than 30 days after last treatment, until study completion, up to approximately 168 days. All deaths refer to the sum of on-treatment and post-treatment deaths.
Time Frame	On-treatment – up to 12 weeks; Post-treatment - greater than 30 days after last treatment, until study completion, up to approximately 168 days
Analysis Population Description	Safety Set

	LKA651	**LKA651 + Lucentis**	**Lucentis**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase
Number of Participants Analyzed [units: participants]	28	30	33

All Collected Deaths (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
On-Treatment Deaths	0 (%)	0 (%)	0 (%)
Post-Treatment Deaths	1 (3.57%)	0 (%)	0 (%)
All Deaths	1 (3.57%)	0 (%)	0 (%)

Safety Results

Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Source Vocabulary for Table Default	MedDRA (25.0)

Collection Approach for Table Default	Systematic Assessment

	LKA651 N = 28	LKA651 + Lucentis N = 30	Lucentis N = 33	Total N = 91
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Total
Total Number Affected	1 (3.57%)	0 (0%)	0 (0%)	1 (1.1%)
Total Number At Risk	28	30	33	91

Serious Adverse Events

Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

	LKA651 N = 28	LKA651 + Lucentis N = 30	Lucentis N = 33	Total N = 91

Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	Total
Total # Affected by any Serious Adverse Event	3 (10.71%)	4 (13.33%)	1 (3.03%)	8 (8.79%)
Total # at Risk by any Serious Adverse Event	28	30	33	91
Cardiac disorders				
Angina unstable	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Eye disorders				
Retinal detachment	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Gastrointestinal disorders				
Cyclic vomiting syndrome	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Varices oesophageal	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Infections and infestations				
COVID-19	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
COVID-19 pneumonia	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Pneumonia	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Metabolism and nutrition disorders				
Dehydration	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Bone cancer metastatic	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)

Prostate cancer metastatic	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Nervous system disorders				
Haemorrhagic stroke	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Psychiatric disorders				
Confusional state	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events are reported from first dose of study treatment until end of study treatment plus 12 weeks post treatment, up to a maximum timeframe of approximately 24 weeks (approximately 168 days).
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	LKA651 N = 28	**LKA651 + Lucentis N = 30**	**Lucentis N = 33**	**Total N = 91**
Arm/Group Description	LKA651 5 mg Intravitreal injection, every 4 weeks	LKA651 1 mg + Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites)	Lucentis 0.3 mg (U.S. sites) or 0.5 mg (ex U.S. sites) Intravitreal	Total

	for a total of 3 doses in the treatment phase	Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	injection, every 4 weeks for a total of 3 doses in the treatment phase	
Total # Affected by any Other Adverse Event	20 (71.43%)	16 (53.33%)	19 (57.58%)	55 (60.44%)
Total # at Risk by any Other Adverse Event	28	30	33	91
Blood and lymphatic system disorders				
Anaemia	1 (3.57%)	2 (6.67%)	1 (3.03%)	4 (4.40%)
Cardiac disorders				
Atrial fibrillation	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Atrioventricular block first degree	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Coronary artery disease	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Sinus bradycardia	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Eye disorders				
Abnormal sensation in eye	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Anterior chamber flare	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Conjunctival haemorrhage	1 (3.57%)	5 (16.67%)	2 (6.06%)	8 (8.79%)
Corneal erosion	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Cystoid macular oedema	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Dacryostenosis acquired	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Diabetic retinal oedema	3 (10.71%)	1 (3.33%)	2 (6.06%)	6 (6.59%)
Diabetic retinopathy	1 (3.57%)	1 (3.33%)	1 (3.03%)	3 (3.30%)
Dry eye	0 (0.00%)	1 (3.33%)	1 (3.03%)	2 (2.20%)
Epiretinal membrane	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)

Eye pain	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Eyelids pruritus	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Lenticular opacities	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Macular oedema	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.20%)
Ocular hypertension	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.20%)
Punctate keratitis	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Retinal cyst	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Retinal exudates	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Retinal haemorrhage	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Retinal oedema	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Visual acuity reduced	3 (10.71%)	0 (0.00%)	0 (0.00%)	3 (3.30%)
Vitreoretinal traction syndrome	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Vitreous haemorrhage	1 (3.57%)	0 (0.00%)	2 (6.06%)	3 (3.30%)
Gastrointestinal disorders				
Gastrooesophageal reflux disease	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Hepatobiliary disorders				
Hepatic steatosis	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Hepatotoxicity	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Infections and infestations				
Adenoviral conjunctivitis	0 (0.00%)	1 (3.33%)	1 (3.03%)	2 (2.20%)
Conjunctivitis	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Coronavirus infection	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
COVID-19	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.20%)
Herpes zoster	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)

Nasopharyngitis	0 (0.00%)	2 (6.67%)	0 (0.00%)	2 (2.20%)
Sinusitis	0 (0.00%)	2 (6.67%)	0 (0.00%)	2 (2.20%)
Urinary tract infection	1 (3.57%)	1 (3.33%)	1 (3.03%)	3 (3.30%)
Injury, poisoning and procedural complications				
Foot fracture	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Skin laceration	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Thoracic vertebral fracture	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
XIIth nerve injury	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Investigations				
Blood cholesterol increased	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Blood creatine phosphokinase increased	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Blood creatinine increased	2 (7.14%)	0 (0.00%)	0 (0.00%)	2 (2.20%)
Blood glucose increased	1 (3.57%)	1 (3.33%)	0 (0.00%)	2 (2.20%)
Blood triglycerides increased	1 (3.57%)	0 (0.00%)	1 (3.03%)	2 (2.20%)
Blood urea increased	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Glycosylated haemoglobin increased	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Intraocular pressure increased	1 (3.57%)	1 (3.33%)	0 (0.00%)	2 (2.20%)
Lipase increased	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Lymphocyte count decreased	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Pancreatic enzymes increased	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Prostatic specific antigen increased	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
SARS-CoV-2 test positive	1 (3.57%)	1 (3.33%)	0 (0.00%)	2 (2.20%)
Urine ketone body present	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Urine leukocyte esterase positive	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)

Metabolism and nutrition disorders				
Diabetes mellitus	0 (0.00%)	0 (0.00%)	2 (6.06%)	2 (2.20%)
Hypercholesterolaemia	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Hyperglycaemia	2 (7.14%)	1 (3.33%)	1 (3.03%)	4 (4.40%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Hyperlipasaemia	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Hyperlipidaemia	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Hypertriglyceridaemia	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Hypocalcaemia	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Hypomagnesaemia	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Hyponatraemia	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Type 2 diabetes mellitus	0 (0.00%)	2 (6.67%)	1 (3.03%)	3 (3.30%)
Vitamin B complex deficiency	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Vitamin D deficiency	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Musculoskeletal and connective tissue disorders				
Back pain	1 (3.57%)	1 (3.33%)	0 (0.00%)	2 (2.20%)
Myopathy	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Sjogren's syndrome	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Nervous system disorders				
Headache	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
VIth nerve paralysis	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Psychiatric disorders				
Anxiety	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)

Renal and urinary disorders				
Acute kidney injury	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Chronic kidney disease	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Nephrolithiasis	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Urinary incontinence	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0 (0.00%)	1 (3.33%)	0 (0.00%)	1 (1.10%)
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure	1 (3.57%)	0 (0.00%)	0 (0.00%)	1 (1.10%)
Epistaxis	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Hypoxia	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Vascular disorders				
Essential hypertension	0 (0.00%)	0 (0.00%)	1 (3.03%)	1 (1.10%)
Hypertension	3 (10.71%)	1 (3.33%)	3 (9.09%)	7 (7.69%)

Other Relevant Findings

None

Conclusion:

Overall, the study failed to demonstrate superiority of LKA651 over Lucentis both as monotherapy and in combination.

A higher proportion of adverse events (AEs) was reported in the LKA651 monotherapy arm (71.4%) as compared to the LKA651+Lucentis arm (53.3%) and the Lucentis monotherapy arm (57.6%).

There was no significant difference in the number of patients with severe AEs amongst the treatment arms (4 patients from LKA651 monotherapy arm, 2 patients from LKA651+Lucentis arm and 1 patient from Lucentis monotherapy arm).

There was 1 study drug-related AE leading to discontinuation of study treatment, which was from the LKA651 monotherapy arm. The event was temporal retinal detachment of right eye and was of severe intensity.

There was one death due to haemorrhagic stroke in the LKA651 monotherapy arm.

No significant changes were observed or reported in vital signs across the treatment arms. There were no changes in the clinical biochemistry across the arms.

Immunogenicity results suggest that there were 17 patients who had positive samples overall at any time from the LKA651 arm, 14 from the LKA651+Lucentis arm and 8 from the Lucentis arm.

No change in foveal avascular zone by Fluorescein angiography (FA) was observed in any of the three treatment arms on Days 29, 57, and 85.

Because of the limited number of concentrations above the lower limit of quantification, no pharmacokinetics (PK) parameters were derived, no plot of PK data was released for LKA651 and no summary table of Lucentis concentrations by time point was provided.

Date of Clinical Trial Report

24 July 2023