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

Summary

EudraCT number	2018-000031-28
Trial protocol	DE ES
Global end of trial date	31 August 2022

Results information

Result version number	v1
This version publication date	31 August 2023
First version publication date	31 August 2023

Trial information

Trial identification

Sponsor protocol code	CLKA651X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03927690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2022
Global end of trial reached?	Yes
Global end of trial date	31 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	91
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study population consisted of male and female patients with DME, who were 18 to 85 years of age at screening, and who were either treatment naive or experienced i.e. had been treated with anti VEGF therapy > 90 days before baseline.

Pre-assignment period milestones

Number of subjects started	91
Number of subjects completed	91

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LKA651

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	LKA651
Investigational medicinal product code	LKA651
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

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

Arm title	LKA651 + Lucentis

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	LKA651
Investigational medicinal product code	LKA651
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

LKA651 1 mg intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase

Investigational medicinal product name	50242-080-01
Investigational medicinal product code	50242-080-01
Other name	Ranibizumab
Pharmaceutical forms	Solution for injection

Routes of administration	Intravitreal use

Dosage and administration details:

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

Arm title	Lucentis

Arm description:

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

Arm type	Active comparator
Investigational medicinal product name	50242-080-01
Investigational medicinal product code	50242-080-01
Other name	Ranibizumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

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 subjects in period 1	LKA651	LKA651 + Lucentis	Lucentis
Started	28	30	33
Completed	21	27	31
Not completed	7	3	2
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	3	1	1
Adverse event, non-fatal	1	-	-
Lost to follow-up	2	2	1

Baseline characteristics

Reporting groups	
Reporting group title	LKA651
Reporting group description:	
LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	
Reporting group title	LKA651 + Lucentis
Reporting group description:	
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	
Reporting group title	Lucentis
Reporting group description:	
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	

Reporting group values	LKA651	LKA651 + Lucentis	Lucentis
Number of subjects	28	30	33
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	18	20
From 65-84 years	11	12	13
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	61.6	63.8	61.2
standard deviation	± 8.58	± 8.18	± 9.02
Sex: Female, Male Units: Participants			
Female	9	13	10
Male	19	17	23
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	2	1	0
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	3	0	0
White	23	27	32
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		

Number of subjects	91		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	55		
From 65-84 years	36		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	32		
Male	59		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	3		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	3		
White	82		
More than one race	0		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	LKA651
Reporting group description:	
LKA651 5 mg Intravitreal injection, every 4 weeks for a total of 3 doses in the treatment phase	
Reporting group title	LKA651 + Lucentis
Reporting group description:	
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	
Reporting group title	Lucentis
Reporting group description:	
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	

Primary: Overall incidence of Adverse Events

End point title	Overall incidence of Adverse Events[1]
End point description:	
Incidence of adverse events (AEs) is defined as number of participants with AEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs. 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 participants who falls multiple times in one category is counted only once. Disc = discontinuation Trt = study treatment	
End point type	Primary
End point timeframe:	
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).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are not applicable for AE data. Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	33	
Units: Participants				
AEs, Patients with AEs	20	16	19	
AEs of mild intensity	16	15	19	
AEs of moderate intensity	8	6	3	
AEs of severe intensity	4	2	1	
Study drug-related AEs	2	1	2	
Serious AEs	3	4	1	
AEs leading to disc. of study treatment	1	0	0	
Study-drug related AEs leading to disc. of trt	1	0	0	
Non-serious AEs	20	16	19	

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of ocular Adverse Events by preferred term in study eye

End point title	Incidence of ocular Adverse Events by preferred term in study eye[2]

End point 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.

End point type	Primary

End point timeframe:

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).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are not applicable for AE data. Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	33	
Units: Participants				
Patients with at least one ocular AE in study eye	11	7	9	
Conjunctival haemorrhage	1	4	2	
Diabetic retinal oedema	2	1	2	
Diabetic retinopathy	1	1	1	
Visual acuity reduced	3	0	0	
Vitreous haemorrhage	1	0	2	
Dry eye	0	1	1	
Macular oedema	2	0	0	
Ocular hypertension	2	0	0	
Abnormal sensation in eye	0	0	1	
Anterior chamber flare	0	1	0	
Corneal erosion	1	0	0	
Cystoid macular oedema	1	0	0	
Dacryostenosis acquired	1	0	0	
Eye pain	1	0	0	
Eyelids pruritus	0	0	1	
Lenticular opacities	0	0	1	
Punctate keratitis	0	1	0	
Retinal cyst	1	0	0	
Retinal detachment	1	0	0	
Retinal exudates	1	0	0	

Retinal haemorrhage	1	0	0	
Vitreoretinal traction syndrome	0	0	1	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with non-ocular Adverse Events (>=2%)[3]

End point 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.

End point type	Primary

End point timeframe:

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).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis are not applicable for AE data. Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	33	
Units: Participants	16	15	14	

Statistical analyses

No statistical analyses for this end point

Primary: Intraocular pressure (IOP) in study eye

End point title	Intraocular pressure (IOP) in study eye[4]

End point description:

Intraocular pressure was measured per the study site’s regular practice.

End point type	Primary

End point timeframe:

Screening, and Day 85

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	33	
Units: mmHg				
arithmetic 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)	

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Primary

End point timeframe:

Days 2, 8, 15, 29, 43, 57, and 85

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	33	
Units: Scores on a scale				
arithmetic mean (confidence interval 90%)				
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 analyses

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 2	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.887
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-2.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.2
upper limit	1

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description:	
Day 2	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.431
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	0.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.6
upper limit	3.2

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 8	
Comparison groups	LKA651 v Lucentis

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.647
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.4
upper limit	3.4

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description:	
Day 8	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.13
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	2.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.1
upper limit	6

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 15	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.818
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-2.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.9
upper limit	2

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 15	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.457
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	0.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.6
upper limit	4.1

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description: Day 29	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.906
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-3.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.9
upper limit	0.8

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 29	
Comparison groups	LKA651 + Lucentis v Lucentis

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.566
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.1
upper limit	3.3

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 43	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.686
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-1.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.6
upper limit	3.1

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description:	
Day 43	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.28
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.5
upper limit	5.2

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 57	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.849
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-2.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.3
upper limit	1.4

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description:	
Day 57	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.254
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.2
upper limit	5.2

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 85	
Comparison groups	LKA651 v Lucentis

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.866
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	-2.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.6
upper limit	1.3

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description:	
Day 85	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.198
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.9
upper limit	5.8

Primary: Inner Macular Thickness (inferior)

End point title	Inner Macular Thickness (inferior)[5]
End point description:	
Macular thickness was measured by spectral domain optical coherence tomography (SD-OCT).	
End point type	Primary
End point timeframe:	
Week 12 (Day 85)	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	28	31	
Units: micrometer				
arithmetic mean (standard deviation)	503.06 (± 137.235)	400.82 (± 53.180)	390.48 (± 48.097)	

Statistical analyses

No statistical analyses for this end point

Primary: Inner Macular Thickness (temporal)

End point title	Inner Macular Thickness (temporal)[6]

End point description:

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

End point type	Primary

End point timeframe:

Week 12 (Day 85)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	28	31	
Units: micrometer				
arithmetic mean (standard deviation)	505.27 (± 141.410)	414.64 (± 67.032)	404.93 (± 56.099)	

Statistical analyses

No statistical analyses for this end point

Primary: Outer Macular Thickness (inferior)

End point title	Outer Macular Thickness (inferior)[7]

End point description:

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

End point type	Primary

End point timeframe:

Week 12 (Day 85)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	28	31	
Units: micrometer				
arithmetic mean (standard deviation)	388.66 (± 88.128)	349.39 (± 44.538)	342.88 (± 50.612)	

Statistical analyses

No statistical analyses for this end point

Primary: Outer Macular Thickness (temporal)

End point title	Outer Macular Thickness (temporal)[8]

End point description:

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

End point type	Primary

End point timeframe:

Week 12 (Day 85)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	28	31	
Units: micrometer				
arithmetic mean (standard deviation)	404.60 (± 103.616)	371.83 (± 70.124)	352.24 (± 56.793)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants without changes in foveal avascular zone as measured by Fluorescein angiography (FA) in study eye[9]

End point description:

Foveal avascular zone was assessed by fluorescein angiography (FA).

EoS = End of Study

End point type	Primary

End point timeframe:

Days 29, 57, 85, End of Study (Up to Day 140)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summary statistics are available.

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	25	30	
Units: Participants				
Day 29 - NO CHANGE (n=3,16,11)	3	16	11	
Day 57 - NO CHANGE (n=3,16,7)	3	16	7	
Day 85 - NO CHANGE (n=21,25,29)	21	25	29	
EoS (Up to Day 140) NO CHANGE (n=17,23,30)	17	22	30	
EoS (Up to Day 140) CANNOT GRADE (n=0,23,0)	999	1	999	

Statistical analyses

No statistical analyses for this end point

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

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

End point 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 backtransformed to show results as a ratio to baseline.

End point type	Primary

End point timeframe:

Days 8, 15, 29, 43, 57, 85

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	28	32	
Units: µm				
geometric mean (confidence interval 90%)				
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) Day 85 (n=23,27,31)	0.95 (0.89 to 1.00) 0.97 (0.91 to 1.05)	0.75 (0.70 to 0.80) 0.75 (0.70 to 0.80)	0.80 (0.76 to 0.84) 0.78 (0.73 to 0.83)	

Statistical analyses

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description: Day 8	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.998
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.08
upper limit	1.33

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 8	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.527
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.09

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description: Day 15	
Comparison groups	LKA651 v Lucentis

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.999
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1
upper limit	1.33

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description:	
Day 15	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.716
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.12

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 29	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.13
upper limit	1.31

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 29	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.281
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	0.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	1.05

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 43	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.04

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description: Day 43	
Comparison groups	LKA651 v Lucentis

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2
upper limit	1.46

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 57	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.09
upper limit	1.28

Statistical analysis title	LKA651 v Lucentis
Statistical analysis description:	
Day 85	
Comparison groups	LKA651 v Lucentis
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	1.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.14
upper limit	1.38

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 57	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.083
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	0.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	1.01

Statistical analysis title	LKA651 + Lucentis v Lucentis
Statistical analysis description: Day 85	
Comparison groups	LKA651 + Lucentis v Lucentis
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.254
Method	Mixed model repeated measures analysis
Parameter estimate	Difference (Test vs Reference)
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.06

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

End point title	Number of participants who needed retreatment with anti-VEGF in study eye after week 12
End point description:	
End point type	Secondary
End point timeframe: Week 12 (Day 85) up to Day 140	

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	29	32	
Units: Participants	16	16	21	

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

Week 12 (Day 85) up to Day 140

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	29	32	
Units: Days after Day 85 (Week 12)				
median (confidence interval 95%)	55.0 (17.0 to 999)	34.0 (12.0 to 999)	31.0 (9.0 to 109.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of Pharmacokinetics - serum concentrations of LKA651

End point title	Summary statistics of Pharmacokinetics - serum concentrations of LKA651

End point 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.

End point type	Secondary

End point timeframe:

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

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	0[10]	
Units: ng/mL				
arithmetic mean (standard deviation)				
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 - 4 hrs post dose (n=0,6,0)	999 (± 999)	7.60 (± 18.6)	()	
Day 43 (n=1,6,0)	0.00 (± 0.00)	0.00 (± 0.00)	()	
Day 57 - 4 hrs post dose (n=0,6,0)	999 (± 999)	0.00 (± 0.00)	()	
Day 85 (n=19,23,0)	0.00 (± 0.00)	0.00 (± 0.00)	()	

Notes:

[10] - Serum concentrations of LKA651 do not apply to the Lucentis arm

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Area under the curve over the dosing interval 0 to 28 days.

End point type	Secondary

End point timeframe:

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

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: h*ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[11] - Could not be derived b/c of limited number of LKA651 concentrations above the LLoQ

[12] - Could not be derived b/c of limited number of LKA651 concentrations above the LLoQ

[13] - Could not be derived b/c of limited number of LKA651 concentrations above the LLoQ.

Statistical analyses

No statistical analyses for this end point

Secondary: Summary statistics of Pharmacokinetics - serum concentrations of Lucentis

End point title	Summary statistics of Pharmacokinetics - serum concentrations of Lucentis

End point description:

End point type	Secondary

End point timeframe:

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

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[14] - Could not be derived b/c of limited number of Lucentis concentrations above the LLoQ

[15] - Could not be derived b/c of limited number of Lucentis concentrations above the LLoQ

[16] - Could not be derived b/c of limited number of Lucentis concentrations above the LLoQ

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Area under the curve over the dosing interval 0 to 28 days.

End point type	Secondary

End point timeframe:

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

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: h*ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[17] - Could not be derived b/c of limited number of Lucentis concentrations above the LLoQ

[18] - Could not be derived b/c of limited number of Lucentis concentrations above the LLoQ

[19] - Could not be derived b/c of limited number of Lucentis concentrations above the LLoQ

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point 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 Day 169.
All deaths refer to the sum of on-treatment and post-treatment deaths.

End point type	Post-hoc

End point timeframe:

On-treatment – up to 12 weeks; Post-treatment - greater than 30 days after last treatment, until study completion, up to Day 169

End point values	LKA651	LKA651 + Lucentis	Lucentis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	30	33	
Units: Participants				
On-Treatment Deaths	0	0	0	
Post-Treatment Deaths	1	0	0	
All Deaths	1	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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).

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	LKA651

Reporting group description:

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

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Lucentis

Reporting group description:

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

Reporting group title	LKA651 + Lucentis Combo

Reporting group description:

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

Serious adverse events	LKA651	Total	Lucentis
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 28 (10.71%)	8 / 91 (8.79%)	1 / 33 (3.03%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone cancer metastatic			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			

subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Cyclic vomiting syndrome			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			

subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LKA651 + Lucentis Combo		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone cancer metastatic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer metastatic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LKA651	Total	Lucentis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 28 (71.43%)	55 / 91 (60.44%)	19 / 33 (57.58%)
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	3 / 28 (10.71%)	7 / 91 (7.69%)	3 / 33 (9.09%)
occurrences (all)	3	8	4
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Hypoxia			

subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	2 / 28 (7.14%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Blood glucose increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Blood triglycerides increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 91 (2.20%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Blood urea increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Intraocular pressure increased			

subjects affected / exposed	1 / 28 (3.57%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Lipase increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Pancreatic enzymes increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 28 (3.57%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Prostatic specific antigen increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Urine ketone body present			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Thoracic vertebral fracture			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
XIIth nerve injury			

subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Atrioventricular block first degree			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Coronary artery disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Sinus bradycardia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Tachycardia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
VIth nerve paralysis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 28 (3.57%)	4 / 91 (4.40%)	1 / 33 (3.03%)
occurrences (all)	1	4	1
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Anterior chamber flare			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			

subjects affected / exposed	1 / 28 (3.57%)	8 / 91 (8.79%)	2 / 33 (6.06%)
occurrences (all)	1	10	2
Corneal erosion			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Dacryostenosis acquired			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Cystoid macular oedema			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Diabetic retinal oedema			
subjects affected / exposed	3 / 28 (10.71%)	6 / 91 (6.59%)	2 / 33 (6.06%)
occurrences (all)	4	8	3
Diabetic retinopathy			
subjects affected / exposed	1 / 28 (3.57%)	3 / 91 (3.30%)	1 / 33 (3.03%)
occurrences (all)	1	4	1
Dry eye			
subjects affected / exposed	0 / 28 (0.00%)	2 / 91 (2.20%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Epiretinal membrane			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Eyelids pruritus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Eye pain			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Lenticular opacities			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Ocular hypertension			
subjects affected / exposed	2 / 28 (7.14%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	3	3	0
Macular oedema			

subjects affected / exposed	2 / 28 (7.14%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Punctate keratitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Retinal exudates			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Retinal cyst			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Visual acuity reduced			
subjects affected / exposed	3 / 28 (10.71%)	3 / 91 (3.30%)	0 / 33 (0.00%)
occurrences (all)	4	4	0
Retinal oedema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Retinal haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Vitreous haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)	3 / 91 (3.30%)	2 / 33 (6.06%)
occurrences (all)	1	3	2
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Hepatic steatosis			

subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Chronic kidney disease			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Nephrolithiasis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Urinary incontinence			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Myopathy			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Sjogren's syndrome			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Adenoviral conjunctivitis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 91 (2.20%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
COVID-19			
subjects affected / exposed	2 / 28 (7.14%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Conjunctivitis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Coronavirus infection			

subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Herpes zoster			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 91 (2.20%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)	3 / 91 (3.30%)	1 / 33 (3.03%)
occurrences (all)	1	3	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Diabetes mellitus			
subjects affected / exposed	0 / 28 (0.00%)	2 / 91 (2.20%)	2 / 33 (6.06%)
occurrences (all)	0	2	2
Hyperglycaemia			
subjects affected / exposed	2 / 28 (7.14%)	4 / 91 (4.40%)	1 / 33 (3.03%)
occurrences (all)	2	4	1
Hyperkalaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Hyperlipasaemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0

Hypocalcaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Vitamin B complex deficiency			
subjects affected / exposed	0 / 28 (0.00%)	1 / 91 (1.10%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 28 (0.00%)	3 / 91 (3.30%)	1 / 33 (3.03%)
occurrences (all)	0	3	1

Non-serious adverse events	LKA651 + Lucentis Combo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 30 (53.33%)		
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood triglycerides increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Blood urea increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Intraocular pressure increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Lipase increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pancreatic enzymes increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Prostatic specific antigen increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Urine ketone body present			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Skin laceration			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
XIIth nerve injury			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Atrioventricular block first degree			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Coronary artery disease			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Sinus bradycardia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
VIth nerve paralysis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Anterior chamber flare			

subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Conjunctival haemorrhage				
subjects affected / exposed	5 / 30 (16.67%)			
occurrences (all)	7			
Corneal erosion				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Dacryostenosis acquired				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Cystoid macular oedema				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Diabetic retinal oedema				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Diabetic retinopathy				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	2			
Dry eye				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Epiretinal membrane				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Eyelids pruritus				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Eye pain				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Lenticular opacities				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Ocular hypertension				

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Macular oedema			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Punctate keratitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Retinal exudates			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Retinal cyst			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Retinal oedema			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Retinal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Vitreous haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatotoxicity			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hepatic steatosis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Chronic kidney disease			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nephrolithiasis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Myopathy			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Sjogren's syndrome			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infections and infestations			
Adenoviral conjunctivitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Conjunctivitis			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Coronavirus infection			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		

Hyperlipasaemia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Vitamin B complex deficiency subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2019	The purpose of this amendment was to address recommendations and requests from Health Authorities and the EC CTA review process. In addition, one inclusion criteria was changed to increase the retinal thickness required for entry into the study, which ensured that patients with significant DME were enrolled and increased the potential benefit of treatment. Two exploratory objectives were removed: measurement of systemic serum EPO, since preliminary assessment of serum EPO levels in Study CLKA651X2104 before and after treatment with LKA651 5mg remained unaffected. Also, analysis of serum biomarkers was removed because the relationship between these biomarkers and disease progression was yet to be identified.
05 December 2019	The purpose of this amendment was to alter some of the eligibility criteria in light of final PK and safety information from Study CLKA651X2104, in addition to favorable preliminary safety information from the first 4 patients recruited in the current study. PK analysis demonstrated that systemic serum exposure of total LKA651 was low in Study CLKA651X2104, with only 6 out of 12 patients in the top 2 doses (2.5 mg and 5 mg) having detectable LKA651 serum concentrations through Day 5 (4 days post dose). Therefore, eligibility criteria based on systemic conditions, including the cut-off for hemoglobin and heart failure classification were relaxed. Furthermore, drawing of blood samples for PK throughout the study was reduced.
11 March 2020	The purpose of this amendment was to alter the eligibility criteria, allowing previously treated patients to be enrolled in the study and to add an interim analysis: The amendment allowed enrollment of treatment-naive patients while also allowing patients who had been treated with anti-VEGF therapy more than 90 days prior to baseline. The 90-day washout period was used to allow for patients with recurrent macular edema >320 µm (as per inclusion criteria) who could benefit from LKA651 and/or Lucentis therapy. The interim analysis was planned to be conducted when approximately 2/3 of target population enrollment (60 patients) had reached Day 85, was to be used primarily for internal decision-making purposes regarding further development of LKA651.
01 December 2020	The purpose of this amendment was to reduce the number and duration of in-clinic visits, in light of the favorable safety findings from the sentinel safety cohorts. Visits were reduced to lower patient and site burden. Due to the reduced number of visits, for the remaining patients to enroll into the study, there would be fewer overall blood draws for PK sampling, and language was updated to reflect that PK analysis will be performed in a subset of patients. 1 inclusion and 3 exclusion criteria were also amended
20 January 2021	The purpose of this amendment was to clarify the exclusion criteria pertaining to history of laser photocoagulation in the study eye. Exclusion criteria #1 was updated to be aligned with the updated Exclusion criteria #3 (updated in Amendment 4).
06 July 2022	The purpose of this amendment was to amend the secondary endpoint by removing the DRSS. This amendment also added the ICDR for diabetic retinopathy to the exploratory endpoint for evaluating diabetic retinopathy progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Notes: