Clinical trial results:
A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Xlucane versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

Summary

EudraCT number	2018-002930-19
Trial protocol	EE LT HU SK LV CZ BG PL ES RO
Global end of trial date	11 November 2021

Results information

Result version number	v1 (current)
This version publication date	02 April 2023
First version publication date	02 April 2023

Trial information

Trial identification

Sponsor protocol code	XBR1001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03805100
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Xbrane Biopharma
Sponsor organisation address	Retzius väg 8, Solna, Sweden, 171 65
Public contact	Clinical Affairs, Xbrane Biopharma, +46 (0) 85-590 56 00, info@xbrane.com
Scientific contact	Clinical Affairs, Xbrane Biopharma, +46 (0) 85-590 56 00, info@xbrane.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	07 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2021
Global end of trial reached?	Yes
Global end of trial date	11 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that the proposed biosimilar candidate Xlucane is equivalent to Lucentis® in subjects with wAMD as assessed by the change in BCVA from Baseline to Week 8.

Protection of trial subjects:

Subjects were monitored onsite prior to and following each injection (for at least 60 minutes) to permit any early treatment and appropriate management if needed.
Subjects were advised that the days following study medication administration, they were at risk of developing endophthalmitis. If they patient experienced red eye, sensitivity to light, pain or developed a change in vision they were instructed to seek immediate care from the study doctor or an ophthalmologist.

Other medications that were considered necessary for the subject's welfare and that were not expected to interfere with the evaluation of the study medication could be given at the discretion of the Investigator, with the exceptions:
- Any systemic treatment or ocular treatment with an investigational agent
- Systemic anti-VEGF therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 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	Poland: 38
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Slovakia: 20
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Bulgaria: 36
Country: Number of subjects enrolled	Czechia: 49
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	Hungary: 89
Country: Number of subjects enrolled	Latvia: 10
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	India: 83
Country: Number of subjects enrolled	Israel: 86

Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Ukraine: 20
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	582
EEA total number of subjects	302

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	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)	69
From 65 to 84 years	438
85 years and over	75

Subject disposition

Recruitment

Recruitment details:

582 enrolled and randomized in a 1:1 ratio to receive either Lucentis® or Xlucane (ranibizumab; Ximluci®) in the study eye once every 4 weeks for 52 weeks.

Pre-assignment

Screening details:

Newly diagnosed, active subfoveal Choroidal Neovascularization (CNV) lesion secondary to age-related macular degeneration (AMD) in the study eye.
Best Corrected Visual Acuity (BCVA) of ≤ 73 and ≥ 49 ETDRS letter score in the study eye
Age ≥ 50 years at screening

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lucentis

Arm description:

Ranibizumab,
Intravitreal injection of 0.05ml (0.5mg)

Arm type	Active comparator
Investigational medicinal product name	Lucentis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravitreal use

Dosage and administration details:

Inravitreal injection of 0.05ml (0.5mg)

Investigational medicinal product name	Xlucane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection of 0.05ml (0.5mg)

Arm title	Xlucane

Arm description:

Ranibizumab Biosimilar
Registered product Ximluci®,
Intravitreal injection of 0.05ml (0.5mg)

Arm type	Ranibizumab Biosimilar

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Lucentis	Xlucane
Started	290	292
Completed	241	245
Not completed	49	47
Treatment failure, as assesed by the investigator	1	1
Adverse event, serious fatal	1	4
Consent withdrawn by subject	22	17
Noncompliance with study drug or stude schedule	1	-
Adverse event, non-fatal	10	5
Unspecified	8	15
Lost to follow-up	6	4
Use of non permitted concurrent therapy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lucentis
Reporting group description:	
Ranibizumab, Intravitreal injection of 0.05ml (0.5mg)	
Reporting group title	Xlucane
Reporting group description:	
Ranibizumab Biosimilar Registered product Ximluci®, Intravitreal injection of 0.05ml (0.5mg)	

Reporting group values	Lucentis	Xlucane	Total
Number of subjects	290	292	582
Age categorical Units: Subjects			
Adults (18-64 years)	35	34	69
From 65-84 years	220	218	438
85 years and over	35	40	75
Age continuous Units: years			
median	74	74	
inter-quartile range (Q1-Q3)	68 to 79	69 to 81	-
Gender categorical Units: Subjects			
Female	157	168	325
Male	133	124	257

End points

End points reporting groups

Reporting group title	Lucentis
Reporting group description:	
Ranibizumab, Intravitreal injection of 0.05ml (0.5mg)	
Reporting group title	Xlucane
Reporting group description:	
Ranibizumab Biosimilar Registered product Ximluci®, Intravitreal injection of 0.05ml (0.5mg)	

Primary: Change in BCVA letters at Week 8 compared to baseline using the ETDRS protocol

End point title	Change in BCVA letters at Week 8 compared to baseline using the ETDRS protocol
End point description:	
All statistical analyses were performed using SAS® version 9.4. In general, data were summarised by means of summary statistics. Continuous data were presented as the number of observations, mean, standard deviation (SD), minimum, 25th percentile (Q1), median, 75th percentile (Q3), and maximum. Categorical data were presented as counts and percentages. The data were presented for each treatment group and additionally by visit (if applicable). An overall summary across treatment groups was also included for descriptive summaries.	
End point type	Primary
End point timeframe:	
Baseline to week 8	

End point values	Lucentis	Xlucane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[1]	292		
Units: BCVA Letter Score (Letters)				
median (inter-quartile range (Q1-Q3))	70 (62 to 77)	68 (59 to 75.5)		

Notes:

[1] - 290 patients randomized to the Lucentis arm. 1 patient randomized never treated.

Statistical analyses

Statistical analysis title	Mixed model for repeated measures (MMRM)
Comparison groups	Lucentis v Xlucane
Number of subjects included in analysis	581
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.009 [2]
Method	t-test, 2-sided
Variability estimate	Standard deviation

Notes:

[2] - To prove the products to be biosimilar, the CI (90% for United States, 95% for the rest of the world) for the LS means difference had to be within the equivalence margin of +/- 3.5 letters.

Secondary: Change in BCVA letters at Week 52 compared to baseline using the ETDRS protocol

End point title	Change in BCVA letters at Week 52 compared to baseline using the ETDRS protocol

End point description:

All statistical analyses were performed using SAS® version 9.4. In general, data were summarised by means of summary statistics. Continuous data were presented as the number of observations, mean, standard deviation (SD), minimum, 25th percentile (Q1), median, 75th percentile (Q3), and maximum. Categorical data were presented as counts and percentages. The data were presented for each treatment group and additionally by visit (if applicable). An overall summary across treatment groups was also included for descriptive summaries.

End point type	Secondary

End point timeframe:

Baseline to week 52

End point values	Lucentis	Xlucane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[3]	292		
Units: BCVA letter score (Letters)				
median (inter-quartile range (Q1-Q3))	73 (65 to 80)	73 (60.5 to 79)		

Notes:

[3] - 290 patients randomized to the Lucentis arm. 1 patient randomized never treated

Statistical analyses

Statistical analysis title	Mixed model for repeated measures (MMRM)

Statistical analysis description:

To prove the products to be biosimilar, the CI (90% for United States, 95% for the rest of the world) for the LS means difference had to be within the equivalence margin of +/- 3.5 letters.

Comparison groups	Lucentis v Xlucane
Number of subjects included in analysis	581
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.183
Method	t-test, 2-sided
Variability estimate	Standard deviation

Secondary: Change in Central Foveal Thickness (CFT) week 8 compared to baseline measured by OCT

End point title	Change in Central Foveal Thickness (CFT) week 8 compared to baseline measured by OCT

End point description:

End point type	Secondary

End point timeframe:
Baseline to week 8.

End point values	Lucentis	Xlucane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[4]	292		
Units: µm				
median (inter-quartile range (Q1-Q3))	-89 (-163 to -40)	-81 (-145 to -36)		

Notes:
[4] - 290 patients randomized to the Lucentis arm. 1 patient randomized never treated

Statistical analyses

Statistical analysis title	Mixed model for repeated measures (MMRM)
Comparison groups	Lucentis v Xlucane
Number of subjects included in analysis	581
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.828
Method	t-test, 2-sided

Secondary: Change in Central Foveal Thickness (CFT) week 52 compared to baseline measured by OCT

End point title	Change in Central Foveal Thickness (CFT) week 52 compared to baseline measured by OCT

End point description:

End point type	Secondary

End point timeframe:
Baseline to week 52

End point values	Lucentis	Xlucane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[5]	292		
Units: µm				
median (inter-quartile range (Q1-Q3))	-104 (-196 to -46)	-84 (-150 to -34)		

Notes:
[5] - 290 patients randomized to the Lucentis arm. 1 patient randomized never treated

Statistical analyses

Statistical analysis title	Mixed model for repeated measures (MMRM)
Comparison groups	Lucentis v Xlucane
Number of subjects included in analysis	581
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.65
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occuring during the study, from time of inform consent to 28 days (+/- 5 days) or receiving last dose of study drug, up to 53 weeks.

Adverse event reporting additional description:

AEs (ocular or non-ocular) as well as injection site reactions were recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Lucentis

Reporting group description: -

Reporting group title	Xlucane

Reporting group description: -

Serious adverse events	Lucentis	Xlucane	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 290 (12.07%)	33 / 292 (11.30%)	
number of deaths (all causes)	3	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			

subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkins disease			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulva cancer			

subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	0 / 290 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 290 (0.00%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 290 (0.34%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 290 (0.00%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Artrial fibrilation			
subjects affected / exposed	2 / 290 (0.69%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infraction			
subjects affected / exposed	3 / 290 (1.03%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Pericardial effusion			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 290 (0.69%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Endophthalmitis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular vasospasm			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Haemorrhage			
subjects affected / exposed	1 / 290 (0.34%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal pigment epithelial tear			
subjects affected / exposed	1 / 290 (0.34%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	1 / 8	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colonic haematoma			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	2 / 290 (0.69%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 290 (0.69%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
End stage renal disease			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Athralgia			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Appendiceal Abscess			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 290 (0.34%)	5 / 292 (1.71%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 2	
COVID-19 pneumonia			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	1 / 290 (0.34%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 290 (0.34%)	2 / 292 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 290 (0.00%)	3 / 292 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 290 (0.00%)	1 / 292 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 290 (0.34%)	0 / 292 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lucentis	Xlucane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 290 (11.38%)	25 / 292 (8.56%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 290 (5.86%)	10 / 292 (3.42%)	
occurrences (all)	19	10	
Eye disorders			
Conjunctival Haemorrhage			
subjects affected / exposed	16 / 290 (5.52%)	15 / 292 (5.14%)	
occurrences (all)	22	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2019	Amendment includes clarifications and updates for requests by US FDA. Addition of unmasked analysis of primary efficacy endpoint to monitor the progress of the study after all patients complete month 2 and clarification for the purpose of both the planned interim analysis. Clarification of inclusion criteria 1 and 5 and exclusion criterion 1.
06 May 2020	Clarifies the equivalence margin of +/- 3.5, as agreed with EMA/FDA. Updated PK substudy sample size, due to risk with Covid-19 exposure. Clarifies the aim of the unmasked analysis. Clarifies exclusion criteria 1, 5 and 6 Clarifies statistical analysis Clarification on the syringe provided with the IMP
26 November 2020	Clarification regarding maintenance of masking in connection to the interim analysis. Provision of BD needles and syringes, suspended until further notice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported