Clinical trial results:
A PHASE 2, RANDOMISED, DOUBLE-MASKED, SHAM-CONTROLLED, MULTI-CENTRE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRIPLASMIN IN INDUCING TOTAL POSTERIOR VITREOUS DETACHMENT (PVD) IN SUBJECTS WITH NON-PROLIFERATIVE DIABETIC RETINOPATHY (NPDR) (CIRCLE)

Summary

EudraCT number	2015-002415-15
Trial protocol	DE GB CZ BE HU ES FR IT
Global end of trial date	18 November 2019

Results information

Result version number	v1 (current)
This version publication date	30 November 2020
First version publication date	30 November 2020

Trial information

Trial identification

Sponsor protocol code	TG-MV-015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02681809
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ThromboGenics
Sponsor organisation address	Gaston Geenslaan 1, Leuven, Belgium, B-3001
Public contact	Global Clinical Development, ThromboGenics, 32 (0)16751310, info@oxurion.com
Scientific contact	Global Clinical Development, ThromboGenics, 32 (0)16751310, info@oxurion.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	13 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2019
Global end of trial reached?	Yes
Global end of trial date	18 November 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of up to 3 intravitreal injections of ocriplasmin (0.0625mg or 0.125mg), in subjects with moderate to very severe NPDR, to induce total PVD in order to reduce the risk of disease progression to PDR

Protection of trial subjects:

All study procedures, including the intravitreal injections, were performed by qualified and trained personnel. Only eligible subjects were randomised and only subjects who did not meet any withdrawal criteria received repeat injections. All subjects were supervised in the immediate post-injection period with appropriate medical treatment readily available. Subjects were followed up for 24 months after the first injection. Adverse events were recorded throughout the study period. At each study visit, a full ophthalmic examination and BCVA assessment were performed. An independent DMC was established to maintain a general safety oversight and to monitor the benefit / risk balance for the subjects in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	22 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	48
EEA total number of subjects	32

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)	32
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a Screening visit during which in- and exclusion criteria were checked by the Investigator. In addition, specific criteria needed to be confirmed by the central reading center / by the central laboratory

Period 1

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

Blinding implementation details:

IMP handling and administration was done by unmasked personnel

Arms

Are arms mutually exclusive?	Yes
Arm title	ocriplasmin 0.0625mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ocriplasmin 0.5 mg/0.2 mL concentrate for solution for injection
Investigational medicinal product code	
Other name	JETREA 0.5 mg/0.2 mL concentrate for solution for injection
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

up to 3 intravitreal injections with ocriplasmin 0.0625mg, approximately 1 month apart

Arm title	ocriplasmin 0.125mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ocriplasmin 0.5 mg/0.2 mL concentrate for solution for injection
Investigational medicinal product code	
Other name	JETREA 0.5 mg/0.2 mL concentrate for solution for injection
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

up to 3 intravitreal injections with ocriplasmin 0.125mg, approximately 1 month apart

Arm title	sham

Arm description:

Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator mimicked intravitreal injection procedure.

Arm type	sham injection

No investigational medicinal product assigned in this arm

Number of subjects in period 1	ocriplasmin 0.0625mg	ocriplasmin 0.125mg	sham
Started	20	19	9
Completed	15	15	8
Not completed	5	4	1
Consent withdrawn by subject	3	1	-
Adverse event, non-fatal	-	1	1
Lost to follow-up	2	2	-

Baseline characteristics

Reporting groups	
Reporting group title	ocriplasmin 0.0625mg
Reporting group description: -	
Reporting group title	ocriplasmin 0.125mg
Reporting group description: -	
Reporting group title	sham

Reporting group description:

Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator mimicked intravitreal injection procedure.

Reporting group values	ocriplasmin 0.0625mg	ocriplasmin 0.125mg	sham
Number of subjects	20	19	9
Age categorical Units: Subjects			
Adults (18-64 years)	12	14	6
From 65-84 years	8	5	3
Age continuous Units: years			
arithmetic mean	57.7	55.4	54.3
standard deviation	± 12.14	± 10.15	± 13.01
Gender categorical Units: Subjects			
Female	6	5	2
Male	14	14	7

Reporting group values	Total		
Number of subjects	48		
Age categorical Units: Subjects			
Adults (18-64 years)	32		
From 65-84 years	16		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	13		
Male	35		

End points

End points reporting groups

Reporting group title	ocriplasmin 0.0625mg
Reporting group description: -	
Reporting group title	ocriplasmin 0.125mg
Reporting group description: -	
Reporting group title	sham

Reporting group description:

Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator mimicked intravitreal injection procedure.

Primary: Total PVD by the Month 3 visit, confirmed on both B-scan ultrasound and SD-OCT (6mm), as assessed by the masked B-scan expert reader and the masked CRC, respectively

End point title	Total PVD by the Month 3 visit, confirmed on both B-scan ultrasound and SD-OCT (6mm), as assessed by the masked B-scan expert reader and the masked CRC, respectively[1]

End point description:

End point type	Primary

End point timeframe:

at Month 3

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: Recruitment in the study was discontinued early due to slow recruitment rate. This led to a total of 48 randomized subjects instead of the planned 115 per protocol amendment 2. By consequence, the study was not powered for its primary endpoint. The endpoint was therefore evaluated only descriptively. No statistical hypothesis testing was performed.

End point values	ocriplasmin 0.0625mg	ocriplasmin 0.125mg	sham	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	18	8	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular treatment-emergent adverse events in the study eye

End point title	Ocular treatment-emergent adverse events in the study eye

End point description:

Incidence of ocular treatment-emergent adverse events in the study eye

End point type	Secondary

End point timeframe:

From first injection until the end of the study (Month 24)

End point values	ocriplasmin 0.0625mg	ocriplasmin 0.125mg	sham	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	9	
Units: subjects	15	14	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first injection until the end of the study (Month 24)

Adverse event reporting additional description:

Adverse events include non-ocular and ocular events (both in study eye and non-study eye)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	ocriplasmin 0.0625mg
Reporting group description: -	
Reporting group title	ocriplasmin 0.125mg
Reporting group description: -	
Reporting group title	sham

Reporting group description:

Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator to mimic intravitreal injection procedure.

Serious adverse events	ocriplasmin 0.0625mg	ocriplasmin 0.125mg	sham
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	8 / 19 (42.11%)	1 / 9 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of Colon			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral Injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula Fracture			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella Fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral Ischaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Generalised Oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ciliary Zonular Dehiscence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (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
Retinal Haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Respiratory Tract Infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Wall Abscess			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter Site Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ocriplasmin 0.0625mg	ocriplasmin 0.125mg	sham
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	17 / 19 (89.47%)	7 / 9 (77.78%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	1 / 9 (11.11%)
occurrences (all)	1	3	1
Deep Vein Thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypertensive Crisis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Peripheral Ischaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Gait Disturbance			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injection Site Haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injection Site Pain			

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pulmonary Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Investigations			
Intraocular Pressure Increased			
subjects affected / exposed	4 / 20 (20.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	6	0	2
Glycosylated Haemoglobin Increased			
subjects affected / exposed	0 / 20 (0.00%)	3 / 19 (15.79%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Intraocular Pressure Decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Pelvic Fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Post Procedural Oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Radius Fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			

Colour Blindness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 20 (10.00%)	2 / 19 (10.53%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Loss of Consciousness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Paralysis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye Pain			
subjects affected / exposed	2 / 20 (10.00%)	5 / 19 (26.32%)	1 / 9 (11.11%)
occurrences (all)	2	7	1
Diabetic Retinal Oedema			
subjects affected / exposed	4 / 20 (20.00%)	1 / 19 (5.26%)	2 / 9 (22.22%)
occurrences (all)	4	3	3
Cataract			
subjects affected / exposed	3 / 20 (15.00%)	3 / 19 (15.79%)	0 / 9 (0.00%)
occurrences (all)	4	4	0

Visual Acuity Reduced			
subjects affected / exposed	2 / 20 (10.00%)	4 / 19 (21.05%)	0 / 9 (0.00%)
occurrences (all)	2	4	0
Vitreous Floaters			
subjects affected / exposed	2 / 20 (10.00%)	3 / 19 (15.79%)	0 / 9 (0.00%)
occurrences (all)	2	6	0
Conjunctival Haemorrhage			
subjects affected / exposed	4 / 20 (20.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	4	1	0
Macular Oedema			
subjects affected / exposed	0 / 20 (0.00%)	4 / 19 (21.05%)	0 / 9 (0.00%)
occurrences (all)	0	5	0
Visual Impairment			
subjects affected / exposed	3 / 20 (15.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	4	1	0
Vitreous Haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	3 / 19 (15.79%)	0 / 9 (0.00%)
occurrences (all)	2	3	0
Photophobia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	0 / 9 (0.00%)
occurrences (all)	1	4	0
Photopsia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	0 / 9 (0.00%)
occurrences (all)	1	4	0
Diabetic Retinopathy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	2 / 9 (22.22%)
occurrences (all)	2	0	2
Dry Eye			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Eye Irritation			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Macular Fibrosis			
subjects affected / exposed	2 / 20 (10.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	3	1	0

Retinal Haemorrhage			
subjects affected / exposed	2 / 20 (10.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Vision Blurred			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Cataract Subcapsular			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Lacrimation Increased			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Punctate Keratitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Cataract Cortical			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Iridocyclitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Lenticular Opacities			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Ocular Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Cataract Nuclear			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Corneal Oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Cystoid Macular Oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Eyelid Ptosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Ocular Hyperaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Optic Disc Haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Optic Nerve Disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Retinal Aneurysm			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Retinal Cyst			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Retinal Detachment			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Retinal Exudates			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal Sphincter Insufficiency			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Dermatitis Herpetiformis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	1 / 9 (11.11%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Joint Swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 20 (10.00%)	3 / 19 (15.79%)	2 / 9 (22.22%)
occurrences (all)	2	3	2
Cellulitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Localised Infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Nosocomial Infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2016	Sample size was reduced and eligibility criteria were updated to improve recruitment

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.

Recruitment in the study was discontinued early due to slow recruitment rate. This led to a total of 48 randomized subjects instead of the planned 115 per protocol amendment 2. By consequence, the study was not powered for its primary endpoint.

Notes: