Clinical trial results:
A Phase III Multicenter Randomized, Sham Controlled, Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasia type 2

Summary

EudraCT number	2017-003234-82
Trial protocol	GB FR
Global end of trial date	09 August 2022

Results information

Result version number	v1 (current)
This version publication date	04 August 2024
First version publication date	04 August 2024

Trial information

Trial identification

Sponsor protocol code	NTMT-03-A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03316300
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Neurotech Pharmaceuticals Inc
Sponsor organisation address	900 Highland Corporate Drive, Suite 101, Cumberland, RI, United States, 02864
Public contact	Kevin Hibbert, Neurotech Pharmaceuticals, k.hibbert@neurotechusa.com
Scientific contact	Kevin Hibbert, Neurotech Pharmaceuticals, k.hibbert@neurotechusa.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	30 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of this study is to evaluate the efficacy and safety of NT-501 for the treatment of MacTel.

Primary objective:
To determine the rate of change in the area of ellipsoid zone (EZ) loss (photoreceptor inner segment/outer segment [IS/OS]; macular photoreceptor loss) over 24 months, as measured by spectral domain-optical coherence tomography (SD-OCT) in the study eye of subjects with macular telangiectasia type 2 (MacTel).

The secondary objective:
To evaluate the safety of NT-501 in subjects with MacTel.

Protection of trial subjects:

Ethics committee approval

Background therapy:

None

Evidence for comparator:

A sham surgical procedure was performed to mimic the implant procedure; there was no comparator product.

Actual start date of recruitment	17 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	United States: 78
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	France: 15
Worldwide total number of subjects	120
EEA total number of subjects	15

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)	78
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening period for up to 30 days

Pre-assignment

Screening details:

NTMT-03-A: 120 subjects enrolled (5 participants withdrew after randomization) but prior to the implantation/sham surgery procedure; 61 subjects in NT-501 arm and 59 subjects in sham arm.

Period 1

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

Blinding implementation details:

The subjects and all personnel at the image reading center remained masked to the treatment assignment throughout the study. In addition, the refractionist, VA examiner, and photographers/imagers were masked to treatment assignment (NT-501 implantation or sham procedure) at all follow-up visits. The ophthalmologist, surgeon, and clinic coordinator were instructed not to discuss the assigned treatment with the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	NT-501

Arm description:

Test product

Arm type	Experimental
Investigational medicinal product name	NT-501 Implant
Investigational medicinal product code	NT-501
Other name	
Pharmaceutical forms	Implant
Routes of administration	Intravitreal use

Dosage and administration details:

Each implant consisting of hCNTF-secreting NTC-201-6A.02 cells encapsulated within supportive matrices and surrounded by a semipermeable polymer membrane.
The NTC-201-6A cells continuously secrete CNTF from the NT-501 implant into the vitreous cavity.
Implanted by a qualified Health Care Professional.

Arm title	Sham Procedure

Arm description:

A sham surgical procedure was performed to mimic the implant procedure; there was no comparator product.

Arm type	sham surgical procedure
Investigational medicinal product name	Sham procedure
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Intravitreal use

Dosage and administration details:

The sham surgery involved a superficial conjunctival incision performed under local anesthetic and closure with a single suture.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The subjects and all personnel at the image reading center remained masked to the treatment assignment throughout the study. In addition, the refractionist, VA examiner, and photographers/imagers were masked to treatment assignment (NT-501 implantation or sham procedure) at all follow-up visits. The ophthalmologist, surgeon, and clinic coordinator were instructed not to discuss the assigned treatment with the subject.

Number of subjects in period 1	NT-501	Sham Procedure
Started	61	59
Completed	53	52
Not completed	8	7
Consent withdrawn by subject	3	2
Eligible and did not enroll in amendment	4	4
Adverse event, non-fatal	1	-
COVID-19	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	78	78	
From 65-84 years	42	42	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	82	82	
Male	38	38	

Subject analysis sets	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomized subjects who underwent either NT-501 implantation surgery or sham surgery and had at least 1 safety measurement.

Subject analysis set title	Modified Intention-to-Treat population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population comprised all randomized subjects who underwent either NT-501 implantation surgery or sham surgery

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included all subjects in the mITT population who had no important protocol deviations (ie, deviations that may have had a substantial impact on the primary efficacy endpoint).

Reporting group values	Safety population	Modified Intention-to-Treat population	Per Protocol Population
Number of subjects	115	115	111
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	74	74	72
From 65-84 years	41	41	39
85 years and over			
Gender categorical			
Units: Subjects			
Female	79	79	77
Male	36	36	34

End points

End points reporting groups

Reporting group title	NT-501
Reporting group description:	
Test product	
Reporting group title	Sham Procedure
Reporting group description:	
A sham surgical procedure was performed to mimic the implant procedure; there was no comparator product.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized subjects who underwent either NT-501 implantation surgery or sham surgery and had at least 1 safety measurement.	
Subject analysis set title	Modified Intention-to-Treat population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT population comprised all randomized subjects who underwent either NT-501 implantation surgery or sham surgery	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population included all subjects in the mITT population who had no important protocol deviations (ie, deviations that may have had a substantial impact on the primary efficacy endpoint).	

Primary: Primary Efficacy Endpoint

End point title	Primary Efficacy Endpoint
End point description:	
The rate of change in the area of EZ loss (IS/OS; macular photoreceptor loss) from baseline through month 24, as assessed using SD-OCT in the study eye of subjects with MacTel.	
End point type	Primary
End point timeframe:	
End point timeframe is 2 years Baseline, Month 6, 12, 16, 20 and 24. Month 6 was collected but not included in the primary analyses.	

End point values	NT-501	Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	57		
Units: mm^2				
number (not applicable)	0.075	0.166		

Statistical analyses

Statistical analysis title	Statistical Analysis - NT-501 vs Sham Procedure

Statistical analysis description:

The efficacy and safety of the NT-501 implant that delivers a daily dose of CNTF in comparison to sham surgery with no implant, in participants with confirmed MacTel.

Comparison groups	NT-501 v Sham Procedure
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	longitudinal mixed model
Parameter estimate	Mean difference (net)
Point estimate	-0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.0176

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the Clinical Trial	
Adverse event reporting additional description:	
Please note that only non-ocular and ocular events in the study eye have been reported. The Adverse events reported are those that occurred through month 24.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	NT-501
Reporting group description:	
Test product	
Reporting group title	Sham Procedure
Reporting group description:	
A sham surgical procedure was performed to mimic the implant procedure; there was no comparator product.	

Serious adverse events	NT-501	Sham Procedure	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 58 (20.69%)	7 / 57 (12.28%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Suture related complication			

subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
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 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (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	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NT-501	Sham Procedure	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 58 (93.10%)	47 / 57 (82.46%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Eye naevus			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Colorectal adenoma			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Salivary gland neoplasm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 58 (1.72%)	5 / 57 (8.77%)	
occurrences (all)	1	5	
Deep vein thrombosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Essential hypertension			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Raynaud's phenomenon			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Mole excision			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Skin neoplasm excision			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Chest pain			

subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Seasonal allergy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Erectile dysfunction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	

Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Anxiety			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Biopsy prostate abnormal			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Endoscopy gastrointestinal			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Heart rate irregular			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Staphylococcus test positive			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Suture related complication				
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)		
occurrences (all)	2	1		
Cataract traumatic				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Corneal abrasion				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Hyphaema				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Fall				
subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)		
occurrences (all)	1	2		
Tooth fracture				
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)		
occurrences (all)	2	1		
Soft tissue injury				
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)		
occurrences (all)	1	1		
Back injury				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Comminuted fracture				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Contusion				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Dental restoration failure				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Foot fracture				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		

Joint dislocation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Ligament injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Muscle injury			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Procedural nausea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Tendon injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Wound dehiscence			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Wrist fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Corneal dystrophy			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Angina pectoris			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Arrhythmia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Coronary artery occlusion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Coronary artery disease			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 58 (6.90%)	3 / 57 (5.26%)	
occurrences (all)	4	3	
Neuropathy peripheral			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Balance disorder			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Carotid artery occlusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Cubital tunnel syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Memory impairment			

subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Parkinson's disease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Radiculopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Sinus headache			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Excessive cerumen production			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Vertigo			

subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	18 / 58 (31.03%)	12 / 57 (21.05%)	
occurrences (all)	18	12	
Dry eye			
subjects affected / exposed	8 / 58 (13.79%)	6 / 57 (10.53%)	
occurrences (all)	8	6	
Delayed dark adaptation			
subjects affected / exposed	12 / 58 (20.69%)	1 / 57 (1.75%)	
occurrences (all)	12	1	
Eye pain			
subjects affected / exposed	8 / 58 (13.79%)	5 / 57 (8.77%)	
occurrences (all)	8	5	
Foreign body sensation in eyes			
subjects affected / exposed	6 / 58 (10.34%)	7 / 57 (12.28%)	
occurrences (all)	6	7	
Eye pruritus			
subjects affected / exposed	9 / 58 (15.52%)	3 / 57 (5.26%)	
occurrences (all)	9	3	
Miosis			
subjects affected / exposed	10 / 58 (17.24%)	0 / 57 (0.00%)	
occurrences (all)	10	0	
Vision blurred			
subjects affected / exposed	7 / 58 (12.07%)	3 / 57 (5.26%)	
occurrences (all)	7	3	
Ocular discomfort			
subjects affected / exposed	8 / 58 (13.79%)	1 / 57 (1.75%)	
occurrences (all)	8	1	
Conjunctival hyperaemia			
subjects affected / exposed	4 / 58 (6.90%)	3 / 57 (5.26%)	
occurrences (all)	4	3	
Vitreous floaters			
subjects affected / exposed	7 / 58 (12.07%)	0 / 57 (0.00%)	
occurrences (all)	7	0	

Conjunctival oedema			
subjects affected / exposed	4 / 58 (6.90%)	2 / 57 (3.51%)	
occurrences (all)	4	2	
Choroidal neovascularisation			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Cataract			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	
occurrences (all)	3	1	
Cataract subcapsular			
subjects affected / exposed	3 / 58 (5.17%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Eye irritation			
subjects affected / exposed	4 / 58 (6.90%)	0 / 57 (0.00%)	
occurrences (all)	4	0	
Iridocyclitis			
subjects affected / exposed	3 / 58 (5.17%)	1 / 57 (1.75%)	
occurrences (all)	3	1	
Photopsia			
subjects affected / exposed	4 / 58 (6.90%)	0 / 57 (0.00%)	
occurrences (all)	4	0	
Visual impairment			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Vitreous haemorrhage			
subjects affected / exposed	4 / 58 (6.90%)	0 / 57 (0.00%)	
occurrences (all)	4	0	
Blepharospasm			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Anterior chamber cell			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Eye discharge			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	

Punctate keratitis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Uveitis			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Vitreous detachment			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Abnormal sensation in eye			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Anisocoria			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Corneal pigmentation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Cystoid macular oedema			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Delayed light adaptation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Diplopia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Eccentric fixation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Lenticular opacities			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Macular oedema			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	

Meibomian gland dysfunction				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Night blindness				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Photophobia				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Presbyopia				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Retinal artery embolism				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Retinal haemorrhage				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Retinal thickening				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Ulcerative keratitis				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Visual acuity reduced				
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Visual field defect				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Vitreoretinal traction syndrome				
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Cataract nuclear				
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)		
occurrences (all)	1	1		

Epiretinal membrane			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Keratitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Diverticulum			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Food poisoning			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Irritable bowel syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Large intestine polyp			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pancreatic cyst			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hepatic steatosis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Blister			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Neurodermatitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Micturition urgency			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 58 (12.07%)	1 / 57 (1.75%)	
occurrences (all)	7	1	
Arthritis			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	
occurrences (all)	3	2	
Osteoarthritis			
subjects affected / exposed	2 / 58 (3.45%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Tendonitis			
subjects affected / exposed	3 / 58 (5.17%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Bone lesion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Osteonecrosis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Osteopenia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Spinal osteoarthritis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Conjunctivitis viral			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	3 / 58 (5.17%)	4 / 57 (7.02%)	
occurrences (all)	3	4	
Upper respiratory tract infection			
subjects affected / exposed	3 / 58 (5.17%)	2 / 57 (3.51%)	
occurrences (all)	3	2	
Influenza			
subjects affected / exposed	0 / 58 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Tooth infection			
subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Herpes zoster			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	

Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Sepsis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Abscess jaw			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Abscess limb			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Cellulitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Infected bite			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Staphylococcal infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	

Subcutaneous abscess			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Suspected COVID-19			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Wound abscess			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Vitamin D deficiency			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2019	Protocol Version 4.0 Global
12 April 2021	Protocol Version 6.1
31 August 2021	Protocol Verison 7.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported