



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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	NT-501
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Reporting group description:

Test product

Reporting group title	Sham Procedure
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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			

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

Obstructive sleep apnoea syndrome subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 57 (0.00%) 0	
Anxiety subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Investigations			
Intraocular pressure increased subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 57 (1.75%) 1	
Biopsy prostate abnormal subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Blood glucose increased subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Endoscopy gastrointestinal subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Heart rate irregular subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Staphylococcus test positive subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 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 occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Ligament injury subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Muscle injury subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Procedural nausea subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Skin laceration subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Tendon injury subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Upper limb fracture subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Wound dehiscence subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Wrist fracture subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Congenital, familial and genetic disorders			
Type V hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Corneal dystrophy subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Cardiac disorders			

Acute myocardial infarction subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	1 / 57 (1.75%) 1	
Angina pectoris subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	1 / 57 (1.75%) 1	
Arrhythmia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	2 / 57 (3.51%) 2	
Coronary artery occlusion subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Tachycardia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Coronary artery disease subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	1 / 57 (1.75%) 1	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	3 / 57 (5.26%) 3	
Neuropathy peripheral subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 57 (0.00%) 0	
Balance disorder subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Carotid artery occlusion subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Cubital tunnel syndrome subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 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 occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Eye disorders			
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	18 / 58 (31.03%) 18	12 / 57 (21.05%) 12	
Dry eye subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 8	6 / 57 (10.53%) 6	
Delayed dark adaptation subjects affected / exposed occurrences (all)	12 / 58 (20.69%) 12	1 / 57 (1.75%) 1	
Eye pain subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 8	5 / 57 (8.77%) 5	
Foreign body sensation in eyes subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 6	7 / 57 (12.28%) 7	
Eye pruritus subjects affected / exposed occurrences (all)	9 / 58 (15.52%) 9	3 / 57 (5.26%) 3	
Miosis subjects affected / exposed occurrences (all)	10 / 58 (17.24%) 10	0 / 57 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 7	3 / 57 (5.26%) 3	
Ocular discomfort subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 8	1 / 57 (1.75%) 1	
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4	3 / 57 (5.26%) 3	
Vitreous floaters subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 7	0 / 57 (0.00%) 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 occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Night blindness subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Photophobia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Presbyopia subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Retinal artery embolism subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Retinal haemorrhage subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Retinal thickening subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Ulcerative keratitis subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Visual field defect subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Vitreoretinal traction syndrome subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Cataract nuclear subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	1 / 57 (1.75%) 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 occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Pancreatic cyst subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Toothache subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 57 (5.26%) 3	
Blister subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Neurodermatitis subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 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 occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Spinal osteoarthritis subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
Infections and infestations			
Conjunctivitis viral subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	
Hordeolum subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	4 / 57 (7.02%) 4	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	2 / 57 (3.51%) 2	
Influenza subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	3 / 57 (5.26%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 57 (1.75%) 1	
Sinusitis subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 57 (1.75%) 1	
Tooth infection subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	2 / 57 (3.51%) 2	
Herpes zoster subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	2 / 57 (3.51%) 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	0 / 58 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	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