Clinical trial results:
A First-in-Human Study to Evaluate the Safety and Tolerability of QR-421a in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the USH2A Gene

Summary

EudraCT number	2018-002433-38
Trial protocol	FR
Global end of trial date	14 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	PQ-421a-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03780257
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ProQR Therapeutics
Sponsor organisation address	Zernikedreef 9, Leiden, Netherlands, 2333 CK
Public contact	Clinical Trial Manager, ProQR Therapeutics, 31 881667000, clinical@proqr.com
Scientific contact	Clinical Trial Manager, ProQR Therapeutics, 31 881667000, clinical@proqr.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 October 2021
Global end of trial reached?	Yes
Global end of trial date	14 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
- To evaluate the safety and tolerability of QR-421a.

Secondary objectives:
- To evaluate the efficacy of QR-421a, as assessed by functional and structural outcome measures
- To evaluate the dose-response and duration of structural and functional effects of a single dose of QR-421a
- To evaluate the serum pharmacokinetics (PK) of QR-421a

Exploratory objectives:
- To evaluate changes in Patient-Reported Outcome (PRO) measures
- To evaluate serum biomarkers

Protection of trial subjects:

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP.
QR-421a was administered via intravitreal (IVT) injection to maximize exposure to study drug at the intended target tissue, the retina. QR-421a was administered in a unilateral manner to the subject's worse eye, a common practice in the development of ophthalmic products. Following IVT injection of QR-421a, subjects were monitored for increases in intraocular pressure (IOP) and signs of inflammation and endophthalmitis during the post-injection period. Subjects were also seen at 1, 2, and 7 days after each injection.
An independent Data Monitoring Committee (DMC) was involved to recommend on dose escalation and provided safety oversight for the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	20
EEA total number of subjects	8

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)	19
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty subjects were enrolled in this study. The study plan included up to 3 cohorts. Each cohort was to have at least 4 subjects treated and 2 to receive sham-procedure (for cohort 1 and 2). Additional dose levels could have been evaluated based on ongoing safety and efficacy data monitoring, but were never utilized.

Pre-assignment

Screening details:

Key inclusion criteria were: >= 18 years at Screening, a clinical diagnosis of RP with Usher syndrome type 2 or NSRP, a molecular diagnosis for 1 or more pathogenic exon 13 mutations in the USH2A gene, and impairment of VF as determined by perimetry with a continuous area of central field >= 10 degrees diameter in any axis in the treatment eye.

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

Blinding implementation details:

Each sentinel subject was treated in an open-label fashion, as were subjects enrolled in expansion Cohort 2b (100 µg) and Cohort 3 (200 µg). All other subjects were double-masked and randomized at a ratio of 2:1 for QR-421a and sham, respectively.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (50 µg)

Arm description:

Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject’s treated eye (TE).

Arm type	Experimental
Investigational medicinal product name	Ultevursen
Investigational medicinal product code	QR-421a
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

QR-421a solution for injection, 15 mg/mL, at a dose of 50µg. Subjects received QR-421a by a single unilateral IVT injection.
Each subject received a single dose in their worse eye, as defined by the BCVA at the most recent screening visit and subsequently referred to as the TE and were assessed for safety and tolerability at follow-up visits.

Arm title	Cohort 2 (100 µg)

Arm description:

Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject’s treated eye (TE).

Arm type	Experimental
Investigational medicinal product name	Ultevursen
Investigational medicinal product code	QR-421a
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

QR-421a solution for injection, 15 mg/mL, at a dose of 100µg. Subjects received QR-421a by a single unilateral IVT injection.
Each subject received a single dose in their worse eye, as defined by the BCVA at the most recent screening visit and subsequently referred to as the TE and were assessed for safety and tolerability at follow-up visits.

Arm title	Cohort 3 (200 µg)

Arm description:

Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).

Arm type	Experimental
Investigational medicinal product name	Ultevursen
Investigational medicinal product code	QR-421a
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

QR-421a solution for injection, 15 mg/mL, at a dose of 200µg. Subjects received QR-421a by a single unilateral IVT injection.
Each subject received a single dose in their worse eye, as defined by the BCVA at the most recent screening visit and subsequently referred to as the TE and were assessed for safety and tolerability at follow-up visits.

Arm title	Sham group

Arm description:

Subjects received a sham procedure closely mimicking the active injection without globe penetration.

Arm type	Sham procedure

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Cohort 1 (50 µg)	Cohort 2 (100 µg)	Cohort 3 (200 µg)
Started	4	7	3
Completed	4	7	3

Number of subjects in period 1	Sham group
Started	6
Completed	6

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (50 µg)
Reporting group description:	
Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).	
Reporting group title	Cohort 2 (100 µg)
Reporting group description:	
Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).	
Reporting group title	Cohort 3 (200 µg)
Reporting group description:	
Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).	
Reporting group title	Sham group
Reporting group description:	
Subjects received a sham procedure closely mimicking the active injection without globe penetration.	

Reporting group values	Cohort 1 (50 µg)	Cohort 2 (100 µg)	Cohort 3 (200 µg)
Number of subjects	4	7	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	7	3
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	51.5	54.0	39.0
full range (min-max)	30 to 65	25 to 58	33 to 54
Gender categorical Units: Subjects			
Female	4	3	3
Male	0	4	0

Reporting group values	Sham group	Total	
Number of subjects	6	20	
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)	6	19	
From 65-84 years	0	1	
85 years and over	0	0	
Age continuous			
Units: years			
median	44.5		
full range (min-max)	24 to 60	-	
Gender categorical			
Units: Subjects			
Female	2	12	
Male	4	8	

End points

End points reporting groups

Reporting group title	Cohort 1 (50 µg)
Reporting group description:	
Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).	
Reporting group title	Cohort 2 (100 µg)
Reporting group description:	
Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).	
Reporting group title	Cohort 3 (200 µg)
Reporting group description:	
Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).	
Reporting group title	Sham group
Reporting group description:	
Subjects received a sham procedure closely mimicking the active injection without globe penetration.	

Primary: Incidence and severity of ocular AEs (Treated Eye)

End point title	Incidence and severity of ocular AEs (Treated Eye)[1]
End point description:	
Only the incidence is reported in a tabular format. Nine subjects in the treatment group had mild severity ocular TEAEs in the TE (3 subjects in each group) and 1 subject in the 50 µg group had a moderate severity ocular AE.	
End point type	Primary
End point timeframe:	
Treatment emergent AEs until End of Study.	

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: No statistics were planned for safety.

End point values	Cohort 1 (50 µg)	Cohort 2 (100 µg)	Cohort 3 (200 µg)	Sham group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	3	6
Units: subjects	4	3	3	5

Statistical analyses

No statistical analyses for this end point

Primary: Incidence and severity of non-ocular AEs

End point title	Incidence and severity of non-ocular AEs[2]
End point description:	
Only the incidence is reported in a tabular format. Five subjects in the treatment group had mild severity non-ocular TEAEs in the TE (1 subjects in each group, except for 2 subjects in the 50 µg group), 7 subjects had moderate severity non-ocular TEAEs (2 subjects in each group, except for 1 subject in	

the 200 µg group), and 1 subject in the sham-group experienced 2 severe non-ocular TEAEs.

End point type	Primary

End point timeframe:

Treatment emergent AEs until End of Study.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistics were planned for safety.

End point values	Cohort 1 (50 µg)	Cohort 2 (100 µg)	Cohort 3 (200 µg)	Sham group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	3	6
Units: subjects	4	3	2	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Information regarding occurrence of (S)AEs was captured throughout the study. Treatment Emergent Ocular Adverse Events for the Treated Eye are provided.

Adverse event reporting additional description:

(S)AEs were collected from screening, and classed as medical history, non-treatment emergent AE or AE depending on relation to study drug administration. Duration (start and stop dates), severity/grade, outcome, treatment, and relationship to study drug were recorded. Pre-specified ocular related AEs were considered AEs of Special Interest.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Cohort 1 (50 µg)

Reporting group description:

Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).

Reporting group title	Cohort 2 (100 µg)

Reporting group description:

Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).

Reporting group title	Cohort 3 (200 µg)

Reporting group description:

Subjects received their dose of ultevursen (QR-421a) on Day 1 via IVT injection into the subject's treated eye (TE).

Reporting group title	Sham group

Reporting group description:

Subjects received a sham procedure closely mimicking the active injection without globe penetration.

Serious adverse events	Cohort 1 (50 µg)	Cohort 2 (100 µg)	Cohort 3 (200 µg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Appendicitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sham group		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
White blood cell count increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1 (50 µg)	Cohort 2 (100 µg)	Cohort 3 (200 µg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 7 (57.14%)	3 / 3 (100.00%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Intra-ocular injection complication			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	3	1	1
Lacrimation increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Anterior chamber cell			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Conjunctival haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Vision blurred			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	4
Anterior chamber flare			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cataract subcapsular			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Conjunctival hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Conjunctivitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cystoid macular oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	4
Dry eye			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Eye irritation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Eye pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Loss of visual contrast sensitivity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Macular fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metamorphopsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ocular hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Posterior capsule opacification			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Retinal cyst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Retinal disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Vitreous floaters			

subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vitreous opacities			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Corneal opacity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Foreign body sensation in eyes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Maculopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Swelling of eyelid			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Sham group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Intra-ocular injection complication			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Post procedural haemorrhage			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye pain			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Anterior chamber cell			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Anterior chamber flare			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cataract subcapsular			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Conjunctival hyperaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Conjunctivitis allergic			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cystoid macular oedema			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Dry eye				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Eye irritation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Eye pruritus				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Loss of visual contrast sensitivity				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Macular fibrosis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Metamorphopsia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ocular hyperaemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ocular hypertension				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Posterior capsule opacification				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Retinal cyst				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Retinal disorder				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Visual impairment				

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Vitreous floaters			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vitreous opacities			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Corneal opacity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Foreign body sensation in eyes			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Maculopathy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Swelling of eyelid			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vitreous detachment			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2019	• Increase in the follow-up duration from 12 to 24 months, to enhance subject patient safety and to maximize information derived from the trial; revision of screening duration from 2-6 to 8 weeks, to decrease subject burden • Revision in the timing of when replacement of subjects can occur • Increase in time to treatment of the CE from 24 weeks to 12 months, for safety purposes • Removal of kinetic perimetry and near infrared imaging, and the addition of LLVA and FAF as endpoints • Changes to timing of repeated measures of specified visual assessments to reduce redundancy and allow more flexibility in the screening window (for practical reasons) • Updates in the description of the study population, including revision of inclusion and exclusion criteria pertaining to: o BCVA entry limits (deletion) o Kinetic VF requirements (deletion) o SD-OCT entry criteria (modification) o Nystagmus, cardiovascular disease (deletion) o Amblyopia (modification) o eGFR, LFTs entry criteria, coagulation parameters, systemic disease (deletion) o Intraocular or periocular surgery or IVT injection (modification) • The addition of the potential for re-screening of screen failures • Inclusion of more stringent birth control criteria and requirements for females of child-bearing potential • Clarification that use of general anesthesia is not allowed • Removal of physical examination by Investigators • Removal of the use of external experts to assess changes in retinal structure or visual function • Modification of and addition to AESI criteria
19 August 2019	• Modification in the staggering of dosing between sentinel subjects and remaining subjects for Cohorts 2+ from 4 weeks to 1 week
17 January 2020	• Modification of overall study duration • Addition of FST as an outcome measure • Change in study design such that expansion cohorts and additional cohorts will be open-label rather than double-masked
08 May 2020	• Removal of ERG assessment throughout study • Removal of Streetlab substudy • Removal of wording regarding treatment of the CE and/or redosing of the TE • Removal of study visits at Month 4 and Month 5 • Reduction of study assessments in the Month 9 visit to only safety assessments • Removal of FAF assessment at Month 18 • Reduced blood sampling schedules for hematology and coagulation, serum chemistry, PK, and serum biomarkers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported