Clinical trial results:
An Open-Label, Single Arm, Multiple Dose, Dose Escalation Study to Evaluate the Safety and Tolerability of QR-110 in Subjects with Leber's Congenital Amaurosis (LCA) due to c.2991+1655A>G Mutation (p. Cys998X) in the CEP290 Gene

Summary

EudraCT number	2017-000813-22
Trial protocol	BE
Global end of trial date	02 October 2019

Results information

Result version number	v1 (current)
This version publication date	14 March 2021
First version publication date	14 March 2021

Trial information

Trial identification

Sponsor protocol code	PQ-110-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03140969
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ProQR Therapeutics
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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	21 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2019
Global end of trial reached?	Yes
Global end of trial date	02 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety and tolerability of QR-110 administered via intravitreal injection (IVT) in subjects with Leber Congenital Amaurosis type 10 (LCA10) due to the c.2991+1655A>G (p.Cys998X) mutation
The secondary objectives of the study were to evaluate the:
• Serum pharmacokinetics of QR-110 administered by IVT injection in subjects with LCA10 due to the c.2991+1655A>G (p.Cys998X) mutation
• Efficacy of QR-110 administered by IVT injection in subjects with LCA10 due to the c.2991+1655A>G (p.Cys998X) mutation

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-110 was administered via IVT injection to maximize exposure to study drug at the intended target tissue, the retina. QR-110 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-110, 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 and 7 days after each injection. If sedation or anesthesia was performed during the administration of the IVT injection, general health monitoring was provided by the study anesthesiologist pre- and post-sedation/anesthesia, according to local institutional guidelines. A Data Monitoring Committee (DMC) was involved to recommend on dose escalation and provided safety oversight for the study.

Background therapy:

There are currently no approved therapies for the treatment of LCA10.

Evidence for comparator:

No placebo or sham injections were administered.

Actual start date of recruitment	15 May 2017
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	Belgium: 2
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	11
EEA total number of subjects	2

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)	2
Adolescents (12-17 years)	3
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

11 subjects were enrolled in this study. The study plan included up to 6 cohorts (3 adult and 3 pediatric). Each planned cohort was to have at least 2 subjects, and each dose level was to be tested in 1 adult cohort and 1 pediatric cohort.

Pre-assignment

Screening details:

Key inclusion criteria were: >= 6 years at Screening, a clinical diagnosis of LCA with a molecular diagnosis of homozygosity or compound heterozygosity for the c.2991+1655A>G (p.Cys998X) mutation in the CEP290 gene and a best-corrected visual acuity equal or better than light perception and equal or worse than logMAR +0.6 in the treatment eye

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No randomization or masking has been used in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: 160/80 µg (loading dose/maintenance dose)

Arm description:

One 160 µg loading dose, followed by up to three 80 µg maintenance doses.

Arm type	Experimental
Investigational medicinal product name	QR-110
Investigational medicinal product code	QR-110
Other name	sepofarsen
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

QR-110 solution for injection, 10 mg/mL. Subjects receive QR-110 by IVT injection.
QR-110 was to be administered once every 3 months for up to 4 doses per subject (ie, an initial loading dose at Day 1, followed by 3 maintenance doses at Month 3, 6 and 9).

Arm title	Cohort 2: 320/160 µg (loading dose/maintenance dose)

Arm description:

One 320 µg loading dose, followed by up to three 160 µg maintenance doses.

Arm type	Experimental
Investigational medicinal product name	QR-110
Investigational medicinal product code	QR-110
Other name	sepofarsen
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

QR-110 solution for injection, 10 mg/mL. Subjects receive QR-110 by IVT injection.
QR-110 was to be administered once every 3 months for up to 4 doses per subject (ie, an initial loading dose at Day 1, followed by 3 maintenance doses at Month 3, 6 and 9.).
Following the observed incidence of cataracts and retinal events, the Sponsor decided in consultation with the DMC to stop administration of the 320/160 µg doses, and to prolong the dosing interval for

subjects in the 160/80 µg dose group.
While the protocol allowed testing of up to 3 dose levels, no dose escalation was performed to the 500 µg/270 µg dose based on efficacy observations; instead, additional subjects were allocated to the 160 µg/80 µg and 320 µg/160 µg dose cohorts.

Number of subjects in period 1	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)
Started	6	5
Completed	6	5

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: 160/80 µg (loading dose/maintenance dose)
Reporting group description:	
One 160 µg loading dose, followed by up to three 80 µg maintenance doses.	
Reporting group title	Cohort 2: 320/160 µg (loading dose/maintenance dose)
Reporting group description:	
One 320 µg loading dose, followed by up to three 160 µg maintenance doses.	

Reporting group values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)	Total
Number of subjects	6	5	11
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	6
Children (6-17 years)	3	2	5
Age continuous Units: years			
arithmetic mean	23.7	19.4	
standard deviation	± 15.06	± 6.88	-
Gender categorical Units: Subjects			
Female	2	4	6
Male	4	1	5

End points

End points reporting groups

Reporting group title	Cohort 1: 160/80 µg (loading dose/maintenance dose)
Reporting group description:	
One 160 µg loading dose, followed by up to three 80 µg maintenance doses.	
Reporting group title	Cohort 2: 320/160 µg (loading dose/maintenance dose)
Reporting group description:	
One 320 µg loading dose, followed by up to three 160 µg maintenance doses.	

Primary: Frequency of Ocular AEs in Treatment Eyes

End point title	Frequency of Ocular AEs in Treatment Eyes[1]
End point description:	
Frequency of all ocular treatment emergent adverse events (TEAEs) in the treatment eyes (ie, treated eyes)	
End point type	Primary
End point timeframe:	
From baseline until End of Study (12 months)	
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: Incidence and severity of adverse events were summarized descriptively.	

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: number of events	15	45		

Statistical analyses

No statistical analyses for this end point

Primary: Severity of Ocular AEs

End point title	Severity of Ocular AEs[2]
End point description:	
Number of subjects with mild, moderate or severe ocular treatment emergent adverse events (TEAEs)	
End point type	Primary
End point timeframe:	
From baseline until End of Study (12 months)	
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: Incidence and severity of adverse events were summarized descriptively.	

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: nr of subjects				
mild	3	1		
moderate	1	1		
severe	1	3		

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of Ocular AEs in Contralateral Eyes (CE)

End point title	Frequency of Ocular AEs in Contralateral Eyes (CE)[3]

End point description:

Frequency of all ocular treatment emergent adverse events (TEAEs) in contralateral eyes (ie, untreated eyes)

End point type	Primary

End point timeframe:

From baseline to End of Study (Month 12)

Notes:

[3] - 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: Incidence and severity of adverse events were summarized descriptively.

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of events	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of non-ocular AEs

End point title	Frequency of non-ocular AEs

End point description:

Frequency of all non-ocular Adverse Events (AEs)

End point type	Secondary

End point timeframe:

From baseline until End of Study (12 months)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: number of events	21	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of non-ocular AEs

End point title	Severity of non-ocular AEs

End point description:

Number of subjects with mild, moderate or severe non-ocular adverse events (AEs).

End point type	Secondary

End point timeframe:

From baseline until End of Study (12 months)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: nr of AEs				
mild	5	4		
moderate	0	1		
severe	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA change from baseline in Treatment Eye (TE)

End point title	BCVA change from baseline in Treatment Eye (TE)

End point description:

Change of BCVA value at Month 12 versus BCVA value at baseline in the treatment eye (= treated eye). Baseline defined as the average pre-treatment value (ie, the average of Screening and Day 1 [pre-dose] values).

Smaller values are indicative of better status.

End point type	Secondary

End point timeframe:

From baseline until End of study (12 months).

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: logMAR				
arithmetic mean (standard deviation)	-0.93 (± 1.049)	-0.11 (± 0.155)		

Statistical analyses

No statistical analyses for this end point

Secondary: Red FST Change from Baseline in Treatment Eye (TE)

End point title	Red FST Change from Baseline in Treatment Eye (TE)

End point description:

Change from Month 12 to baseline in retinal sensitivity in the treatment eye (= treated eye) based on red FST.
Data from 1 subject is missing.
Month 12 data for 1 subject was imputed using LOCF.
Smaller values are indicative of better status.

End point type	Secondary

End point timeframe:

From baseline until End of Study (Month 12)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: log cd/m2				
arithmetic mean (standard deviation)	-0.7 (± 0.33)	-1.3 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blue FST Change from Baseline in Treatment Eye (TE)

End point title	Blue FST Change from Baseline in Treatment Eye (TE)

End point description:

Change from Month 12 to baseline in retinal sensitivity based on blue FST in the treatment eye (= treated eye).
Data from 1 subject is missing.
Month 12 data for 1 subject was imputed using LOCF.
Smaller values are indicative of better status.

End point type	Secondary

End point timeframe:

From Baseline until End of Study (Month 12)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: log cd/m2				
arithmetic mean (standard deviation)	-0.6 (± 0.76)	-1.0 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mobility Course Composite Score Change from Baseline in Treatment Eye (TE)

End point title	Mobility Course Composite Score Change from Baseline in Treatment Eye (TE)

End point description:

Change from Month 12 to baseline in mobility course composite score in the treatment eye (ie, treated eye). The mobility course composite score represents the most difficult course and light level combination passed.
Data from 1 subject is missing.

End point type	Secondary

End point timeframe:

From baseline until End of Study (Month 12)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: score				
arithmetic mean (standard deviation)	4.00 (± 3.114)	0.25 (± 1.323)		

Statistical analyses

No statistical analyses for this end point

Secondary: Red FST Change from Baseline in Contralateral Eye (CE)

End point title	Red FST Change from Baseline in Contralateral Eye (CE)

End point description:

Change from Month 12 to baseline in retinal sensitivity in the untreated contralateral eye, based on red FST.
Data from 1 subject is missing.
Month 12 data for 1 subject was imputed using LOCF.
Smaller values are indicative of better status.

End point type	Secondary

End point timeframe:

From baseline until End of Study (Month 12)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: log cd/m2				
arithmetic mean (standard deviation)	0.0 (± 0.42)	-0.5 (± 0.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA change from baseline in Contralateral Eye (CE)

End point title	BCVA change from baseline in Contralateral Eye (CE)

End point description:

Change of BCVA value at Month 12 versus BCVA value at baseline in the untreated contralateral eye.
Baseline defined as the average pre-treatment value (ie, the average of Screening and Day 1 [pre-dose] values).
Smaller values are indicative of better status.

End point type	Secondary

End point timeframe:

From baseline to End of Study (12 months)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: logMAR				
arithmetic mean (standard deviation)	-0.22 (± 0.264)	0.008 (± 0.0856)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blue FST Change from Baseline in Contralateral Eye (CE)

End point title	Blue FST Change from Baseline in Contralateral Eye (CE)

End point description:

Change from Month 12 to baseline in retinal sensitivity in the untreated contralateral eye, based on blue FST.
Data from 1 subject is missing.
Month 12 data for 1 subject was imputed using LOCF.
Smaller values are indicative of better status.

End point type	Secondary

End point timeframe:

from baseline until End of Study (Month 12)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: log cd/m2				
arithmetic mean (standard deviation)	0.1 (± 0.39)	-0.1 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mobility Course Composite Score Change from Baseline in Contralateral Eye (CE)

End point title	Mobility Course Composite Score Change from Baseline in Contralateral Eye (CE)

End point description:

Change from baseline to Month 12 in Mobility Course Composite Score in the contralateral eye (ie, untreated eyes). The mobility course composite score represents the most difficult course and light level combination passed.
Data from 1 subject missing.

End point type	Secondary

End point timeframe:

From baseline until End of Study (Month 12)

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: Score				
arithmetic mean (standard deviation)	2.67 (± 2.714)	0.38 (± 0.750)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum pharmacokinetics

End point title	Serum pharmacokinetics

End point description:

PK calculations were not performed, since all measurements indicated serum levels were below the LLOQ (1.02 ng/mL) following administration of up to 4 doses, except for one subject who had a QR-110 level of 1.53 ng/mL which is slightly above the LLOQ ; this occurred 3 hours after the first (loading) dose of 320 µg and was not observed at subsequent timepoints for PK sampling.

End point type	Secondary

End point timeframe:

Samples for analysis of QR-110 serum concentration were taken pre-dose and 3 hours post-dose on Day 1 and at the end of the study in all subjects.

End point values	Cohort 1: 160/80 µg (loading dose/maintenance dose)	Cohort 2: 320/160 µg (loading dose/maintenance dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[4]	5[5]		
Units: ng/mL				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Notes:

[4] - All levels were below LLOQ

[5] - Only 1 subject showed levels above LLOQ (1.53 ng/mL)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

(S)AEs were collected from screening, and classed as medical history, non-treatment emergent AE or AE depending on relation to study drug administration.

Adverse event reporting additional description:

Ten of 11 subjects experienced a total of 61 AEs, of which 33 were treatment related. Reported ocular AEs were mostly mild in severity. The most common AEs were cataract-related (8 of 11 subjects), resulting in an SAE for 6 subjects. Three subjects had an AE indicative of retinal changes. AEs of special interest are depicted.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	cohort 1: 160/80 µg

Reporting group description:

Subjects received one 160 µg loading dose, followed by up to three 80 µg maintenance doses.

Reporting group title	cohort 2: 320/160 µg

Reporting group description:

Subjects received one 320 µg loading dose, followed by up to three 160 µg maintenance doses. Following the observed incidence of cataracts and retinal events, the Sponsor decided in consultation with the DMC to stop administration of the 320/160 µg doses, and to prolong the dosing interval for subjects in the 160/80 µg dose group.

Serious adverse events	cohort 1: 160/80 µg	cohort 2: 320/160 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	4 / 5 (80.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Eye disorders			
Cataract	Additional description: All SAEs consisted of the PT of cataract (verbatim terms: cataract [4 subjects] and cataract surgery [2 subjects]); each case of cataract was assessed as serious due to lens replacement surgery being performed.		
subjects affected / exposed	2 / 6 (33.33%)	4 / 5 (80.00%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	cohort 1: 160/80 µg	cohort 2: 320/160 µg	
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 6 (50.00%)	5 / 5 (100.00%)	
Eye disorders			
Cystoid macular oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Retinal cyst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Retinal degeneration			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Cataract	Additional description: For 8 subjects >=1 cataract-related AEs were reported reflecting different stages of cataract development. For 6 subjects the cataract resulted in an SAE due to the need for lens replacement surgery."		
subjects affected / exposed	3 / 6 (50.00%)	5 / 5 (100.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2017	Revisions made to historic genotyping and sequencing requirements (non-substantial amendment)
08 November 2017	Revisions made to add the Cardiff Visual Ability Questionnaire for Children Clarification of Exclusion Criteria 7 through 9 regarding acceptable laboratory values at Screening Revisions to endpoints to enhance nature and quality of data derived from the study (non-substantial amendment)
04 June 2018	Revised BCVA for Inclusion Criteria (substantial amendment not submitted in Belgium)
27 July 2018	Revised efficacy assessments and subject disposition, demographics and baseline disease characteristics to indicate that the average of the measures represented a more accurate assessment of the baseline value, considering all collected values and stabilizing the baseline. Revised BCVA for inclusion criteria Allowed for interim analyses to support the design of subsequent QR-110 clinical studies. Revised Schedule of Events This substantial amendment was not submitted in Belgium
02 August 2018	Added exploratory endpoints that can be done at the investigator's discretion at any protocol visit (non-substantial).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30559420