PROTOCOL TITLE:	An Open-Label, Dose Escalation and Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Tolerability of Sepofarsen in Pediatric Subjects <8 Years of Age With Leber Congenital Amaurosis Type 10 (LCA10) Due to the C.2991+1655A>G (P.cys998x) Mutation.
PROTOCOL NUMBER:	PQ-110-005
STUDY PHASE:	2/3
SPONSOR:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
FINAL CLINICAL TRIAL SUMMARY REPORT DATE:	04 November 2022
Clinical Trial Summary Report Version:	Version 1.0

DISCLAIMER
This report has been prepared to meet the minimum regulatory reporting standards for a clinical trial which has been terminated prematurely, for reasons unrelated to safety issues. The reader is advised of potential short comings, including but not limited to inconsistent, inaccurate, or incomplete data. The data contained in this report should be interpreted with caution.

2 SYNOPSIS

Name of Sponsor/Company:

ProQR Therapeutics
Zernikedreef 9
2333 CK Leiden
The Netherlands

Name of Investigational Product:

Sepofarsen Solution for Intravitreal Injection

Name of Active Ingredient:

Sepofarsen (formerly QR-110)

Title of Study:

An Open-Label, Dose Escalation and Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Tolerability of Sepofarsen in Pediatric Subjects <8 Years of Age With Leber Congenital Amaurosis Type 10 (LCA10) Due to the C.2991+1655A>G (P.cys998x) Mutation.

IND Number:

130557

EudraCT Number:

2020-000535-45
This study forms part of a Paediatric Investigation Plan

Clinical Protocols and Amendments

PQ-110-005 V1 – 19 Jun 2020
PQ-110-005 V1.1 UK – 02 Nov 2020
PQ-110-005 V1.2 DE – 30 Nov 2020
PQ-110-005 V1.2 UK – 18 Mar 2021
PQ-110-005 V1.3 DE – 18 Mar 2021
PQ-110-005 V2 – 10 Mar 2021
PQ-110-005 V2.1 DE – 10 May 2021

Study Center(s): The study was conducted in 7 study centers in Belgium, Brazil, Canada, Germany, Italy and The Netherlands.

Study Period (years):	**Phase of development:**	**Results Analysis Stage:**
First subject screened: 23 March 2021 Last subject Last Visit: 18 October 2022	Phase 2/3	Complete

Objectives:

Primary:

To evaluate safety and tolerability of sepofarsen in subjects with LCA10 <8 years of age.

Secondary:

To evaluate the effect of sepofarsen on structural and functional ophthalmic outcome measures.

Number of subjects (planned):

15 subjects.

Further Information:

Global Interruptions of Restarts: None.

Limitations and Caveats for the Study: This report has been prepared to meet the minimum regulatory reporting standards for a clinical trial which has been terminated prematurely, for reasons unrelated to safety issues. The reader is advised of potential short comings, including but not limited to inconsistent, inaccurate, or incomplete data. The data contained in this report should be interpreted with caution.

Diagnosis and main criteria for inclusion:

Subjects were included if they met all the following Inclusion Criteria:

1. Male or female child, <8 years of age at Screening able to provide age-appropriate assent for trial participation, if required per local regulations, with a parent or legal guardian willing and able to provide written permission for the subject's participation prior to performing any trial related procedures.
2. A clinical diagnosis of LCA and a molecular diagnosis of homozygosity or compound heterozygosity for the c.2991+1655A>G mutation in the *CEP290* gene, based on genotyping analysis at Screening. A historic genotyping report from a certified laboratory is acceptable with Sponsor approval.
3. Best Corrected Visual Acuity (BCVA) equal to or better than Logarithm of the Minimum Angle of Resolution (logMAR) + 4.0 (Light Perception), and equal to or worse than logMAR + 0.4 (approximate Snellen equivalent 20/50) in the treatment eye, using the best pre-dose BCVA reading of the two most recent readings obtained prior to first dose.
4. Detectable outer nuclear layer (ONL) in the area of the macula as determined by the Investigator at Screening.
5. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as determined by the Investigator.
6. Able to complete all study assessments and comply with the protocol and has a parent or caregiver willing and able to follow study instructions and attend study visits with the subject as required, in the opinion of the Investigator.

Subjects were excluded if they met any of the following Exclusion Criteria:

1. Presence of additional homozygous or compound heterozygous pathogenic mutations (other than the c.2991+1655A>G mutation in the *CEP290* gene) in genes associated with other recessive inherited retinal degenerative diseases or syndromes (eg, Usher syndrome) based on genetic analysis.
2. Presence of (likely) pathogenic mutations in genes associated with dominant or X-linked inherited retinal degenerative diseases or syndromes (eg. autosomal dominant retinitis pigmentosa, X-linked Retinoschisis) based on genetic analysis.
3. Presence of any significant ocular or non-ocular disease/disorder (including lab/medication abnormalities) which, in the opinion of the Investigator and with concurrence of the Medical Monitor, may either put the subject at risk because of participation in the trial, may influence the results of the trial, or the subject's ability to participate in the trial. This includes but is not limited a subject who: 1) is not an appropriate candidate for antisense oligonucleotide treatment, 2) has concurrent cystoid macular edema (CME) in the treatment eye.
4. History or presence of ocular herpetic diseases (including herpes simplex virus, varicella zoster or cytomegalovirus) in the treatment eye.
5. Presence of any active ocular infection in either eye.
6. Presence of any of the following lens opacities in the treatment eye: cortical opacity ≥ +2, posterior subcapsular opacity ≥ +2, or a nuclear sclerosis ≥ +2, and which: 1) is clinically significant in the opinion of the Investigator, or 2) would adequately prevent clinical and photographic evaluation of the retina.
7. Receipt within 1 month prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an intravitreal (IVT) injection or planned intraocular surgery or procedure during the course of the trial. Subjects who received an intraocular or periocular surgery between 1 to 3 months prior Screening,

may only be considered for inclusion (at the discretion of the Investigator) if there are no clinically significant complications of surgery present.

8. Current treatment or treatment within the past 12 months with therapies known to influence the immune system (including but not limited to cytostatics, interferons, TNF-binding proteins, drugs acting on immunophilins, or antibodies with known impact on the immune system). Subjects that have been treated with systemic steroids within the past 12 months or that require intermittent use of topical steroids may be considered for inclusion based on Investigator judgement, dependent on the status of the underlying disease.
9. Current treatment or treatment within the past 3 months or planned treatment with drugs known to be toxic to the lens, retina, or the optic nerve including, but not limited to, systemic/intraocular steroids, amiodarone, desferrioxamine/desferoxamine, chloroquine/hydroxychloroquine sulfate (Plaquenil), tamoxifen, ethambutol, phenothiazine derivatives including chlorpromazine, fluphenazine (decanoate), levomepromazine, and thioridazine.
10. A history of glaucoma in the treatment eye or raised intraocular pressure in the treatment eye that is not controlled with medication at the time of Screening.
11. Use of any investigational drug or device within 3 months or 5 half-lives of Day 1, whichever is longer, or plans to participate in another study of a drug or device during the trial period.
12. Any prior receipt of genetic or stem-cell therapy for ocular or non-ocular disease.

Test product, dosage and mode of administration:

Sepofarsen (QR-110) Solution for Injection, For intravitreal Administration. Dose levels of 10 µg, 20 µg, 40 µg and 80 µg will be studied.

Duration of treatment:

Up to 24 months

Reference therapy (Comparator), dosage and mode of administration:

None

Background therapy:

None

Criteria for evaluation

Primary:

- Incidence and severity of ocular adverse events (AEs).
- Incidence and severity of non-ocular AEs.

Secondary:

- Change from baseline to Month 12 in:
    - BCVA
    - Retinal sensitivity measured by FST (white, red, and blue)

Exploratory:

- Spectral domain optical coherence tomography (SD-OCT)
- Visual Evoked Potential (VEP) (at selected sites)
- Patient-reported and caregiver-reported questionnaires as measured by:
    - the Patient Global Impressions of Severity (PGI-S)
    - the caregiver version of the PGI-S
    - the Patient Global Impressions of Change (PGI-C)
    - the caregiver version of the PGI-C

Statistical methods:

In August 2022, ProQR decided to prematurely terminate PQ-110-005 (Brighten) and, per ProQR's instruction, subjects were unmasked prior to Database Lock on 20th October 2022.

In this context, the statistical analysis is abbreviated and describes the populations for analysis, data handling rules, statistical methods, and formats for data presentation that will be required for the close out of the study, after all randomized subjects have completed the end of study visit and the database is locked.

Summary tabulations and listings were produced for the close out of the study and provide the basis for the appropriate sections of this clinical trial summary report.

SUMMARY

SAFETY RESULTS:

The disposition of subjects is outlined in Table 1 below. In total, 25 subjects were screened, 9 subjects were screen failed. Of the 16 subjects enrolled, all received study treatment in the Treatment Eye. No subjects prematurely discontinued from the study for safety reasons.

The longest duration of follow up from the first dose during the study was to Month 15.

During the study, subjects received 10 µg (N=1), 20 µg (N=1) or 40 µg (N=3) sepofarsen in the open-label part of the study and then subjects entering the masked part of the study received 40 µg (N=6) or 80 µg (N=5) sepofarsen.

Table 1: PQ-110-005 Study Disposition

	Sepofarsen 10 µg N=1	**Sepofarsen 20 µg** N=1	**Sepofarsen 40 µg** N=9	**Sepofarsen 80 µg** N=5	**All Subjects** N=16
Screened, n					25 (100%)
Enrolled, n (%)	1	1	9	5	16 (64%)
Dosed in the Treatment Eye, n (%)	1 (6.3%)	1 (6.3%)	9 (56.3%)	5 (31.3%)	16 (100%)
Premature Discontinuation from Study, n (%)	0	0	8 (50%)	4 (25%)	12 (75%)
Primary Reason for Premature Discontinuation from Study, n (%)			Sponsor Decision – Study prematurely closed, 8 (50%)	Sponsor Decision – Study prematurely closed, 4 (25%)	Sponsor Decision – Study prematurely closed, 12 (75%)

Half (8 out of 16) the subjects reported at least one ocular treatment emergent adverse event (TEAE) in the Treatment Eye and 1 out of 16 subjects reported an ocular TEAE in the Contralateral Eye. No TEAEs led to treatment discontinuation. There were no subjects that reported a severe TEAE. There were 1 out of 16 subjects reported an adverse event of special interest (AESI) and 1 out of 16 subjects reported a serious adverse event (SAE).

Table 2: PQ-110-005 Overview of Ocular TEAEs

	Sepofarsen 10 µg N=1	**Sepofarsen 20 µg** N=1	**Sepofarsen 40 µg** N=9	**Sepofarsen 80 µg** N=5	**All Subjects** N=16
Number of Ocular TEAEs	2	1	8	2	13
Treatment Eye	2	1	8	1	12
Contralateral Eye	0	0	0	1	1
Number of Subjects with at Least One Ocular TEAE, n (%)	1 (100%)	1 (100%)	5 (55.6%)	1 (20%)	8 (50%)
Treatment Eye	1 (100%)	1 (100%)	5 (55.6%)	1 (20%)	8 (50%)
Contralateral Eye	0	0	0	1 (20%)	1 (6.3%)
Number of Subjects with At Least One Ocular TEAE of Special Interest, n (%)	0	0	1 (11.1%)	0	1 (6.3%)
Treatment Eye	0	0	1 (11.1%)	0	1 (6.3%)
Contralateral Eye	0	0	0	0	0
Number of Subjects with At Least One	0	0	1 (11.1%)	0	1 (6.3%)

Ocular Serious TEAE, n (%)					
Treatment Eye	0	0	1 (11.1%)	0	1 (6.3%)
Contralateral Eye	0	0	0	0	0

Table 3: PQ-110-005 Ocular TEAEs (Preferred Term)

Subjects with Event; N (%)	**Sepofarsen 10 µg** N=1		**Sepofarsen 20 µg** N=1		**Sepofarsen 40 µg** N=9		**Sepofarsen 80 µg** N=5		**All Subjects** N=16	
System Organ Class and Preferred Term	TE	CE	TE	CE	TE	CE	TE	CE	TE	CE
Eye disorders	1 (100%)	0	1 (100%)	0	5 (55.6%)	0	0	0	7 (43.8%)	0
Conjunctival haemorrhage	1 (100%)	0	0	0	2 (22.2%)	0	0	0	3 (18.8%)	0
Vitreous floaters	0	0	1 (100%)	0	0	0	0	0	1 (6.3%)	0
Punctate keratitis	0	0	0	0	1 (11.1%)	0	0	0	1 (6.3%)	0
Visual acuity reduced	0	0	0	0	1 (11.1%)	0	0	0	1 (6.3%)	0
Foreign body sensation in eyes	0	0	0	0	1 (11.1%)	0	0	0	1 (6.3%)	0
Conjunctival hyperaemia	0	0	0	0	1 (11.1%)	0	0	0	1 (6.3%)	0
Optic disc vascular disorder	0	0	0	0	1 (11.1%)	0	0	0	1 (6.3%)	0
Retinal vascular disorder	0	0	0	0	1 (11.1%)	0	0	0	1 (6.3%)	0
Injury, poisoning and procedural complications	1 (100%)	0	0	0	0	0	0	0	1 (6.3%)	0
Procedural pain	1 (100%)	0	0	0	0	0	0	0	1 (6.3%)	0
Investigations	0	0	0	0	0	0	1 (20%)	1 (20%)	1 (6.3%)	1 (6.3%)
Corneal reflex decreased	0	0	0	0	0	0	1 (20%)	1 (20%)	1 (6.3%)	1 (6.3%)

TE=Treatment Eye, CE=Contralateral Eye

Table 4: PQ-110-005 Non-Ocular TEAEs (Preferred Term)

Subjects with Event; N (%)	**Sepofarsen 10 µg** N=1	**Sepofarsen 20 µg** N=1	**Sepofarsen 40 µg** N=9	**Sepofarsen 80 µg** N=5	**All Subjects** N=16
System Organ Class and Preferred Term					
Infections and infestations	1 (100%)	0	4 (44.4%)	1 (20%)	6 (37.5%)
Nasopharyngitis	1 (100%)	0	1 (11.1%)	0	2 (12.5%)
Influenza	0	0	1 (11.1%)	0	1 (6.3%)
COVID-19	0	0	1 (11.1%)	0	1 (6.3%)
Gastroenteritis	0	0	1 (11.1%)	0	1 (6.3%)
Gastroenteritis viral	0	0	1 (11.1%)	0	1 (6.3%)
Upper respiratory tract infection	0	0	0	1 (20%)	1 (6.3%)
Furuncle	0	0	0	1 (20%)	1 (6.3%)
Oral candidiasis	0	0	0	1 (20%)	1 (6.3%)
Rhinitis	0	0	0	1 (20%)	1 (6.3%)
Injury, poisoning and procedural complications	0	0	1 (11.1%)	1 (20%)	2 (12.5%)

Ligament sprain	0	0	1 (11.1%)	0	1 (6.3%)
Procedural vomiting	0	0	0	1 (20%)	1 (6.3%)
Gastrointestinal disorders	0	0	1 (11.1%)	1 (20%)	2 (12.5%)
Vomiting	0	0	1 (11.1%)	0	1 (6.3%)
Gastritis	0	0	1 (11.1%)	0	1 (6.3%)
Nausea	0	0	0	1 (20%)	1 (6.3%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (11.1%)	0	1 (6.3%)
Oropharyngeal pain	0	0	1 (11.1%)	0	1 (6.3%)
Nervous system disorders	0	0	1 (11.1%)	0	1 (6.3%)
Headache	0	0	1 (11.1%)	0	1 (6.3%)

Table 5: PQ-110-005 Adverse Events of Special Interest (AESI)

Subject	Study Treatment	AE (Preferred Term)	Treatment Eye	Severity	Relationship	Outcome
A	40 µg	Visual acuity reduced	TE	Mild	Possibly related	Not Recovered/Not Resolved

Table 6: PQ-110-005 Serious Adverse Events

Subject	Study Treatment	AE (Preferred Term)	Treatment Eye	Severity	Relationship to IMP	Outcome
A	40 µg	Optic disc vascular disorder	TE	Mild	Not Related*	Resolved

* The event is considered definitely related to the IVT procedure to administer investigational medicinal product (IMP).

The most frequently reported AEs by system organ class (SOC) was Eye disorders reported by 7/16 subjects (43.8%).

By PT, the only event occurring in more than one subject was Conjunctival haemorrhage occurring in 3/16 (18.8%) of subjects reported as related to IVT procedure and not related to IMP.

Subject A reported an AESI that occurred after dosing in the study, this being visual acuity reduced (mild in severity) that was considered possibly related to IMP. The onset of this event was 16 hours after dosing and in the same subject that reported Optic disc vascular disorder immediately following dosing.

One SAE was reported by subject A in the study, this being Optic disc vascular disorder (mild in severity) that was considered not related to IMP but definitely related to the procedure to administer IMP.

No deaths were reported.

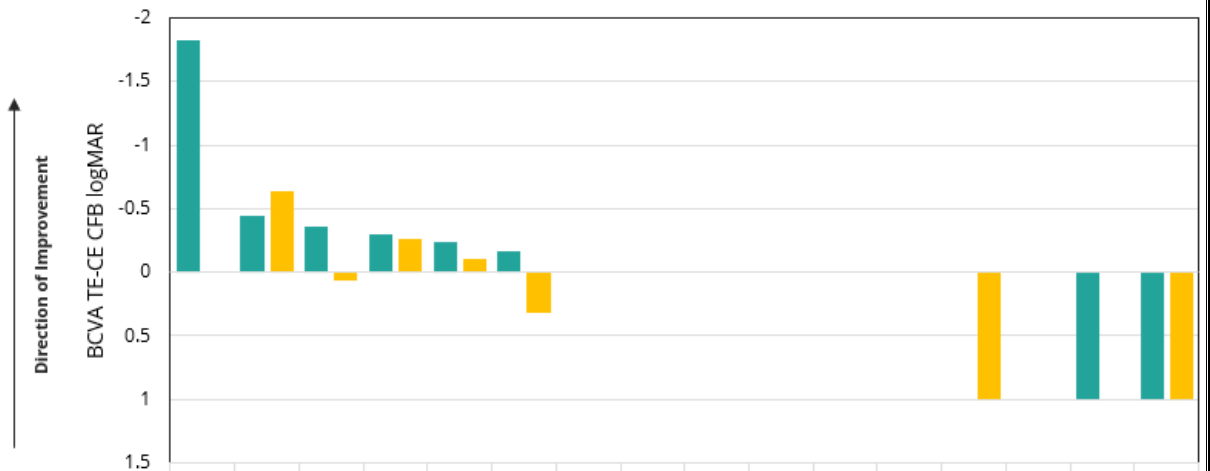
EFFICACY RESULTS:

The data are insufficient to draw strong conclusions regarding efficacy in study PQ-110-005 as most subjects (9/16) were Light Perception (LP) at baseline and showed no improvement to visual acuity throughout the study. However, six subjects demonstrated numeric improvements in the Treatment Eye (TE) after treatment with sepofarsen (Figure 1). In contrast, two subjects demonstrated a deterioration after treatment, however one of these subjects deteriorated from LP to No Light Perception (NLP) in both eyes (starting with the Contralateral Eye (CE)). This subject was noted by the Investigator to have vision fluctuation typical of LCA10 and also to have

'low collaboration due to cognitive deficit'. The other subject deteriorated from Hand Motion (HM) to LP in the TE on Day 2 of the study.

It is difficult to completely rationalize the improvements in both the TE and CE for some subjects, but this could be variability in a young, low vision population, or alternatively improvements in vision in a treated eye is enabling better vision in the untreated eye via indirect methods.

Figure 1: PQ-110-005 Individual Subject BCVA (logMAR)



Baseline BCVA (TE)	3	1.7	1.26	1.4	0.84	1.36	4	4	4	4	4	4	4	4	3	4
Last Visit Completed	EOS	M9	EOS	EOS	M6	M3	M12	M12	M9	M12	EOS	EOS	EOS	EOS	EOS	EOS
Dose of sepofarsen	80 µg	80 µg	40 µg	40 µg	80 µg	80 µg	10/40 µg	40 µg	40 µg	20/40 µg	40 µg	40 µg	80 µg	40 µg	40 µg	40 µg
CFB TE	-1.82	-0.44	-0.36	-0.3	-0.24	-0.16	0	0	0	0	0	0	0	0	1	1
CFB CE	0	-0.64	0.06	-0.26	-0.1	0.32	0	0	0	0	0	0	1	0	0	1

CONCLUSION

Sepofarsen was well-tolerated in the subjects that were dosed in study PQ-110-005.

There are insufficient data to draw strong conclusions regarding the efficacy of sepofarsen in study PQ-110-005; however, six subjects have demonstrated numeric improvements in BCVA in the treated eye.

Date of Report: 04 November 2022