A Double-Masked, Randomized, Controlled, Multiple-Dose Study to Evaluate the Efficacy, Safety, Tolerability and Systemic Exposure of QR-110 in Subjects with Leber*s Congenital Amaurosis (LCA) due to c.2991+1655A>G Mutation (p.Cys998X) in the CEP290 Gene

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Primary: To evaluate the efficacy of QR-110 administered by intravitreal (IVT) injection.Secondary:1. To evaluate the safety and tolerability of QR-110 administered via IVT injection.2. To evaluate changes in patient-reported outcome (PRO) measures...

Ethical review	Approved WMO
Status	Completed
Health condition type	Eye disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55773

Source
ToetsingOnline

Brief title
PQ-110-003

Condition

- Eye disorders congenital
- Congenital eye disorders (excl glaucoma)

Synonym
Leber□s Congenital Amaurosis. Leber's Disease

Research involving
Human

Sponsors and support

Primary sponsor: ProQR Therapeutics
Source(s) of monetary or material Support: ProQR Therapeutics

Intervention

Keyword: Leber□s Congenital Amaurosis (LCA), Multiple-Dose Study, QR-110

Outcome measures

Primary outcome

The change from baseline in BCVA (based on ETDRS and/or BRVT) at 12 months of

treatment versus sham-procedure

Secondary outcome

Key secondary endpoint: Change from baseline in mobility course score at 12

months of treatment versus sham, as assessed by a masked central reader

Secondary endpoints:

• Change from baseline in BCVA:

- By >= 3 lines (or >= 0.3 logMAR change) in subjects with BCVA equal to

or better than 1.7 logMAR at baseline

- By a clinically meaningful improvement in subjects with BCVA worse

than 1.7 logMAR at baseline

• Change from baseline in mobility course score

• Change from baseline in BCVA based on Freiburg Visual Acuity and contrast

Test (FrACT)

• Change from baseline in light sensitivity to FST (white, red, and blue)

• Change from baseline in ellipsoid zone (EZ) width/area assessed by spectral

domain optical coherence tomography SD-OCT

• Change from baseline in low luminance visual acuity (LLVA)

• Change from baseline in oculomotor instability

• Change from baseline as determined by fundus autofluorescence (FAF) imaging

• Change from baseline as determined by microperimetry

• Change from baseline in PRO measures, as measured by:

- The Visual Function Questionnaire-25 (VFQ-25) score (adult subjects)

- The Cardiff Visual Ability Questionnaire for Children (CVAQC)

(pediatric subjects)

- The Patient Global Impressions of Severity (PGI S)

- The Patient Global Impressions of Change (PGI C)

• Systemic exposure to QR-110

• Ocular and non-ocular AEs

Study description

Background summary

Leber*s congenital amaurosis (LCA) is a severe inherited retinal degenerative disease resulting in blindness, often in early childhood. In subjects with LCA due to the p.Cys998X mutation in the CEP290 gene (subsequently referred to as CEP290 p.Cys998X mutation), visual symptoms are usually detectable before 1 year of age and further deterioration over time has also been reported. Subjects show severe vision disturbances from an early age and slow progressive loss of remaining vision. There are currently no approved therapies for the treatment of LCA due to the CEP290 p.Cys998X mutation and a large unmet medical

need exists.
The primary goal of the development plan for QR-110 is to provide a treatment to overcome the genetic defect in subjects with at least 1 CEP290 allele containing the CEP290 p.Cys998X mutation, resulting in functional vision restoration or preservation. The intended route of administration is intravitreal injection

Study objective

Primary: To evaluate the efficacy of QR-110 administered by intravitreal (IVT) injection.

Secondary:
1. To evaluate the safety and tolerability of QR-110 administered via IVT injection.
2. To evaluate changes in patient-reported outcome (PRO) measures in subjects treated with QR-110
3. To evaluate the systemic exposure of QR-110 administered by IVT injection.

Study design

The study is a double-masked, randomized, controlled, multiple-dose study to evaluate the efficacy, safety, tolerability and systemic exposure of QR 110 administered via IVT injection in subjects with LCA due to the CEP290 p.Cys998X mutation.
At study start subjects will be randomized to one of the following treatment groups:
1) Group 1: QR-110 (160 µg loading dose administered on Day 1, 80 µg maintenance dose administered at Month 3 and every 6 months thereafter [160/80 µg]; n = 10)
2) Group 2: QR-110 (80 µg loading dose administered on Day 1, 40 µg maintenance dose administered at Month 3 and every 6 months thereafter [80/40 µg]; n = 10)
3) Group 3: Sham-pr ocedure (administered on Day 1, Month 3 and every 6 months thereafter; n = 10)
Once at least 6 subjects per treatment group have been treated for at least 3 months, an interim analysis (IA) will be performed. Based on observed treatment effect size at the IA time point a sample-size re-estimation will be performed according to predefined criteria (see under Statistical Methodology).
Initially the worse eye (defined by visual acuity at Screening) will be treated and will be called the treatment eye hereafter. If both eyes have the same visual acuity, the Investigator should determine the eye with the worse visual function as the treatment eye, according to other measures of ophthalmic function (eg. Full-field Stimulus Testing [FST] or mobility course score). If the visual function is the same per the Investigator*s assessment, then the treatment eye will be determined at the Investigator*s discretion.
After th e first eye has been treated for at least 12 months, treatment of the

contralateral eye and cross-over of the subjects assigned to sham may be initiated in eligible eyes, based on assessment of benefit/risk, and with concurrence of the Medical Monitor.
Frequent study visits and safety monitoring by the investigator will be in place, together with oversight by the Medical Monitor and the Data Monitoring Committee (DMC). The Investigator or the Medical Monitor (in consultation with the DMC) may decide to hold (delay or skip) or discontinue study treatment for an individual subject. Stopping criteria are described in Section 4.2.2.
Subjects who discontinue study treatment will continue to be followed for safety and efficacy.
For subjects completing the study and deriving therapeutic benefit, the Sponsor plans on providing continued access to the study drug until drug registration, as long as the benefit/risk continues to be positive.
Study Plan
The study includes a 28 day screening period.
During the screening period, subjects will be assessed according to the eligibility criteria. Historic genotyping results from a certified genetic laboratory are acceptable with Sponsor approval. For subjects without a historic genotyping result, genotyping and gene sequencing analysis to determine the presence of the CEP290 p.Cys998X mutation will be performed. It is recommended that screening will be conducted in a stepwise manner, so that eligibility is confirmed first with less intensive assessments and more intensive assessments are conducted after eligibility by all other criteria have been confirmed.
Subjects who meet all eligibility criteria will be enrolled into the study and will receive their first study treatment on Day 1. QR-110 will be administered via IVT injection in accordance with the procedures outlined by the American Academy of Ophthalmology and as outlined in the Study Reference Manual. Subjects in the sham-procedure group will undergo a procedure that will closely mimic the active injection, but there will be no penetration of the globe. Administration of study treatment , as well as clinical monitoring of the subject during and right after administration of study treatment, will be performed by an unmasked physician, but clinical assessments (including efficacy and safety assessments) will be performed by a separate, masked physician where possible. After each administration of study treatment, subjects will be monitored for safety, including intraocular pressure (IOP) and signs of inflammation.
Efficacy and safety assessments, including best-corrected visual acuity (BCVA), mobility course score, retinal imaging, functional assessments of vision and patient-reported outcome (PRO) measures, will be performed at selected study visits. All assessments will be performed on both eyes. The primary endpoint will be assessed at 12 months of treatment. Analysis of all other efficacy and safety parameters will also be reported at that time point. All efficacy and safety parameters will continue to be followed during the 24-month treatment period. Collection of serum samples for evaluation of systemic exposure will take place as outlined in the Schedule of Events (SOE) (Appendix 1 of the

protocol).

Intervention

The current study will evaluate 2 dose levels (see also the study schematic in the protocol):
• Loading dose of 160 microgram followed by an 80 microgram maintenance dose at Month 3 and subsequent maintenance doses at a 6 monthly interval
• Loading dose of 80 microgram, followed by a 40 microgram maintenance dose at Month 3 and subsequent maintenance doses at a 6 monthly interval
In addition, treatment of the contralateral eye (to occur in the second year) will involve only a 6-monthly dosing interval.

Study burden and risks

In the first 12 months: a maximum of 3 treatments for the eye with the least eyesight.
After 12 months: if the second eye is eligible for treatment a maximum of 2 treatments in the second eye. If both eyes are treated: a different eye will receive treatment every 3 months. In total there are 25 visits. There will be 18 visits to the research center and 7 telephone calls. The study drug will be administered via intravitreal injection. In addition to the administration of the study drug, various tests are performed. Please see the ICF for a detailed description of the various tests.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Relating to Study Initiation : The subject is eligible for the study and thus eligible to receive QR-110 or fake-procedure in the treatment eye (ie, the first eye to be treated) if all the following inclusion criteria apply at Screening/Day 1:
1. An adult (>= 18 years) willing and able to provide informed consent for participation -OR- a minor (8 to < 18 years) with a parent or legal guardian willing and able to provide written permission for the subject*s participation prior to performing any study related procedures and pediatric subjects able to provide age appropriate assent for study participation.
2. Male or female, >= 8 years of age at screening with a clinical diagnosis of LCA and a molecular diagnosis of homozygosity or compound heterozygosity for the c.2991+1655A>G mutation, based on genotyping analysis at Screening. Historic genotyping report from a certified laboratory is acceptable with Sponsor approval.
3. BCVA better or equal to Logarithm of the Minimum Angle of Resolution (logMAR) +3.0 (Hand Motion), and equal or worse than logMAR + 0.4 (approximate Snellen equivalent 20/50) in the treatment eye, using the best BCVA reading at Screening and based on the Early Treatment Diabetic Retinopathy Study (ETDRS) or the Berkeley rudimentary vision test (BRVT).
4. Detectable outer nuclear layer (ONL) in the area of the macula as determined by the Investigator at Screening.
5. An electroretinogram (ERG) result consistent with LCA, as determined by the Investigator. A historic ERG result may be acceptable for eligibility.
6. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator.
7. Non-pregnant and non-breastfeeding subjects.

Relating to Treatment Initiation Contralateral Eye:
1. BCVA better or equal to Logarithm of the Minimum Angle of Resolution

(logMAR) +3.0 (Hand Motion), and equal or worse than logMAR + 0.4 (approximate Snellen equivalent 20/50) in the contralateral eye, using the best BCVA reading at Month 12 (see Section 8.1) and based on the
Early Treatment Diabetic Retinopathy Study (ETDRS) or the Berkeley Rudimentary Vision Test (BRVT).
2. Detectable outer nuclear layer (ONL) in the area of the macula of the contralateral eye as determined by the Investigator.
3. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging in the contralateral eye, as assessed by the Investigator.
4. Non-pregnant and non-breastfeeding subjects.

Exclusion criteria

Relating to Study Initiation : The subject is ineligible for the study if any of the following criteria apply at Screening/Day 1:
1. Presence of any significant ocular or non-ocular disease/disorder (including medication and laboratory test 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 study, may influence the results of the study, or the subject*s ability to participate in the study.
2. Use of any investigational drug or device within 90 days or 5 half-lives of Day 1, whichever is longer, or plans to participate in another study of a drug or device during the study period.
3. Any prior receipt of genetic or stem-cell therapy for ocular or non-ocular disease.
4. Receipt within 1 month prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an IVT injection or planned intraocular surgery or procedure during the course of the study. Subjects who received an intraocular or periocular surgery between 1 to 3 months prior Screening, may only be considered for inclusion if there are no clinically significant complications of surgery present, and following approval by the Medical Monitor.
5. Known hypersensitivity to antisense oligonucleotides or any constituents of the injection.
6. Pregnant and breastfeeding subjects.

Relating to Treatment Initiation Contralateral Eye:
1. Presence of any significant ocular or non-ocular disease/disorder (including medication and laboratory test 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 study, may influence the results of the study, or the subject's ability to participate in the study.
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 contralateral eye.

2. A planned IVT injection or intraocular or periocular surgery/procedure (including refractive surgery) in the contralateral eye during the course of the study.
3. Plans to participate in another study of a drug or device during the study period.
4. Pregnant and breastfeeding subjects.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-11-2019
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	17-01-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-03-2019

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-08-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	25-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003501-25-NL
ClinicalTrials.gov	NCT03913143
CCMO	NL68298.000.18

Study results

Date completed:	18-10-2022
Results posted:	28-11-2022
Actual enrolment:	4

First publication
25-11-2022