A Double-Masked, Randomized, Controlled, Multiple-Dose Study to Evaluate the Efficacy, Safety and Tolerability of QR-421a in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the USH2A Gene with Advanced Vision Loss

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Primary • To evaluate the efficacy of QR-421aSecondary• To evaluate the safety and tolerability of QR-421a • To evaluate changes in Patient-Reported Outcome (PRO) measures in subjects treated with QR-421a• To evaluate systemic exposure of QR-421a

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

Summary

ID

NL-OMON52147

Source
ToetsingOnline

Brief title
Sirius (PQ-421a-003)

Condition

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

Synonym

progressive pigmentary retinopathy, rod-cone dystrophy, RP

Research involving
Human

Sponsors and support

Primary sponsor: ProQR Therapeutics IV B.V.
Source(s) of monetary or material Support: ProQR Therapeutics

Intervention

Keyword: QR-421a, Retinitis Pigmentosa (RP), USH2A

Outcome measures

Primary outcome

- Change from baseline in best corrected visual acuity (BCVA) (based on the

Early Treatment Diabetic Retinopathy Study (ETDRS) chart) at 18 months of

treatment versus sham-procedur

Secondary outcome

- Change from baseline in the following outcome

measures:

Other measures of BCVA

Spectral domain optical coherence tomography

(SD-OCT)

Low Luminance Visual Acuity (LLVA)

Microperimetry

Static perimetry

Full-field Stimulus Threshold (FST)

- Change from baseline in PRO measures, as assessed

by:

Veteran Administration Low Vision Visual

Functioning Questionnaire (VA LV VFQ-20)

Patient Global Impressions of Severity (PGI-S)

Patient Global Impressions of Change (PGI-C)

- Ocular and non-ocular adverse events (AEs)

- Exposure of QR-421a in serum

Study description

Background summary

The Sponsor is developing an AON, QR-421a, for the treatment of patients with RP caused by mutations in exon 13 of the USH2A gene. RP is a group of inherited eye disorders causing photoreceptor degeneration that leads to progressive vision loss, which ultimately results in complete blindness. Currently there are no approved therapies for the treatment of RP due to mutations in exon 13 of the USH2A gene and a large unmet medical need exists.
The clinical development program started in the first half of 2019 with the first-in-human (FIH) clinical study (PQ-421a-001), a Phase 1b/2, double-masked, sham-controlled, dose-escalation study to evaluate the safety and tolerability of QR-421a. An interim analysis was performed in March 2021. Available safety and efficacy data from study PQ-421a-001 support the therapeutic potential observed in the nonclinical studies.
Study PQ-421a-003 aims to define safety and quantify the treatment effect of QR-421a administered via IVT injection in subjects with RP due to mutations in exon 13 of the USH2A gene with advanced loss of vision, relative to masked, untreated control subjects, at 2 dose regimens of QR-421a.

Study objective

Primary
• To evaluate the efficacy of QR-421a

Secondary
• To evaluate the safety and tolerability of QR-421a
• To evaluate changes in Patient-Reported Outcome (PRO) measures in subjects treated with QR-421a

• To evaluate systemic exposure of QR-421a

Study design

PQ-421a-003 is a double-masked, randomized, controlled, multiple-dose study to evaluate the efficacy, safety and tolerability of QR-421a in subjects with RP due to mutations in exon 13 of the USH2A gene with advanced vision loss. At study start subjects will be randomized to one of the following treatment groups:

1) Group 1: QR-421a 180/60 µg (180 µg loading dose administered on Day 1, 60 µg maintenance dose administered at Month 3 and every 6 months thereafter; n = 27)
2) Group 2: QR-421a 60/60 µg (60 µg loading dose administered on Day 1,60 µg maintenance dose administered at Month 3 and every 6 months thereafter; n = 27)
3) Group 3: Sham-procedure (administered on Day 1, Month 3 and every 6 months thereafter; n = 27)

After the study eye has been treated for at least 18 months, treatment of the fellow eye and cross-over of subjects assigned to sham-procedure may be initiated in eligible eyes (in a masked manner), based on assessment of benefit-risk

The primary endpoint will be assessed at 18 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.

Intervention

The current study will evaluate 2 dose levels. Subjects will receive loading dose administered on Day 1, and maintenance dose administered at Month 3 and every 6 months. The intended route of administration is intravitreal (IVT) injection.

The subject is eligible for the study and thus eligible to receive QR-421a or sham-procedure in the study eye if all the following inclusion criteria apply at Screening/Day 1. The subject is eligible to receive QR-421a in the fellow eye after the study eye has been treated for at least 18 months.

Study burden and risks

Subjects will receive intravitreal injection or Sham injection every 3 months until M15 (4 times). At month 18 all subjects (in all 3 study arms) could receive an intravitreal injection with Q-421a in the fellow eye. If this is

found safe by physician. At Month 21 subjects, previously in the sham arm, can receive intravitreal injection in the study eye. In total subject can receive 6 intravitreal injections, when they are in the active arm and 2 injections when they are in the sham arm.
Subjects will be followed up to Month 24. In total there are 10 visits to the research center, with 12 telephone visits (at Day 2 ad Day 8 after injection) in the period of 24 months.
The study drug will be administered via intravitreal injection. In addition to the administration of the study drug, various assessments are performed.

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)
Elderly (65 years and older)

Inclusion criteria

- An adult (>= 18 years) willing and able to provide informed consent for participation prior to performing any study related procedure. OR A minor (>12<18) 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.
- Clinical presentation consistent with RP with Usher syndrome type 2 or non-syndromic form of RP (NSRP), based on ophthalmic, audiologic, and vestibular examinations.
- A molecular diagnosis of homozygosity or compound heterozygosity for 1 or more pathogenic exon 13 mutations in the USH2A gene, based on genetic analysis at screening.
- Reliable BCVA, perimetry, and other measurements in both eyes.

Exclusion criteria

- Presence of any significant ocular or non-ocular disease/disorder (or medication and/or 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.
- Known hypersensitivity to antisense oligonucleotides or any constituents of the injection.

Study design

Design

Study phase:	3
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):	15-07-2022
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	12-01-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-05-2022
Application type:	First submission
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	EUCTR2021-002729-74-NL
CCMO	NL78776.000.21

Study results

Date completed:	11-08-2022
Results posted:	14-11-2022

First publication
10-11-2022