CLINICAL TRIAL SUMMARY REPORT

PROTOCOL TITLE:	A Double-Masked, Randomized, Controlled, Multiple-Dose Study to Evaluate the Efficacy, Safety and Tolerability of Ultevursen in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the *USH2A* Gene (SIRIUS)
PROTOCOL NUMBER:	PQ-421a-003
STUDY PHASE:	2/3
SPONSOR:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
REPORT RELEASE DATE:	10-Nov-2022
Version:	1.0 FINAL

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.

Study Summary

Name of Sponsor/Company:

ProQR Therapeutics
Zernikedreef 9
2333 CK Leiden
The Netherlands

Name of Investigational Product:

Ultevursen Solution for Intravitreal (IVT) Injection

Name of Active Ingredient:

Ultevursen (QR-421a)

Title of Study:

A Double-Masked, Randomized, Controlled, Multiple-Dose Study to Evaluate the Efficacy, Safety and Tolerability of Ultevursen in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the *USH2A* Gene (SIRIUS)

EudraCT Number: 2021-002729-74

IND Number: 137660

This study is not part of a Paediatric Investigational Plan.

Study Center(s): Approximately 40 worldwide with planned sites in Belgium, Brazil, Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Spain, United Kingdom and the United States.

Twenty-one (21) sites were active at the time of study termination:

Canada: *1 site*
France: *2 sites*
Germany: *1 site*
Netherlands: *3 sites*
Norway: *1 site*
Spain: *1 site*
United Kingdom: *2 sites*
United States: *10 sites*

Study Period (years):	Phase of Development:	Results Analysis Stage:
First subject screened: November 17, 2021 Last subject visit: October 12, 2022	Phase 2/3	Final

More Information:

Substantial Protocol Amendments: Two substantial amendments were produced for the study:
Version 2.0 – which also served as the basis for local country specific protocol amendments in France, Germany, Italy, Norway, and the United States.
Version 3.0 – which was a global protocol amendment that harmonized all country specific protocols into a

single protocol. This amendment included revisions to the inclusion/exclusion criteria surrounding best corrected visual acuity (BCVA) and visual fields.

Global Interruptions or Re-starts: 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.

Objectives:

Primary:

To evaluate the efficacy of ultevursen (using BCVA).

Secondary:

i) To further evaluate the efficacy of ultevursen (using other secondary efficacy measures);

ii) To evaluate the safety and tolerability of ultevursen;

iii) To evaluate changes in Patient-Reported Outcome (PRO) measures in subjects treated with ultevursen; and

iv) To evaluate systemic exposure of ultevursen.

Number of subjects:

Approximately 81 subjects were planned. At the time of study termination, 7 subjects were randomized and dosed at least once in the study eye/treated eye (TE).

Diagnosis and main criteria for inclusion in the study:

Subjects were included if they met the following Inclusion Criteria:

1. An adult (≥ 18 years) willing and able to provide informed consent for participation prior to performing any study related procedures, and suitable verbal, auditory, written and/or tactile sign language communication as to allow informed consent to be obtained, in the opinion of the Investigator.
   OR
   A minor (12 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. The lower age limit for pediatric populations is subject to local regulatory and ethics committee requirements (e.g., 16 to <18 for Norway).
2. An adult willing to comply with the protocol, follow study instructions, attend study visits as required and willing and able to complete all study assessments.
   OR
   A minor 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.
3. Clinical presentation consistent with RP with Usher syndrome type 2 or non-syndromic form of RP (NSRP), based on ophthalmic, audiologic, and vestibular examinations.
4. 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.
5. BCVA between ≥30 and ≤68 letters (approximate Snellen equivalent 20/250 – 20/50) in the TE, using the mean BCVA reading at Screening and based on the Early Treatment Diabetic Retinopathy Study (ETDRS). Subjects with a mean BCVA between >68 and ≤73 letters will be allowed with documented historic evidence of a BCVA equivalent decline of >5 letters in both eyes (i.e., >1 line decline using Snellen or >0.1 LogMAR) anytime within the last 18 months relative to Screening.

6. BCVA between ≥30 and ≤73 letters (approximate Snellen equivalent 20/250 – 20/40) in the contralateral eye (CE), using the mean BCVA reading at Screening and based on the ETDRS.
7. A difference in mean BCVA readings at Screening between the TE and CE of ≤10 letters (based on ETDRS). BCVA differences between eyes that are greater than 10 letters may be allowed however, the Investigator should discuss the case with the Medical Monitor.
8. Stable BCVA in the TE and CE, defined as 2 separate BCVA measurements at Screening that fall within ≤ 5 letters (based on the ETDRS) for each respective eye.
9. A visible ellipsoid zone (EZ) layer on spectral domain optical coherence tomography (SD-OCT) in the TE, as determined by the Investigator.
10. No limitations to SD-OCT image collection that would prevent high quality, reliable images from being obtained in both eyes, as determined by the Investigator.
11. Reliable BCVA, perimetry, and other measurements in both eyes, as described in the Study Reference Manual and Imaging Manual and determined by the Investigator.
12. No visually significant ocular media opacities and adequate pupillary dilation to permit good quality retinal imaging in both eyes, as assessed by the Investigator.

Subjects who failed screening were eligible to be re-screened following discussion with the Sponsor and/or Medical Monitor.

Test product, dosage and mode of administration:

Ultevursen: 180 µg loading dose on Day 1, 60 µg maintenance dose at Month 3 and every 6 months (180/60 µg)

Ultevursen: 60 µg loading dose on Day 1, 60 µg maintenance dose at Month 3 and every 6 months (60/60 µg)

Sham: Sham procedure on Day 1, sham procedure at Month 3 and every 6 months (Sham)

Duration of treatment:

24 months

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

Sham procedure

Background therapy:

None

Criteria for evaluation

Efficacy:

Primary Efficacy Endpoint:

- Mean change from baseline in BCVA (based on the ETDRS chart) at 18 months of treatment versus sham-procedure

Key Secondary Efficacy Endpoint:

- Proportion of subjects who maintain vision defined by BCVA loss less than 15 letters (based on ETDRS)

Secondary Efficacy Endpoints:

- Change from baseline in the following outcome measures:
    - Other analyses of BCVA

  - EZ area and width as imaged by SD-OCT
  - Low Luminance Visual Acuity (LLVA)
  - Microperimetry
  - Full-field Stimulus Threshold (FST)
- Change from baseline in PRO measures, as assessed by:
  - Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ-20)
  - Patient Global Impressions of Severity (PGI-S)
  - Patient Global Impressions of Change (PGI-C)
- Exposure of ultevursen in serum

Safety:

- Ocular and non-ocular adverse events (AEs)

Statistical methods:

In August 2022, ProQR decided to prematurely terminate PQ-421a-003 and, per ProQR's instruction, subjects were unmasked prior to Database Lock (DBL) in October 2022.

In this context, the statistical analysis plan was abbreviated and described the populations for analysis, data handling rules, statistical methods, and formats for data presentation that were required for the close out of the study, after all randomized subjects completed their end of study (EOS) visit, and after DBL.

Summary tabulations and listings were produced for the close out of the study and provide the basis for the appropriate sections of the CTSR.

SUMMARY -

PQ-421a-003 was a double-masked, randomized, controlled, multiple-dose study intended to evaluate the efficacy, safety, and tolerability of ultevursen in subjects with RP due to mutations in exon 13 of the *USH2A* gene. However, PQ-421a-003 was prematurely terminated (August 2022) by the Sponsor following a re-evaluation of the corporate development strategy for ultevursen and similar investigational antisense oligonucleotide (AON) candidates. The study was not terminated for any reason associated with safety.

At the time of study termination, 7 out of the 81 (8.6%) subjects planned were enrolled and randomized. All subjects underwent an EOS visit as part of study close-out. The last subject visit occurred on 18-Oct-2022, with DBL on 25-Oct-2022 for this CTSR.

As the study was prematurely stopped by Sponsor's decision, no formal statistical analyses were produced.

This CTSR includes summary tables on the following:

i) Disposition and baseline characteristics of subjects enrolled

ii) AEs, AEs of special interest (AESIs) and serious AEs (SAEs)

Targeted monitoring and Sponsor review focused on critical safety variables, including AEs, AESIs, clinical laboratory parameters and changes in SD-OCT. The tables and listings were produced based on raw data and source document verified (SDV) data.

SAFETY RESULTS:

Subject Disposition:

The disposition of subjects is outlined in Table 1 below. In total, 33 subjects were screened and 26 subjects (78.8%) were screen-failed. The majority of screen failures were due to subjects failing to meet entry criteria (19 subjects; 57.6%), with the remaining being screen failed as part of study termination procedures

(i.e., reported outcome: Sponsor decision). Seven (7) subjects (21.2%) were randomized, of which 5 subjects were randomized to active treatment (3 to ultevursen 180/60 µg, 2 to ultevursen 60/60 µg), and 2 subjects were randomized to sham procedure. Five (5) subjects received one dose in the TE, and 2 subjects (1 each from 180/60 µg and 60/60 µg treatment arms) received 2 treatment doses in the TE. No subject received a third dose, nor any dose in the CE. All seven (7) subjects were reported as being discontinued due to Sponsor decision.

All randomized subjects returned to the clinic for their EOS visit and safety follow-up approximately 3 months after their last treatment dose. Subjects allocated to sham treatment were permitted to return to the clinic sooner than 3 months for their EOS visit.

Table 1 – Subject Disposition

	All Subjects (N=33)
Screened Subjects	33 (100%)
Screening Failures	26 (78.8%)
Inclusion/Exclusion Criteria	19 (57.6%)
Sponsor decision	7 (21.2%)
Randomized Subjects	7 (21.2%)
Randomized to Treatment Arm: 180/60 µg	3 (9.1%)
Randomized to Treatment Arm: 60/60 µg	2 (6.1%)
Randomized to Treatment Arm: Sham Procedure	2 (6.1%)
Treated Subjects	7 (21.2%)
Received at least one dose in the TE	7 (21.2%)
Received at least two doses in the TE	2 (6.1%)
Received at least one dose in the CE	0
Completed Study	0
Discontinued Study	7 (21.2%)
Reason for Discontinuation	
Sponsor decision	7 (21.2%)

Demographics and Baseline Characteristics:

No significant differences were seen by treatment with respect to average age, age group distribution, gender and ethnicity (see Table 2). All of the seven subjects randomized were adults (i.e., ≥ 18 years of age) at the time of screening. All subjects enrolled were white by reported race, and predominantly of a heterozygous genotype for exon 13 mutations in the *USH2A* gene (6 subjects; 85.7%). Six subjects, 85.7%, were reported as exhibiting a syndromic phenotype (i.e., Usher syndrome). Baseline BCVA (in ETDRS letters) in the TE was similar across all subjects, with a mean BCVA of 55.4 letters. Baseline BCVA in the CE was more variable between treatment groups and better compared to the TE, with a mean BCVA across all subjects of 67.4 letters.

Table 2 – Demographics and Baseline Characteristics

	Sham Procedure (N= 2)	**60/60 µg (N= 2)**	**180/60 µg (N= 3)**	**All Subjects (N= 7)**
Age [years]				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Mean (SD)	56.0 (4.2)	54.0 (1.4)	47.3 (20.5)	51.7 (12.7)
Median	56.0	54.0	47.0	53.0
Min; Max	53; 59	53; 55	27; 68	27; 68
Age Group				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Adult (>= 18 years)	2 (100.0%)	2 (100.0%)	3 (100.0%)	7 (100.0%)
Pediatric (< 18 years)	0	0	0	0

Gender				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Male	1 (50.0%)	0 (0.0%)	2 (66.7%)	3 (42.9%)
Female	1 (50.0%)	2 (100.0%)	1 (33.3%)	4 (57.1%)
Race				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
White	2 (100.0%)	2 (100.0%)	3 (100.0%)	7 (100.0%)
Ethnicity				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	2 (100.0%)	2 (100.0%)	3 (100.0%)	7 (100.0%)
Genotype				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Homozygous	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
Heterozygous	1 (50.0%)	2 (100.0%)	3 (100.0%)	6 (85.7%)
Randomization Factor				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Syndromic	2 (100.0%)	2 (100.0%)	2 (66.7%)	6 (85.7%)
Non-Syndromic	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (14.3%)
Baseline BCVA [letters]				
TE				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Mean (SD)	59.0 (11.3)	53.0 (14.1)	54.7 (11.1)	55.4 (10.1)
Median	59.0	53.0	56.0	56.0
Min; Max	51; 67	43; 63	43; 65	43; 67
CE				
n (missing)	2 (0)	2 (0)	3 (0)	7 (0)
Mean (SD)	68.5 (2.1)	61.0 (5.7)	71.0 (11.3)	67.4 (8.3)
Median	68.5	61.0	77.0	67.0
Min; Max	67; 70	57; 65	58; 78	57; 78

Safety Summary:

No treatment emergent ocular AESIs and SAEs were reported. No deaths occurred during the study. No subjects discontinued from the study because of a treatment emergent AE (TEAE).

In the TE, 3 out of 7 subjects randomized (42.9%) experienced 9 ocular TEAEs (Table 3). No subjects randomized to sham procedure experienced a TEAE. No discernable trends in ocular TEAEs were seen across the different active treatment arms given the low number of subjects enrolled. All TEAEs were mild or moderate in nature, with no severe TEAEs reported. The majority of these were deemed related to study treatment administration. The most commonly reported TEAE in more than 1 subject by system organ class (SOC) was eye disorders (3 subjects overall; 42.9%), and by preferred term (PT), conjunctival haemorrhage (2 subjects overall, 28.6%) and eye pain (2 subjects overall, 28.6%), occurring in ultevursen treated subjects only (Table 4).

In the CE, 1 out of the 7 subjects (14.3%) experienced 1 ocular TEAE of photopsia (see Table 3). This event was deemed not related to study drug and not related to study treatment administration. By SOC and PT, no TEAE was reported in more than 1 subject.

Table 3 – TEAE Summary by Eye

	Sham Procedure (N= 2)	**60/60 ug (N= 2)**	**180/60 µg (N= 3)**	**All Subjects (N= 7)**
TE				
Total number of TEAEs	0	4	5	9
Number of Subjects with at Least one TEAE	0	1 (50%)	2 (66.7%)	3 (42.9%)
Number of Subjects with at Least one Serious TEAE	0	0	0	0
Number of Subjects with at Least one TEAE of Special Interest	0	0	0	0

Number of Subjects with TEAEs by Worst Severity				
Mild	0	1 (50%)	2 (66.7%)	3 (42.9%)
Moderate	0	0	1 (33.3%)	1 (14.3%)
Severe	0	0	0	0
Number of Subjects with TEAEs Related vs Not Related to Ultevursen				
Related	0	0	0	0
Not Related	0	1 (50%)	2 (66.7%)	3 (42.9%)
Number of Subjects with TEAEs Related vs Not Related to Procedure				
Related	0	1 (50%)	1 (33.3%)	2 (28.6%)
Not Related	0	0	1 (33.3%)	1 (14.3%)
Number of Subjects with TEAEs leading to Treatment Discontinuation	0	0	0	0
Number of Subjects with TEAEs resulting in Death	0	0	0	0
CE				
Total number of TEAEs	0	0	1	1
Number of Subjects with at Least one TEAE	0	0	1 (33.3%)	1 (14.3%)
Number of Subjects with at Least one Serious TEAE	0	0	0	0
Number of Subjects with at Least one TEAE of Special Interest	0	0	0	0
Number of Subjects with TEAEs by Worst Severity				
Mild	0	0	0	0
Moderate	0	0	1 (33.3%)	1 (14.3%)
Severe	0	0	0	0
Number of Subjects with TEAEs Related vs Not Related to Ultevursen				
Related	0	0	0	0
Not Related	0	0	1 (33.3%)	1 (14.3%)
Number of Subjects with TEAEs Related vs Not Related to Procedure				
Related	0	0	0	0
Not Related	0	0	1 (33.3%)	1 (14.3%)
Number of Subjects with TEAEs leading to Treatment Discontinuation	0	0	0	0
Number of Subjects with TEAEs resulting in Death	0	0	0	0

Table 4 – Ocular TEAEs for the TE by SOC and PT

	Sham Procedure (N= 2)	60/60 µg (N= 2)	180/60 µg (N= 3)	All Subjects (N= 7)
Subjects with any TEAEs	0	1 (50%)	2 (66.7%)	3 (42.9%)
Eye disorders	0	1 (50%)	2 (66.7%)	3 (42.9%)
Conjunctival haemorrhage	0	1 (50%)	1 (33.3%)	2 (28.6%)
Eye pain	0	1 (50%)	1 (33.3%)	2 (28.6%)
Visual impairment	0	0	1 (33.3%)	1 (14.3%)
Vision blurred	0	0	1 (33.3%)	1 (14.3%)
Photopsia	0	0	1 (33.3%)	1 (14.3%)

Overall, 3 subjects (1 in each treatment group) experienced 9 non-ocular TEAEs in the study (Table 5). All non-ocular TEAEs were deemed not related to study treatment and not related to study treatment administration. By SOC and PT, no non-ocular TEAE occurred in more than one subject in any treatment group.

Table 5 – Non-ocular TEAEs by SOC and PT

	Sham Procedure (N= 2)	60/60 µg (N= 2)	180/60 µg (N= 3)	All Subjects (N= 7)
Subjects with any TEAEs	1 (50%)	1 (50%)	1 (33.3%)	3 (42.9%)
Number of TEAEs	2	5	2	9

Infections and infestations	1 (50%)	1 (50%)	0	2 (28.6%)
Urinary tract infection	1 (50%)	0	0	1 (14.3%)
Tonsillitis	0	1 (50%)	0	1 (14.3%)
Sinusitis	0	1 (50%)	0	1 (14.3%)
Metabolism and nutrition disorders	1 (50%)	0	0	1 (14.3%)
Iron deficiency	1 (50%)	0	0	1 (14.3%)
Injury, poisoning and procedural complications	0	1 (50%)	0	1 (14.3%)
Tooth injury	0	1 (50%)	0	1 (14.3%)
Ear and labyrinth disorders	0	1 (50%)	0	1 (14.3%)
Vertigo labyrinthine	0	1 (50%)	0	1 (14.3%)
Musculoskeletal and connective tissue disorders	0	1 (50%)	0	1 (14.3%)
Arthralgia	0	1 (50%)	0	1 (14.3%)
Gastrointestinal disorders	0	0	1 (33.3%)	1 (14.3%)
Inguinal hernia	0	0	1 (33.3%)	1 (14.3%)
Congenital, familial and genetic disorders	0	0	1 (33.3%)	1 (14.3%)
Hydrocele	0	0	1 (33.3%)	1 (14.3%)

EFFICACY RESULTS:

No efficacy data were analyzed/summarized.

CONCLUSION

PQ-421a-003 was terminated prematurely based on Sponsor decision. The decision to terminate was not related to safety or risks associated with ultevursen. At study termination, 7 subjects were randomized, of which 5 were allocated to active treatment (3 to ultevursen 180/60 μg, 2 to ultevursen 60/60 μg) and 2 to sham treatment.

In the five subjects randomized to active treatment, ultevursen was well-tolerated with no significant differences seen in the safety profile relative to data obtained in other ultevursen trials. No subject discontinued treatment due to TEAEs.

No deaths, no AESIs and no SAEs were reported.

The Sponsor considers the established positive benefit-risk ratio for ultevursen unchanged by these data.

Date of Report: 10-Nov-2022 FINAL