Cover page

Protocol PQ-421a-004 (CELESTE)

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 EARLY TO MODERATE VISION LOSS

NCT number: NCT05176717

Protocol PQ-421a-004 (CELESTE)

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 EARLY TO MODERATE VISION LOSS

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Name of Test Drug:	Ultevursen (QR-421a)
Phase:	2/3
Methodology:	Double-masked, Randomized, Controlled, Multiple-dose
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
Sponsor Representative:	
Document Date:	09-Sep-2022
Document Version:	1.0

SIGNATURE PAGE

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Author:	
	Signature:_____ _ Date:_____ _

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this prematurely terminated study.

I have discussed any questions I have regarding the contents of this document with the statistical author.

Sponsor Signatory:

ProQR Therapeutics
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Signature:_____
_
Date:_____
_

MODIFICATION HISTORY

Current Version	Date	Amended by	Summary of Changes from previous version	Reason
1.0	09-Sep-2022	N/A	Original document	N/A

Table of Contents

ABBREVIATIONS

Abbreviation	Definition
AD	Analysis Description
AE	Adverse Events
AESI	Adverse Event of Special Interest
BCVA	Best Corrected Visual Acuity
CE	Contralateral Eye
CSR	Clinical Study Report
ETDRS	Early Treatment Diabetic Retinopathy Study
FST	Full-field Stimulus Testing
ICF	Informed Consent Form
ICH	International Council on Harmonization
IRT	Interactive Response Technology
IVT	Intravitreal
LLVA	Low Luminance Visual Acuity
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
PT	Preferred Term
RP	Retinitis Pigmentosa
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
TE	Treated Eye
TEAE	Treatment Emergent Adverse Event
TLF	Table Listing Figure
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Study PQ-421a-004 (Celeste) aimed to define safety and quantify the treatment effect of ultevursen administered via intravitreal (IVT) injection in subjects with RP due to mutations in exon 13 of the USH2A gene with early to moderate loss of vision, relative to masked, untreated control subjects, at 2 dose regimens of ultevursen.

1.2. Study Termination

In this context, the Analysis Description (AD) 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.

The summary tabulations and listings that will be produced for the close out of the study, will provide the basis for the appropriate sections of the abbreviated clinical study report (CSR) or equivalent document.

2. STUDY DESIGN

2.1. Synopsis of Study Design

PQ-421a-004 is a double-masked, randomized, controlled, multiple-dose study to evaluate the efficacy, safety, and tolerability of ultevursen in subjects with RP due to mutations in exon 13 of the USH2A gene with early to moderate vision loss.

At study start subjects has been randomized to one of the following treatment groups:

- Group 1: Ultevursen 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 = 40)

- Group 2: Ultevursen 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 = 40)

- Group 3: Sham-procedure (administered on Day 1, Month 3 and every 6 months thereafter; n = 40)

Please refer to Section 4.2 of the study protocol for details regarding the study design.

2.2. Randomization Methodology

The randomization procedure used to assign study treatment to eligible subjects/eye was through a centralized Interactive Response Technology (IRT), utilizing the randomization schedule generated by the designated unmasked statistician.

Two periods of randomization were planned:

Subjects who satisfy all eligibility criteria at Day 1 were randomized in a 1:1:1 ratio to one of the following groups:

- Ultevursen 180/60 µg
- Ultevursen 60/60 µg
- Sham-procedure

The randomization in both periods has been stratified at Day 1 on one single factor, collected during the Day 1 visit: Syndromic subjects versus Non-Syndromic subjects.

2.3. Study Procedures

Please refer to Section 8.0 of the study protocol for details regarding the study procedures.

2.4. Unmasking

3. POPULATIONS DEFINITIONS

The following Analysis sets will be evaluated and used for presentation and analysis of the data:

- **All Screened Subjects:** Includes all subjects who signed the informed consent form.

- **Safety Population:** All screened subjects who were randomized and received at least one dose of study treatment.

The disposition data will be presented for all screened subjects while all other data will be presented only for subjects in the Safety Population.

4. STATISTICAL METHODS

4.1. Computing Environment

All information and analyses in the tables and listings provided will be performed using SAS statistical software Version 9.4 or later, unless otherwise noted. The Medical History (MH) and Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. The Prior and Concomitant Medications will be coded using World Health Organization (WHO) Drug version Global B3 September 2021.

4.2. Definition of Baseline

Baseline is defined as the data most recently collected prior to the administration of study treatment except for Best Corrected Visual Acuity (BCVA) letter score.

Best corrected visual acuity assessment is conducted in duplicate. For the BCVA letter score (derived from the Early Treatment Diabetic Retinopathy Study [ETDRS]), baseline for the TE and CE is defined as the value which corresponds to the most recent and best visual acuity assessed prior to the first dose of the study treatment or sham. The first rule is to search for the most recent duplicate (i.e., 2 tests on 1 day) prior to dosing. The second rule is that, if there are no such duplicates (i.e., 2 tests on 1 day), the most recent 2 results will be used for baseline evaluation. After determining the most recent 2 results, the largest (best) BCVA ETDRS letter score prior to the administration of study treatment is selected as baseline. If only one assessment is available prior to the first administration of study treatment, that assessment will be used as the baseline value.

4.3. Data Handling

4.3.1. General

Unless otherwise noted, the data reported in the listings will be as reported on the electronic case report form.

4.4. General Statistical Methods

All output will be incorporated into Rich Text Format (RTF) files and bookmarked PDFs, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate disposition and demographic characteristics.

For measurements of continuous variables, summary statistics of absolute values will be reported and will include n, mean, standard deviation, median, and minimum and maximum values. The number of missing values will be displayed in parenthesis next to 'n'. Mean, standard deviation, median, will be presented with one more decimal place compared to the raw data, and minimum and maximum will be presented with the same number of decimal places as the raw data.

For categorical variables, summary tabulations of the number and percentage within each category of the parameter will be presented (as well as the number for missing data). Denominator for percentages is column N. Percentages will be rounded to one decimal place. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%.

Where appropriate, data will be listed by eye (i.e., TE, CE).

In summary tables the study treatments will be presented in the following order: 'Sham-procedure', Ultevursen 60/60 µg', 'Ultevursen 180/60 µg', and if appropriate, 'All Subjects'.

4.5. Study Population

4.5.1. Subject Disposition

Subject disposition, including the number of screened subjects, the number of subjects failed screening, the number of randomized subjects, the number of subjects who received study treatment in the TE, the number of subjects who received study treatment in the CE, who completed the study and the number of subjects who discontinued from the study, along with the reasons will be summarized by treatment group.

A listing of subject disposition will be generated, including the reason for premature study or treatment discontinuation, if applicable.

A listing of screen failure data will also be provided.

4.5.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age as collected, age category (Adult >=18 years, Children <18 years), gender, race, ethnicity, body weight (kg), height (cm), genotype (homozygous, heterozygous), randomization factor (syndromic, non-syndromic) and baseline BCVA (ETDRS letter score for both TE and CE), will be summarized for the Safety Population by treatment group using descriptive statistics.

4.6. Safety – Adverse events

A treatment-emergent AE (TEAE) is defined as an event that was not present prior to administration of the dose of study drug (ultevursen or sham-procedure) and present after the dose or if it represents the exacerbation of an event that was present prior to the dose.

Adverse events will be summarized by treatment group separately as follows:

- For non-ocular AE:
  - by subject, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (System Organ Class [SOC] or Preferred Term [PT])
  - and during the overall study period (i.e., up to the last visit for the last subject).
  - Time to onset will be calculated in hours, relative to the last dose received, irrespective of which eye received the last dose (i.e., TE or CE).
- For ocular AE:
  - by eye frequencies, separately for the TE and the CE, therefore, in any tabulation, an eye contributes only once to the count for a given AE (by SOC or PT). AEs that are reported in both eyes (i.e., OU) will be reported individual by eye in the tabular summaries.
  - and during the overall study period (i.e., up to the last visit for the last subject).
  - Time to onset will be calculated in hours, relative to the last dose received in the eye experiencing the ocular AE.

Unless otherwise stated, any summary of any type of TEAEs which includes the SOC and PT of the events will order the SOC and the PTs within the SOC by descending incidence of PT.

The following summary tables will be produced separately according to the type of AEs (ocular/non-ocular where applicable) as defined above:

- Overview of Ocular Adverse Events for Treatment Eye during the overall study period (Safety Population)
- Overview of Ocular Adverse Events for Contralateral Eye during the overall study period (Safety Population)
- Overview of Non-Ocular Adverse Events during the overall study period (Safety Population)
- Summary of Ocular Treatment-Emergent Adverse Events for Treatment Eye during the overall study period by MedDRA System Organ Class and Preferred Term (Safety Population)
- Summary of Ocular Treatment-Emergent Adverse Events for Contralateral Eye during the overall study period by MedDRA System Organ Class and Preferred Term (Safety Population).
- SAEs
- AESIs

4.6.1. Partial and Missing Date/Time for Adverse Events

Imputation of missing/partial AE date/time will be done only to identify TEAEs.

<u>AE onset dates</u>

- Partially missing onset date/time will be imputed as follows:
    - When only Day is missing:
        - If Month & Year of the onset date are the same as Month & Year of the first administration date, the imputed onset date will be imputed as the minimum of the first administration date/time and the AE resolution date (imputed if needed).
        - Otherwise, the missing day will be replaced by “1.”

- When Day & Month are missing:
  - If Year of the onset date is the same as Year of the first administration date, the imputed onset date will be imputed as the minimum of the first administration date/time and the AE end date (imputed if needed).
  - Otherwise, the missing Day & Month will be replaced by "01 JAN."
- If a partial AE start date is consistent with the actual start date being on Day 1, and either the AE end date information is completely missing, or the complete or imputed AE end date/time information indicates that the AE did not end before Day 1, the imputed AE start date will be Day 1 in the following scenarios:
  - The AE start time is missing (the AE will be flagged as treatment-emergent following the first dose of study treatment)
  - The AE start time is after the date/time of first dosing of study treatment on Day 1 (the AE will be flagged as treatment-emergent following the first dose of study treatment)
  - The AE start time is before the time of first dosing of study treatment on Day 1, and imputing the AE start date as Day 2 instead of Day 1 would be inconsistent with the partially recorded AE start date (e.g., the calendar month for Day 2 is not the same as for Day 1), or with the complete or imputed AE end date/time (in this case, the AE will not be flagged as treatment-emergent following the first dose of study treatment).
    - Missing start time will be imputed with the time of administration if the day of AE start date and administration are identical, or with 00:00 otherwise.

Completely missing onset dates for AEs will be imputed by the first administration date and the AE will be considered as treatment-emergent, unless the end date/time of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the first administration date. If the end date/time is before the first administration date, the AE will not be considered as treatment-emergent

<u>AE end dates</u>

- If Day only is missing, incomplete end dates will be replaced by the last day of the month if it is not resulting in a date later than the date of the subject's last visit. In the latter case, the date of the subject's last visit will be used to impute the incomplete end date.

- If Day & Month are missing, Day & Month will be replaced by 31DEC if it is not resulting in a date later than the date of the subject's last visit. In the latter case, the date of the subject's last visit will be used to impute the incomplete end date.
- If the AE end date is completely missing, the AE will be assumed to be ongoing on the date of the subject's last visit and the incomplete end date will not be imputed.

4.7. Other Data Listings to be Generated

The following by-subject data listings for the Safety Population will be provided:

- Subject Disposition
- Screen Failures (All Screened Subjects)
- Demographic and Baseline Characteristics (Safety Population)
- Non-Ocular Medical History (Safety Population)
- Ocular Medical History (Safety Population)
- Study Drug Administration of the TE (Safety Population)
- Study Drug Administration of the CE (Safety Population)
- BCVA Based on ETDRS (Safety Population)
- Low Luminance Visual Acuity (LLVA) (Safety Population)
- Full-field Stimulus Testing (FST) (Safety Population)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (Safety Population)
- Static perimetry (Safety population)
- Patient Global Impressions of Severity (PGI-S) and Patient Global Impressions of Change (PGI-C) (Safety Population)
- Michigan Retinal Disease Questionnaire (Safety Population)
- Ophthalmic exam (Safety Population)
- Non-Ocular Adverse Events (Safety Population)
- Ocular Adverse Events (Safety Population)
- Prior and/or Concomitant Medications (Safety Population)

- Laboratory results: Hematology, Coagulation, Chemistry and Urinalysis (Safety Population)

5. CHANGES TO PLANNED ANALYSES

As the study is prematurely stopped by Sponsor's decision, no formal statistical analysis will be produced. Only disposition, demographic and baseline characteristics, and overview of AEs will be summarized in tables. By-subjects data listings will be produced based on raw data.

6. REFERENCES

1. International Council on Harmonization, Statistical Principles for Clinical Trials (ICH E9)

7. APPENDICES

The shells of planned outputs are provided in a separate document (PQ-421a-004_List of Planned Outputs_V1.0).