STATISTICAL ANALYSIS PLAN

LT4090-201

A phase II, multicenter, randomized, investigator-masked, 3-parallel groups study to evaluate efficacy and safety of T4090 ophthalmic solution (preservative-free Kinezodianone R HCl 0.2% or 0.3%) versus Rhopressa® ophthalmic solution (preserved netarsudil 0.02%) in patients with open-angle glaucoma or ocular hypertension

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VERSION NUMBER AND DATE: V2.0, 06JAN2025

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 06JAN2025) for Protocol LT4090-201.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
[redacted]	[redacted]
CEC	Corneal Endothelial Cells
[redacted]	[redacted]
CI	Confident Interval
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	Electronic Case Report Form
[redacted]	[redacted]
ICH	International Council for Harmonization
[redacted]	[redacted]
IMP	Investigational Medicinal Product
IOP	Intra-Ocular Pressure
IRT	Interactive Response Technology
ITT	Intent-To-Treat

Abbreviation	**Term**
LS	Least Squares
[redacted]	[redacted]
[redacted]	[redacted]
MDC	Multiple-Dose Container
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
[redacted]	[redacted]
MMRM	Mixed Model for Repeated Measures
[redacted]	[redacted]
NA	Not Applicable
[redacted]	[redacted]
OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
PD	Protocol Deviation
PF	Preservative-Free
[redacted]	[redacted]
[redacted]	[redacted]
PP	Per-Protocol
PT	Preferred Term
REML	Restricted Maximum Likelihood

Abbreviation	**Term**
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Single-Dose Container
SE	Standard Error
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
UD	Unit Dose
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol LT4090-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on Protocol version 2.0 dated 17 April 2024, Protocol Clarification Letter #1 dated 10 June 2024, Protocol Clarification Letter #2 dated 10 July 2024, and electronic Case Report Form (eCRF) version 3.0 dated 27 September 2024.

[redacted]

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objective

The primary objective of the study is to compare the ocular hypotensive efficacy of two concentrations of T4090 (Kinezodianone R HCl 0.2 % and 0.3 %) ophthalmic solution with Rhopressa® ophthalmic solution.

[redacted]

2.3. Estimands

The primary, and secondary estimands to support regulatory decisions are described in the following table:

Table A Objectives and Estimands

Primary Efficacy:

Objective	Estimands	Attributes					
		Treatment	Population	Variable/ Endpoint	[redacted]	[redacted]	Population-Level Summary Measure
To compare the ocular hypotensive efficacy of two concentrations of T4090 (Kinezodianone R HCl 0.2 % and 0.3 %) ophthalmic solution with Rhopressa® ophthalmic solution, and to compare T4090 0.2% with T4090 0.3%	Primary Estimand	T4090 0.2 % or T4090 0.3% or Rhopressa® (administered once daily in each eye)	Patients in whom both eyes were diagnosed with ocular hypertension (OHT) or open-angle glaucoma (OAG), and further defined through the inclusion and exclusion criteria	Change from baseline in the mean diurnal intra-ocular pressure (IOP) at Week 7 in the study eye*	[redacted]	[redacted]	Least squares (LS) means of change from baseline in mean diurnal IOP at Week 7 based on a mixed model with repeated measures (MMRM), with test of treatments effect based on differences of LS means.

3. STUDY DESIGN

3.1. General Description

This is a phase II, multicenter, randomized, investigator-masked, 3-parallel groups, 7-week treatment duration in patients with OAG or OHT. Approximately 126 eligible patients (naïve or using ocular hypotensive medication) were planned to be randomized on a 1:1:1 basis to T4090 (PF Kinezodianone R HCl 0.2% or 0.3%) or Rhopressa®.

The randomization lists are generated using a validated system, which involves a pseudo-random number generator so that the resulting sequence of treatments will be both reproducible and non-predictable. Access to the codes will be controlled and documented.

Randomized patients will attend 3 visits (Visit #3 to #5) at the investigator center during the study treatment period:

- Visit #1: Screening visit,
- Visit #1.1: Optional visit planned according to the investigator´s judgement,
- Visit #1.2: Visit in case of extension of the washout period,
- Visit #2 – Day 1 (D1): Randomization visit,
- Visit #3 – Week 2 (W2) - Day 15 (±2 days),
- Visit #4 – Week 4 (W4) - Day 29 (±3 days),
- Visit #5 – Week 7 (W7) - Day 50 (±3 days): End of treatment visit.

At the Randomization visit (D1; Visit #2), patients will be randomly assigned, after stratification according to their baseline IOP at 8:00 AM [redacted] to one of the following 3 treatment arms:

Test product:

- T4090 (PF Kinezodianone R HCl 0.2%) ophthalmic solution, in single-dose container (SDC),
- T4090 (PF Kinezodianone R HCl 0.3%) ophthalmic solution, in SDC.

Reference product:

- Rhopressa® (preserved netarsudil 0.02%) ophthalmic solution, in multiple-dose container (MDC).

The patient will administer the assigned treatment (T4090 0.2% or T4090 0.3% or Rhopressa®) once daily at 8:00 PM (±1 hour) in the conjunctival cul-de-sac of each eye from Day 1 to the day before the End of treatment visit (Week 7; Visit #5).

The maximum study duration will be 12 weeks: 5-week washout period (including optional 1-week washout extension) (See Section 3.1.1 of the Protocol), and 7-week treatment period. A minimum of 4 visits and a maximum of 7 visits are planned. The number of visits will depend on the patient's screening status (naïve patient or patient using ocular hypotensive medication).

Figure A Overall design of the study (pre-treated patient)

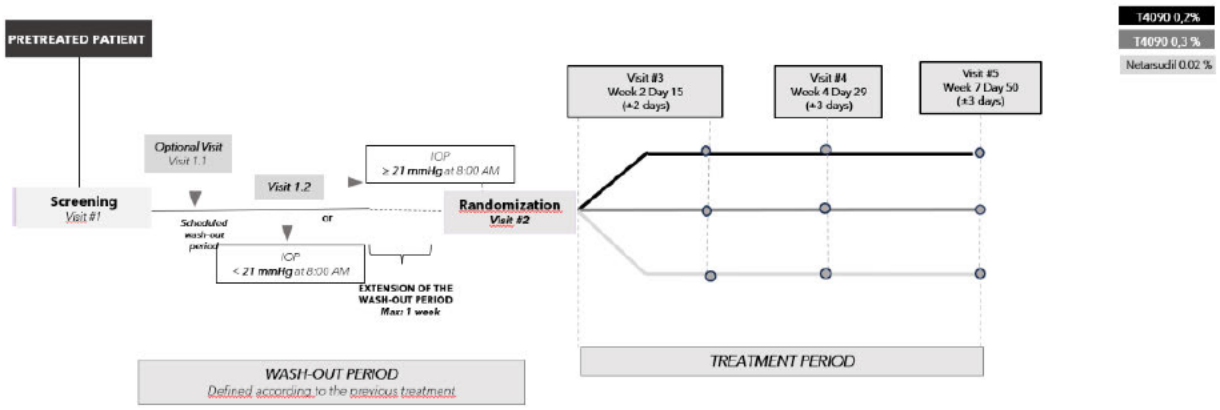
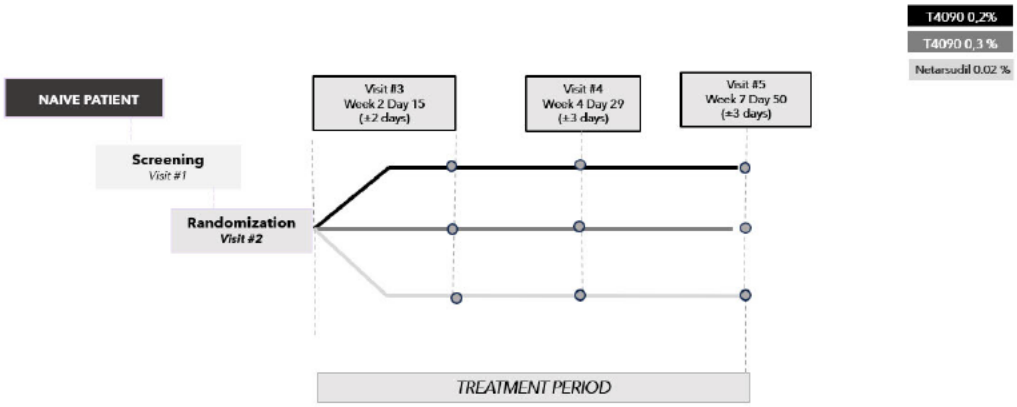


Figure B Overall design of the study (naïve patient)



3.2. Sample Size

This is a Phase II pilot study, and the analysis is to be considered as exploratory. Therefore, no formal sample size calculation is performed. It is planned to randomize 126 patients with a randomization scheme 1:1:1 with a stratification by baseline IOP at 8:00 AM in class [redacted]

3.3. Schedule of Events

Schedule of events can be found in Section 6.1 of the Protocol.

3.4. Changes to Analysis from Protocol

- [redacted]
- In the protocol Section 7.1 it is stated: "When applicable, 95% confidence interval (CI) of the mean will be provided for continuous variables and 95% CI of the proportion will be displayed for each modality of categorical variables.". This has been updated in Section 8 of this SAP to exclude "95% CI of the proportion will be displayed for each modality of categorical variables", as CI for categorical variables was not deemed necessary.
- [redacted]
- [redacted]

- [redacted]
- In the protocol Section 7.4.1.1, it is stated that the MMRM model "will include treatment, visit (W2, W4 and W7), baseline mean diurnal IOP, baseline IOP at 8:00 AM in class [redacted] treatment by visit interaction, and baseline mean diurnal IOP by visit interaction as fixed factors and patient ID as a random factor". This has been updated in Section 16.1.3 of this SAP to exclude "baseline IOP at 8:00 AM in class [redacted]" due to potential collinearity. In addition, "and patient ID as a random factor" is excluded in the SAP for clarification purposes, as no separate random statement with patient ID is required in the analysis model. [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4. PLANNED ANALYSES

The following analysis will be performed for this study:

- Final analysis

4.1. Data Monitoring Committee (DMC)

There will be no DMC for this study.

4.2. Interim Analysis

There will be no interim analysis for this study.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by [redacted] following Customer Authorization of this SAP, Database Lock, Customer Authorization of Analysis Sets and Unblinding of Treatment.

5. ANALYSIS SETS

The following analysis sets will be considered. [redacted] Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. All Patients Screened Set [SCR]

The all patients screened (SCR) set will contain all patients who provide informed consent for this study.

5.2. Intent-to-Treat Set [ITT]

The intent-to-treat (ITT) set will contain all patients who were randomized. For analyses and displays based on ITT, patients will be classified according to randomized treatment.

5.3. Full Analysis Set [FAS]

The full analysis set (FAS) will contain all patients in the ITT set who received at least one dose of study treatment. For analyses and displays based on FAS, patients will be classified according to randomized treatment.

The FAS will be the primary population for efficacy analysis.

5.4. Per-Protocol Analysis Set [PP]

The per-protocol (PP) analysis set will contain all patients in the FAS who did not experience any reason for exclusion [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

For analyses and displays based on PP set, patients will be classified according to treatment received.

The PP set will be considered as secondary population [redacted]

5.5. Safety Analysis Set [SAF]

The safety (SAF) analysis set will contain all patients who received at least one dose of study treatment. For analyses and displays based on SAF, patients will be classified according to treatment received.

[redacted]

The safety set will be the primary population for safety analysis.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Reference start date is defined as the day of the first dose of study treatment (Day 1 is the day of the first dose of study treatment).

Study day will be calculated from the reference start date and will be used to show start/end day of assessments and events. It will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:
  Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date, study day, and any corresponding durations will appear partial or missing in the listings.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on date of first dose of study treatment, excluding measurements reported during washout period (i.e., from Screening visit through to the day prior to Randomization visit) for pre-treated patients. No imputation will be performed if baseline measurement is missing.

[redacted]

The mean diurnal IOP at Randomization visit will be the baseline for analysis of the mean diurnal IOP. For IOP, the value recorded at 8:00 AM at Randomization visit, respectively at 10:00 AM and at 4:00 PM, will be the baseline for analysis of IOP at 8:00 AM, respectively at 10:00 AM and at 4:00 PM.

[redacted]

[redacted]

6.7. Statistical Tests

The default significant level will be 5% and no adjustment of the type I error rate will be [redacted] Confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

For continuous quantitative parameters, treatment groups will be compared using an MMRM. [redacted]

[redacted]

6.8. Common Calculations

For quantitative measurements, absolute and percent change from baseline will be calculated as:

- Absolute change = Test Value at Visit X – Baseline Value,
- Percent change = (Absolute change / Baseline Value) *100.

[redacted]

[redacted]

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following covariates and factors will be used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Baseline IOP – continuous value,
- Treatment (T4090 0.2%, T4090 0.3%, and Rhopressa®),
- Visit (W2, W4, and W7).

[redacted]

[redacted]

7.3. Missing Data

Missing safety data will not be imputed unless described in the specific analysis section. Missing efficacy data will be handled as described in Section 16 of this SAP.

[redacted]

7.5. Multiple Comparisons/ Multiplicity

Analyses will be performed to compare efficacy endpoints between treatment groups (each T4090 concentration versus Rhopressa® and both T4090 concentrations comparison). All analyses are considered as supportive and any

statistical test comparing treatment groups will be made without adjustment for multiplicity.

[redacted]

8. OUTPUT PRESENTATIONS

Variables recorded for each eye will be described separately for the study eye and for the contralateral eye (if applicable).

Continuous variables will be summarized using descriptive statistics: number of non-missing observations (n), mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum (Min) and maximum (Max). When applicable, 95% confidence interval (CI) of the mean will be provided for continuous variables.

Categorical variables will be summarized using frequency distribution: number of non-missing observations (n), count and percentages (%, based on n unless otherwise indicated in the table template) of each modality.

[redacted]

9. DISPOSITION AND WITHDRAWALS

All patients who provided informed consent will be accounted for in this study.

9.1. Disposition

Patient disposition and withdrawals, including number of patients screened/randomized and reasons of discontinued treatment or study, will be presented for the SCR set.

A listing of all disposition data, including early treatment and study discontinued patients and reasons of withdrawals, will be provided for the SCR set.

Details of any inclusion/exclusion criteria which were not met [redacted] will be listed for the SCR set, including the protocol version(s) under which each patient was consented.

The number (%) of patients included in each analysis set (ITT, FAS, PP and SAF) and reason for exclusion from each analysis set will be presented by treatment group and overall, for the ITT set.

A listing of patients with analysis sets inclusion and the reason for exclusion from ITT, FAS, PP and SAF, and including treatment group (planned group and actual group), will be produced for the SCR set.

9.2. Protocol Deviations

[redacted]

The number (%) of patients with deviations by PD category [redacted] will be presented in a summary table by treatment group and overall for the ITT set, including:

- Patients with at least one PD
- Patients with at least one critical PD
- Patients with at least one major PD
- Patients with at least one minor PD
- Patients with at least one important PD

A listing of all PDs will be provided for the ITT set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented by treatment group and overall for the FAS,

and for PP and SAF sets [redacted]. No statistical testing will be carried out for demographic or other baseline characteristics. The following demographic and other baseline characteristics will be reported for this study:

Demographics:

- Age (years) – as continuous, and in two classes: Adult (18-64), Older Adult (65+),
- Sex (Male, Female),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown),
- Iris color (Blue, Gray, Green, Brown, Hazel, Other),
- Baseline IOP at 8:00 am in the study eye in classes [redacted]

A listing of the above demographic data will be provided for the FAS. This listing will also include:

- Childbearing potential (Yes, No) and birth control method – for female only,
- Study Eye (Right, Left), as determined in Section 6.6.

[redacted]

- [redacted]

Baseline values of the efficacy and safety endpoints will be provided in statistical tables with assessments at W2, W4, and W7.

11. HISTORY OF GLAUCOMA OR OHT

History of glaucoma or OHT [redacted] will be presented for the FAS, and for PP and SAF sets [redacted]. The following variables will be summarized by treatment group and overall:

- Treatment status (Naive patient, Previously treated patient),
- Type of previous antiglaucoma treatment (if applicable) [redacted]
- For each eye:

- Diagnosis (Primary OAG, OHT),
- Time since diagnosis (months) [redacted]
- Surgical history related to glaucoma or [redacted] Events will be coded using the Medicinal Dictionary for Regulatory Activities (MedDRA) Version 27.0 or higher. [redacted]

Listings of history of glaucoma or OHT and related surgical history will be provided for the FAS.

12. MEDICAL AND SURGICAL HISTORY AND CURRENT CONDITIONS

Medical and surgical history and current conditions data will be summarized overall and by treatment group, for the FAS, and for PP and SAF sets [redacted]

- Medical history and current conditions data (other than the study disease) are captured [redacted]
- Surgical history data (not related to the study disease) are captured [redacted]

Medical and surgical history and current conditions will be coded using MedDRA Version 27.0 or higher.

The following medical and surgical history and current conditions summaries, presented by SOC and PT, will be reported for this study:

- Ocular medical and surgical history and current conditions [redacted]
- Systemic medical and surgical history and current conditions [redacted]

A listing for medical and surgical history and current conditions will be presented for the FAS.

A separate listing of related procedures/surgeries during the study [redacted] will be provided for the FAS.

13. MEDICATIONS

Medications reported [redacted] will be summarized overall and by treatment group, for the FAS, and for PP and SAF sets [redacted]

Medications will be coded using World Health Organization-Drug Dictionary (WHO-DD) Version March 2024 or higher.

[redacted]

- [redacted]
- [redacted]

Medication will be presented by Anatomical Therapeutic Chemical (ATC) Level 2 and Level 4. [redacted] Separate summaries for prior and concomitant medications based on ocular location (Ocular vs Systemic) will be provided.

A listing for all prior and concomitant medications will be provided for the FAS. [redacted]

14. STUDY TREATMENT EXPOSURE

Exposure to study treatment in days will be presented by treatment group for the SAF set.

[redacted]

15. STUDY TREATMENT COMPLIANCE

[redacted]

- [redacted]
- [redacted]

Compliance (%) to study treatment will be presented separately for the study eye and the contralateral eye by treatment group for the SAF set.

Listings of all data related to study treatment administration, including interruptions, missed doses and time modifications, exposure and compliance will be provided for the SAF set.

[redacted]

16. EFFICACY OUTCOMES

16.1. Primary Efficacy

For this study, the primary clinical question of interest is to compare the ocular hypotensive efficacy of two concentrations of T4090 ophthalmic solution with Rhopressa® ophthalmic solution in terms of lowering the mean diurnal IOP at Week 7 in the study eye (see Section 6.6).

16.1.1. Primary Efficacy Endpoint & Derivation

The primary efficacy endpoint is the change from baseline (see calculation in Section 6.8) in the mean diurnal IOP at Week 7 in the study eye.

[redacted]

Mean diurnal IOP* = (IOP at 8:00 AM + IOP at 10:00 AM + IOP at 4:00 PM) / 3

[redacted]

- [redacted]
- [redacted]
- [redacted]

* If IOP value is missing at any timepoint, the mean diurnal IOP will be missing.

[redacted]

[redacted]

16.1.3. Primary Analysis of Primary Efficacy Endpoint (Primary Estimand)

Descriptive statistics for mean diurnal IOP and change from baseline at Week 7 in the study eye will be provided by treatment group on the FAS.

The primary objective of this study is to test the hypothesis (H0) that there is no difference in change from baseline in the mean diurnal IOP at Week 7 among treatment groups. H0 will be tested against the alternative hypothesis H1 of at least one of the test groups is different to reference group at 0.05 alpha level.

The primary efficacy analysis, performed for the FAS, is evaluated using a restricted maximum likelihood (REML) based, mixed-effects model for repeated measures (MMRM) estimating change from baseline across post-baseline visits. The model will include the fixed, categorical effects of treatment (T4090 0.2%, T4090 0.3%, and Rhopressa®), visit (W2, W4, and W7), and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline mean diurnal IOP value and baseline value-by-visit interaction (see Section 7.1). The general form of the model will then be:

Change = Baseline + Treatment + Visit + Treatment*Visit + Baseline*Visit

[redacted] Significance tests will be based on LS means and Type III sum-of-squares, using a two-sided α=0.05 (two-sided 95% CIs). P-values for the treatment effect and the treatment-by-visit interaction will be [redacted]. The primary comparisons of interest will be the LS mean differences between each T4090 dose and Rhopressa® at Week 7. For the treatment difference of each T4090 concentration versus Rhopressa® and both T4090 concentrations comparison, the model estimate, standard error, two-sided 95% CIs, and p-value will be reported. Additionally, the LS mean, SE, and two-sided 95% CI for change from baseline by visit will be reported for each treatment group.

[redacted]

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF set.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified in the relevant section.

17.1. Ocular and Systemic Adverse Events

Ocular and systemic adverse events (AEs) will be coded using MedDRA central coding dictionary, Version 27.0 or higher. Ocular and systemic AEs will be analyzed separately on the basis of the localization [redacted]

A TEAE is defined as an AE that occurs or worsens in severity after at least one dose of IMP has been administered.

[redacted]

[redacted]

Separate descriptions of treatment-emergent ocular and systemic TEAEs will be performed by treatment group:

- Number and percentage of patients experiencing at least one TEAE, serious TEAE, study treatment related TEAE, study treatment related serious TEAE, TEAE leading to study treatment discontinuation, TEAE leading to death, TEAE by maximum severity, and treatment-emergent adverse event of special interest (AESI - only for ocular AEs),
- Number and percentage of patients experiencing at least one TEAE, as well as the number of TEAEs, by SOC and PT. The same summary table will be performed for serious TEAEs, study treatment related TEAEs, study treatment related serious TEAEs, TEAEs leading to study treatment discontinuation, and treatment-emergent AESI (only ocular),
- Number and percentage of patients experiencing at least one TEAE, by SOC, PT, and maximum severity. The same summary table will be performed for study treatment related TEAEs,
- Number and percentage of patients experiencing at least one TEAE, by SOC, PT, and maximum relationship to study treatment.

Listings will include all AEs (TEAEs and non-TEAEs)[redacted]

17.1.1. All TEAEs

Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and maximum relationship to study treatment.

17.1.1.1. Severity

Severity is classed as "mild", "moderate", and "severe" (increasing severity).[redacted]If a subject reports a TEAE more than once within that SOC/ PT, the AE with the highest severity will be used in the corresponding severity summaries.

17.1.1.2. Relationship to Study Treatment

Relationship, as indicated by the masked investigator, is classed as "not related", and "related" (increasing severity of relationship).[redacted]If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

17.1.2. TEAEs Leading to Discontinuation of Study Treatment

[redacted] A summary of TEAEs leading to discontinuation of study treatment by SOC and PT will be prepared.

17.1.3. Serious Adverse Events

[redacted] A summary of serious TEAEs by SOC and PT will be prepared.

17.1.4. Adverse Events Leading to Death

[redacted] The number of patients with TEAEs leading to death will be included in the overview TEAE summary table. The summary by SOC and PT will be part of the serious TEAE summary.

17.1.5. Adverse Events of Special Interest

Based on observations from previous studies with ROCKi, the following AEs will be considered as AESI, if judged significant by the investigator:

- All AEs related to CEC
- All AEs related to visual impairment (partial or total visual acuity loss)
- Corneal opacity
- Lens opacity/cataract
- Corneal verticillate

[redacted] A summary of treatment-emergent (ocular) AESIs by SOC and PT will be prepared.

17.2. Deaths

If any subject dies during the study [redacted], the information will be presented in a data listing.