

RMP-A03-001 Statistical Analysis Plan

NCT05794204

17 January 2024

Statistical Analysis Plan

Study Code RMP-A03-001

Version Number 1.0

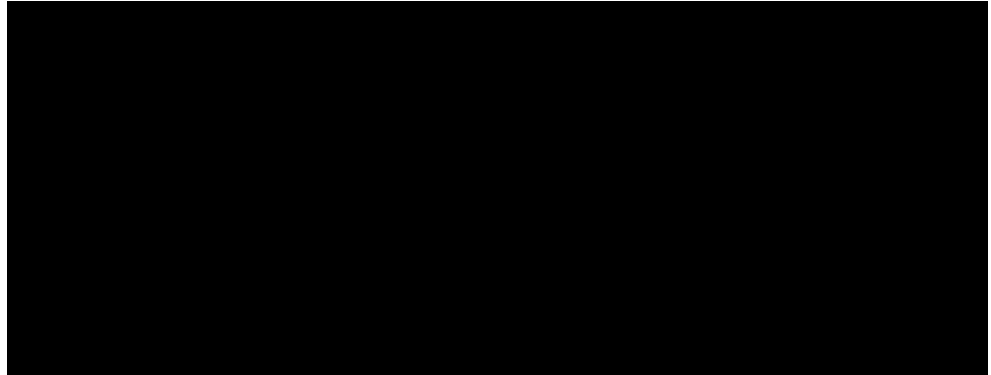
Date January 17, 2024

A Phase 1/2a Study Evaluating the Safety and Efficacy of RMP-A03 Ocular Suspension in Healthy Volunteers and Patients with Pterygium

PROTOCOL DATE: Version 1.0: 11 September 2022
Version 2.0: 29 March 2023

SPONSOR: Suzhou Raymon Pharmaceuticals

PREPARED BY:



APPROVED BY:

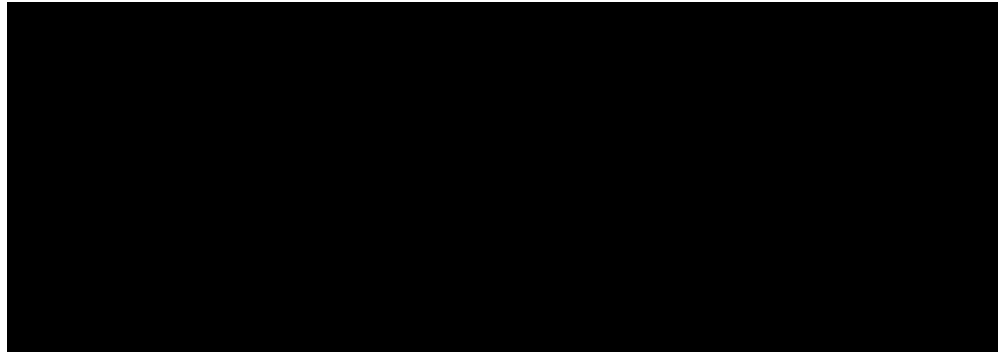


TABLE OF CONTENTS

TITLE PAGE	1
SIGNATURE OF STUDY STATISTICIAN	2
SIGNATURE OF SUZHOU RAYMON PHARMACEUTICALS	3
TABLE OF CONTENTS	4
LIST OF ABBREVIATIONS	6
1 INTRODUCTION	7
2 STUDY OBJECTIVES	7
2.1 Primary Objective	7
2.2 Secondary Objectives	7
3 STUDY OVERVIEW	7
3.1 Study Design	7
3.1.1 Stage 1	7
3.1.2 Stage 2	8
3.1.3 Designation of Study Eye	8
3.2 Randomization and Masking	8
4 STUDY ENDPOINTS	12
4.1 Safety Endpoints in Stage 1 and Stage 2	12
4.2 Efficacy Endpoints in Stage 2	12
4.2.1 Primary Efficacy Endpoint	12
4.2.2 Secondary Efficacy Endpoints	12
[REDACTED]	[REDACTED]
5 ANALYSIS SETS	12
5.1 Enrolled Analysis Set: Stage 1 and Stage 2	12
5.2 Safety Analysis Set: Stage 1 and Stage 2	12
5.3 Intent-to-Treat (ITT): Stage 2 only	13
5.4 Modified Intent-to-Treat (mITT): Stage 2 only	13
5.5 Per-Protocol (PP) Analysis Set: Stage 2 only	13
6 STUDY SUBJECTS	13
6.1 Analysis Sets	13
6.2 Subject Disposition	13
6.3 Demographic and Baseline Characteristics	13
6.4 Medical History	13
6.5 Inclusion/Exclusion Criteria and Subject Eligibility	14
6.6 Protocol Deviations	14
6.7 Investigational Product Administration and Extent of Exposure	14
6.8 Concomitant Medications	14
7 STATISTICAL ANALYSIS METHODS	15
7.1 General Considerations	15
7.1.1 Statistical Notation and Presentation	15
7.1.2 Baseline and Change from Baseline	15
7.1.3 Study Day	15
7.1.4 Handling of Missing or Partial Dates	15
7.2 Missing Data Imputation	16
7.3 Efficacy Analyses	16
7.3.1 Pterygium Hyperemia Grading Analysis	17
7.3.1.1 Mixed Model with Repeated Measures (MMRM)	17
7.3.1.2 Analysis of Covariance (ANCOVA)	17
7.3.2 Pterygium Characteristics Analysis	18
7.4 Safety Analyses	18
7.4.1 Adverse Events	18

7.4.2	Ophthalmic Evaluations	19
7.4.2.1	Best-Corrected Distance Visual Acuity (BCDVA)	20
7.4.2.2	Intraocular Pressure (IOP)	20
7.4.2.3	Slit-lamp Biomicroscopy	20
7.4.2.4	Indirect Ophthalmoscopy (Dilated Fundus Exam)	20
7.4.2.5	Ocular Comfort Index	20
7.4.3	Clinical Laboratory Values	21
7.4.4	Vital Signs and Body Measurements	21
7.4.5	Physical Examinations	21
8	CHANGE TO THE PLANNED ANALYSES FROM PROTOCOL	21
9	POWER AND SAMPLE SIZE	21
10	STATISTICAL SOFTWARE	21

LIST OF TABLES

Table 1. Schedule of Visits and Procedure for RMP-A03-001: Stage 1	10
Table 2: Schedule of Visits and Procedure for RMP-A03-001: Stage 2	11

LIST OF ABBREVIATIONS

Term	Definition
AE(s)	adverse event(s)
AIC	Akaike's information criterion
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BCDVA	best-corrected distance visual acuity
CI	confidence interval
CRF	case report form
ETDRS	early treatment diabetic retinopathy study
IOP	intraocular pressure
IP	investigational product
IRT	interactive response technology
ITT	intent-to-treat
LOCF	last observation carried forward
LSM	least square mean
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model with repeated measures
MTD	maximum tolerated dose
OD	right eye
PT	preferred term
PP	per-protocol
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE(s)	treatment-emergent adverse event(s)
TID	three times per day
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of child bearing potential

1 INTRODUCTION

This document details the planned statistical analyses for Suzhou Raymon Pharmaceuticals protocol RMP-A03-001, a study titled “A Phase 1/2a Study Evaluating the Safety and Efficacy of RMP-A03 Ocular Suspension in Healthy Volunteers and Patients with Pterygium”.

This statistical analysis plan (SAP) was developed based on the Clinical Protocol RMP-A03-001 (version 2 dated March 29, 2023).

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the safety and tolerability of RMP-A03 (Stage 1 and 2).

2.2 Secondary Objectives

- To evaluate the treatment response to RMP-A03 compared to vehicle as determined by change from baseline in pterygium characteristics (Stage 2).

3 STUDY OVERVIEW

3.1 Study Design

This is a first-in-human study with a 2-stage design. Only 1 eye per subject will be enrolled into the study.

See [Figure 1](#) for study flowchart, [Table 1](#) and [Table 2](#) for schedules of visits and procedure for Stage 1 and Stage 2 of RMP-A03-001, respectively.

3.1.1 Stage 1

Stage 1, is an open-label dose escalation, 7-day study to determine the maximum tolerated dose (MTD) of the 4 evaluated doses of RMP-A03 in healthy volunteers. Four escalating doses of RMP-A03 ocular suspension [REDACTED] will be evaluated in Stage 1, given that no safety concerns are identified with each escalating dose. Up to 5 subjects are planned for enrollment into each dose cohort. The first cohort will begin with the lowest dose of study drug (RMP-A03 ocular suspension [REDACTED]).

At the screening visit, following informed consent, demographic information, relevant medical and ophthalmic history will be recorded. All prescription and over-the-counter medications taken 30 days prior to the screening and during the study will be recorded (diagnostic eye drops do not need to be recorded). Urine pregnancy test must be performed for women of childbearing potential (WOCBP). Screening assessments will include a complete physical examination, heart rate and blood pressure, clinical labs, comprehensive ophthalmic assessments, pterygium assessments, and the ocular comfort questionnaire. At Day 1 baseline visit, after completing all

required assessments and confirming eligibility, the study subject will instill a single eye drop of RMP-A03 to the study eye one time at Day 1. The study staff will observe the eye drop instillation. Post-baseline evaluations on Day 1 will include physical examination, heart rate and blood pressure, comprehensive ophthalmic assessments, the ocular comfort questionnaire, and AE collection. Upon confirmation of acceptable tolerability and no immediate safety concerns, study drug will be dispensed at the end of Day 1 and subjects will be instructed to instill 1 drop of study medication in the study eye 3 times daily (TID, at least 3 hours apart), starting from the morning of Day 2 to Day 6. On Day 7, subjects will return to the clinic, and a single eye drop of RMP A03 will be administered in the study eye before completion of the final examinations (see Table 1-1 for study visits and procedures and Figure 1 for the study schematic).

Escalation to the next dose cohort will only occur after the 7-day safety data for all subjects in the preceding cohort has been reviewed and upon confirmation of no safety concerns.

3.1.2 Stage 2

Stage 2 will initiate upon completion of Stage 1 and following determination of MTD among the 4 evaluated doses. Stage 2 is a randomized, doubled-masked, placebo-controlled study comparing the efficacy and safety of RMP-A03 with placebo in patients with pterygium. Approximately 75 patients are planned to be randomized to 1 of 3 treatment groups in a 1:1:1 ratio. These treatment groups will consist of the 2 doses of RMP-A03 and the RMP-A03 vehicle. A single eye drop of RMP-A03 or RMP-A03 vehicle will be applied TID to the study eye for a total of 28 days. Patients will be followed for a total of 84 days. The study will consist of 7 visits as follows: Screening (up to 60 days prior to the baseline visit), Baseline/Day 1, Day 7, Day 14 (Phone Visit), Day 28, Day 56, and Day 84 (see Table 1-2 for study visits and procedures and Figure 1 for the study schematic).

3.1.3 Designation of Study Eye

Study eye will be defined as the eye that meets all of the inclusion and none of the exclusion criteria. If both eyes meet criteria, the eye with higher pterygium vascularity grading will be chosen as the study eye. If both eyes have the same pterygium vascularity grading, the right eye (OD) will be determined as the study eye.

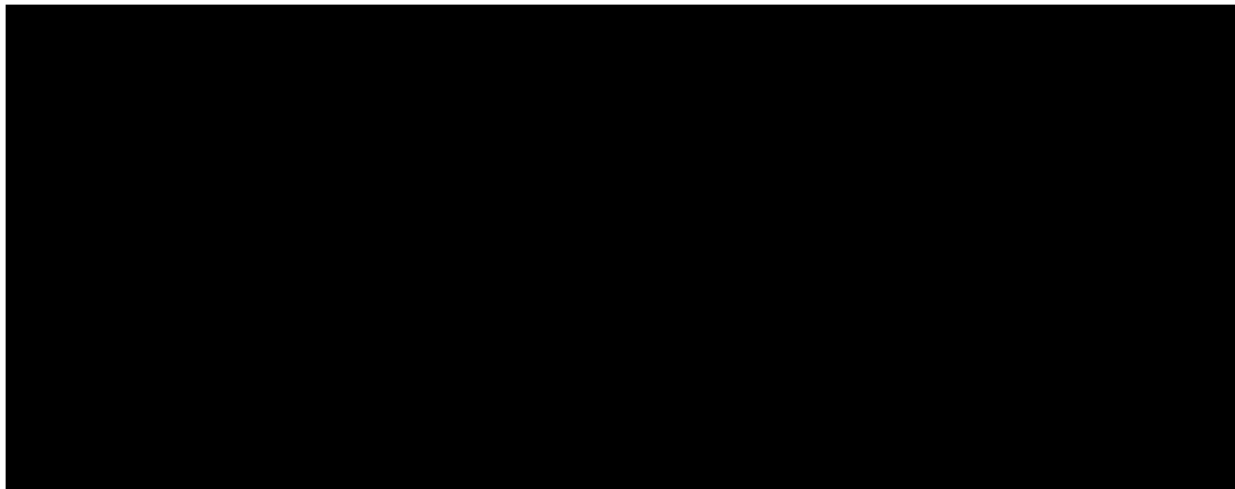
3.2 Randomization and Masking

Stage 1 is open-label. Subjects in Stage 1 who discontinue before enrollment is complete may be replaced in the study. Replacement subjects will be assigned unique subject numbers.

Stage 2 is double-masked. Approximately 75 subjects with pterygium will be randomly assigned to receive 1 of 3 treatments [REDACTED] in a 1:1:1 ratio. Randomization schedule will be optimized to achieve a balanced distribution of treatment assignment by stratifying randomization by baseline pterygium hyperemia grading [REDACTED]. [REDACTED] Subjects and study personnel, including but not limited to investigators, study staff,

central lab, clinical monitors, and designated staff within the Sponsor and the Sponsor's representatives, will remain masked to the study treatment assignments. There will be a small dedicated unmasked team comprised of Sponsor and Sponsor representatives that will manage IP supply, IRT services, and randomization schematics.

Figure 1. Study Flowchart



Upon DMC Review of Stage 1 Safety Data and Determination MTD, the study will move on to Stage 2.

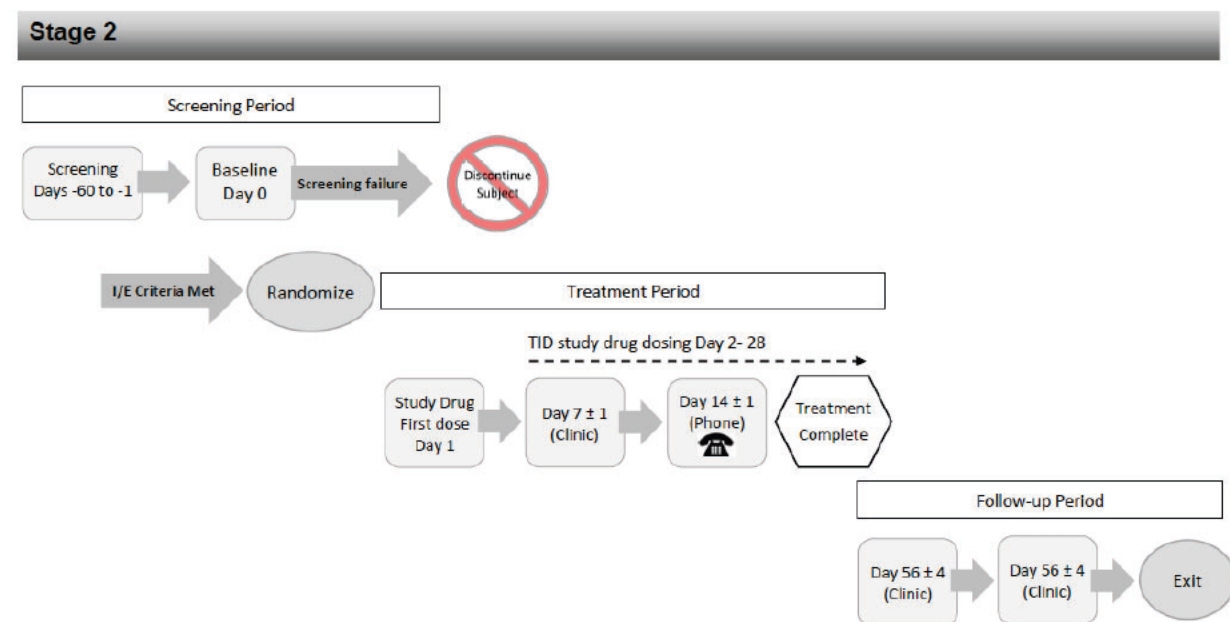


Table 1. Schedule of Visits and Procedure for RMP-A03-001: Stage 1

Procedures	Screening Day -60 to -1 (Visit 1)	Baseline Day 1 (Visit 2)	Post-dose Day 1 (Visit 3)	Follow-up/Exit ¹ Day 7+1 day (Visit 4)
Informed Consent	X			
Inclusion/Exclusion	X	X		
Demographics	X			
Medical/Ophthalmic History	X	X		X
Concomitant Medications	X	X		X
Physical examination	X	X	X	X
Vital Signs	X	X	X	X
Urine Pregnancy Test ²	X	X		X
Clinical Labs	X			X
Adverse Events ³		X	X	X
Ocular Comfort Index	X	X	X	X
BCDVA	X	X	X	X
Intraocular Pressure	X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X
Indirect Ophthalmoscopy	X	X	X	X
Eyedrop Instillation Evaluation	X			
Study Drug Administration		X ⁴		
Study Drug Dispensing			X	
Study Drug Collected				X ⁵

¹ Every effort should be made to complete all Exit procedures at Early Termination

² A negative result on a urine pregnancy test before administration of study drug for women of childbearing potential is required for eligibility

³ AEs should be assessed before and after administration of study drug

⁴ First dose to be administered by in the clinic by study staff after completion of all Baseline assessments

⁵ Collect kit dispensed at Exit visit

Table 2: Schedule of Visits and Procedure for RMP-A03-001: Stage 2

Procedures	Screening Day-60 to -1 (Visit 1)	Baseline Day1 (Visit 2)	Follow-up Day 7±1 day (Visit 3)	Follow-up Day 14±3 days Phone call ¹ (Visit 4)	Follow-up Day 28±3 days (Visit 5)	Follow-up Day 56±4 days (Visit 6)	Follow-up/ Exit ² Day 84±5 days (Visit 7)
Informed Consent	X						
Inclusion/Exclusion	X	X					
Demographics	X						
Medical/Ophthalmic History	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Vital Signs	X	X	X		X	X	X
Urine Pregnancy Test ³	X	X					X
Clinical Labs	X						X
Adverse Events ⁴		X	X	X	X	X	X
Ocular Comfort Index	X	X	X		X	X	X
BCDVA	X	X	X		X	X	X
Intraocular Pressure	X	X	X		X	X	X
Pterygium Photography	X	Study Eye	Study Eye		Study Eye	Study Eye	Study Eye
Pterygium Assessments	X	Study Eye	Study Eye		Study Eye	Study Eye	Study Eye
Slit Lamp Biomicroscopy	X	X	X		X	X	X
Indirect Ophthalmoscopy	X	X	X		X	X	X
Eyedrop Instillation Evaluation	X						
Study Drug Administration		X ⁵					
Study Drug Dispensing		X					
Study Drug Collected							X ⁶

¹ Schedule the Telephone visit (Visit 4) on Day 14. Change in medical history or concomitant medications should be assessed by the investigator for AEs. Study drug compliance issues and reeducation of subjects should be documented in the source documents

² Every effort should be made to complete all Exit procedures at Early Termination

³ A negative result on a urine pregnancy test before administration of study drug for women of childbearing potential is required for eligibility

⁴ AEs should be assessed before and after administration of study drug

⁵ On Day 1, the first dose of the study drug will be administered in the clinic by study staff after completion of all Baseline assessments

⁶ Collect kit dispensed at Exit Visit

4 STUDY ENDPOINTS

4.1 Safety Endpoints in Stage 1 and Stage 2

- Rates of adverse events (AEs)

4.2 Efficacy Endpoints in Stage 2

4.2.1 Primary Efficacy Endpoint

- Change from baseline in pterygium hyperemia grading at Day 28

4.2.2 Secondary Efficacy Endpoints

- Change from baseline in pterygium characteristics at Day 28
 - length
 - encroachment onto the cornea
 - size at limbus



5 ANALYSIS SETS

5.1 Enrolled Analysis Set: Stage 1 and Stage 2

The Enrolled Analysis Set will include all enrolled subjects (non-screen failures). This analysis set will be used for all listings.

5.2 Safety Analysis Set: Stage 1 and Stage 2

The Safety Analysis Set will include all subjects who were randomized and took at least 1 dose of the study drug. Subjects in this analysis set will be analyzed as treated. In Stage 1, this analysis set will be used for all analyses. In Stage 2, this analysis set will be used for all safety analyses.

5.3 Intent-to-Treat (ITT): Stage 2 only

The ITT Analysis Set will include all subjects who were randomized. Subjects in this analysis set will be analyzed as randomized. This analysis set will be used for subject disposition, demographics and baseline characteristics, medical history, protocol deviations, and concomitant medications.

5.4 Modified Intent-to-Treat (mITT): Stage 2 only

The mITT Analysis Set will include all subjects who were randomized and took at least 1 dose of the study medication and have at least one post-dose primary efficacy assessment. Subjects in this analysis set will be analyzed as randomized. Efficacy analysis will be performed on this analysis set.

5.5 Per-Protocol (PP) Analysis Set: Stage 2 only

The PP Analysis Set will include subjects in the mITT Analysis Set who do not have significant protocol deviations that affect the primary endpoint analysis. Protocol deviations will be assessed and the PP Analysis Set selection will be documented in a memo prior to database lock and unmasking. Subjects in this analysis set will be analyzed as randomized. Efficacy analysis will be performed on this analysis set.

6 STUDY SUBJECTS

6.1 Analysis Sets

The number and percentage of subjects in each analysis set will be summarized by treatment group and overall, for the Enrolled Analysis Set. A listing of analysis sets will also be presented.

6.2 Subject Disposition

Subject disposition will be summarized by treatment group (including overall). The number of subjects who were enrolled, randomized, completed, or discontinued from the study, as well as the reason for discontinuation, will be summarized by treatment group. A listing of subject disposition will also be presented.

6.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group (including overall), including age, sex, ethnicity, race, height, weight, and study eye. A listing of demographics and baseline characteristics will also be presented.

6.4 Medical History

Medical history will be coded using version 24.1 or later of the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized by treatment group (including overall), System Organ Class (SOC) and Preferred Term (PT). Multiple histories will be counted only once per subject in each summary level. A listing of medical history will also be presented.

6.5 Inclusion/Exclusion Criteria and Subject Eligibility

Subject eligibility, e.g., inclusion and exclusion criteria failures will be listed for all screened subjects.

6.6 Protocol Deviations

The number and percentage of subjects with any major protocol deviations will be summarized by treatment group (including overall) and deviation category. Multiple deviations will be counted only once per subject in each summary level. All protocol deviations will be presented in a listing.

6.7 Investigational Product Administration and Extent of Exposure

Duration of study drug exposure (days) will be summarized by treatment group (including overall). A listing of study drug exposure will also be presented. Duration of exposure to study drug is calculated as (date of last dose – date of first dose + 1).

6.8 Concomitant Medications

The World Health Organization Drug Dictionary (WHO-DD) will be used to categorize verbatim descriptions of non-study medications into the Anatomical Therapeutic Chemical (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

Prior medication is defined as any medication with a stop date prior to the first dose of study drug. Prior medications will not be summarized but will be provided in a listing. Concomitant medications refer to non-study medications used on or after the first day of receiving the randomized study drug. Among concomitant medications, those started after the first day of receiving the randomized study drug will be defined as new concomitant medication and will be flagged.

Concomitant medications, and new concomitant medications if needed, will be summarized by treatment group (including overall), ATC classification (ATC level 3 and PT). All prior and concomitant medications will be presented in a listing.

7 STATISTICAL ANALYSIS METHODS

7.1 General Considerations

7.1.1 Statistical Notation and Presentation

For continuous variables the following descriptive statistics will be provided: number of subjects, mean, standard deviation (SD), standard error (SE), minimum, maximum, and median. For categorical variables, descriptive statistics will include the number and percentage of subjects in each category, using either the number of subjects in the treatment group or the number of subjects with non-missing values as the denominator for the percentages.

In general, minimum and maximum values will be rounded to the precision of the original value; means and medians will be rounded to one decimal place greater than the precision of the original value; and SDs and SEs will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place. P-values will be presented with four decimal places and values less than 0.0001 will be presented as <0.0001 .

In the case where a safety laboratory variable is recorded as “ $> x$ ”, “ $\geq x$ ”, “ $< x$ ” or “ $\leq x$ ”, a value of x will be taken for summary. In listings, these data will be presented as recorded with the sign.

By subject listings, including data at scheduled and unscheduled visits, will be sorted by treatment group, subject, visit, and timepoint.

7.1.2 Baseline and Change from Baseline

Baseline is defined as the last non-missing observation obtained prior to the administration of the study drug. Change from baseline is defined as post-baseline result minus baseline result.

7.1.3 Study Day

Study day will be calculated as the number of days from first dose of study drug.

For events/assessments on or after first dose of study drug:

- Study day = date of event (or date of assessment) – date of first dose of study drug + 1.

For events/assessments before first dose of study drug:

- Study day = date of event (or date of assessment) – date of first dose of study drug.

7.1.4 Handling of Missing or Partial Dates

No missing data will be imputed for the safety analysis, except for missing or partial start dates of AEs with the imputation rule that missing component(s) will be assumed as the most

conservative value(s) possible. For example, AEs with missing start dates as treatment-emergent adverse events (TEAEs) will be conservatively captured as follows:

- If “day” is the only missing field, impute the “day” as the date of first dose of study drug if their “month” and “year” are the same; otherwise, the first day of the non-missing month.
- If “day” and “month” are the only missing fields, impute the “day” and “month” as the date of first dose of study drug if their “year” is the same; otherwise, January 1 of the non-missing year.

Non-study medications with missing or partial dates will be imputed similarly. If the start date is unknown and end date is “ongoing” then the non-study medication will be considered a concomitant medication, but not a new concomitant medication.

Date imputation will only be used for computational purposes, e.g., defining the treatment-emergent status. Actual data values as they appear in the original CRFs will be shown in data listings.

7.2 Missing Data Imputation

Missing pterygium hyperemia grading and pterygium characteristics data for Day 7 and Day 28 may be imputed using the last observation carried forward (LOCF) method from scheduled or unscheduled post-baseline visits.

7.3 Efficacy Analyses

Efficacy analyses will be performed for both the mITT Analysis Set and the Per Protocol Analysis Set. All hypothesis testing will be two-sided at a significance level of 0.05, with the RMP-A03 vehicle treatment group designated as the reference group.

An error occurred whereby subjects were randomized based on incorrect strata. The sponsor acknowledges slightly imbalance of the number of subjects in randomized treatment across the strata; however, as this is a first-in-human study, it’s important to explore the impact of the actual baseline pterygium hyperemia grading category to the treatment effect on efficacy endpoints, so the analysis will emphasize using the correct baseline grading. As the baseline pterygium hyperemia grading in this study will either be [REDACTED], analysis models are thus proposed to adjust the actual baseline pterygium hyperemia grading as a continuous covariate, rather than the category used during stratification.

7.3.1 Pterygium Hyperemia Grading Analysis

To evaluate the primary and exploratory efficacy endpoints, change from baseline in pterygium hyperemia grading at Day 28, and Day 56 and Day 84, respectively, baseline, post-baseline, and change from baseline values for pterygium hyperemia grading in the study eye will be summarized by treatment group and visit.

7.3.1.1 Mixed Model with Repeated Measures (MMRM)

The treatment difference between the RMP-A03 and RMP-A03 vehicle treatment groups will be evaluated for the change from baseline pterygium hyperemia grading, with the RMP-A03 vehicle treatment group used as reference, using a MMRM. This analysis will use observed data for mITT Analysis Set.

The model will include terms for baseline pterygium hyperemia grading, treatment, visit, and the interaction of treatment and visit, with visit as a repeated measure and subject as random effect.

[REDACTED]

The least squares mean (LSM) and two-sided 95% confidence interval (CI) will be presented for treatment group, and visit. Additionally, the difference between each RMP-A03 treatment group and RMP-A03 vehicle treatment group will be calculated, along with the two-sided 95% CI.

The following is reference code for this analysis:

```
[REDACTED]
```

7.3.1.2 Analysis of Covariance (ANCOVA)

An ANCOVA model will be used to evaluate the difference between the RMP-A03 and RMP-A03 vehicle treatment groups in change from baseline in pterygium hyperemia grading at each post-baseline visit. This analysis will use LOCF for the mITT Analysis Set, and observed data for PP Analysis Set.

The model will include terms for treatment, and actual baseline pterygium hyperemia grading [REDACTED] will be adjusted in the model as a continuous covariate. The LSM and two-sided 95% CI will be presented for each treatment group. Additionally, the difference between

each RMP-A03 dose level and RMP-A03 vehicle will be calculated, along with the two-sided 95% CI.

The following is reference code for this analysis:

A large black rectangular redaction box covering several lines of text, likely the reference code mentioned in the preceding sentence.

7.3.2 Pterygium Characteristics Analysis

To evaluate the secondary and exploratory efficacy endpoints, change from baseline in pterygium characteristic at Day 28, and Day 56 and Day 84, respectively, baseline, post-baseline, and change from baseline values for pterygium corneal encroachment, and pterygium length in the study eye will be summarized by treatment group and visit. To assess the size of pterygium at limbus, the number and percentage of subjects within each level of clock-hours, and T Grading System will be summarized by treatment group and visit. The denominator will be the number of subjects with non-missing values for the visit.

Change from baseline for pterygium corneal encroachment, and pterygium length in the study eye will be analyzed using the same ANCOVA and MMRM models as the primary analysis.

7.4 Safety Analyses

Safety and tolerability will be assessed throughout the study by examination of AEs, ophthalmic examinations, clinical laboratory tests, vital signs, and physical examinations (Stage 1). Safety related tables and listings will be based on the Safety Analysis Set.

7.4.1 Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of study product, whether or not considered related to study drug. All AEs will be coded using MedDRA version 24.1 or later.

A TEAE is defined as any AE with onset on or after the first dose of study drug, until 30 days after last dose.

A study drug related AE is defined as an AE classed as “Possibly Related” or “Related” to the study drug. If an AE has missing causality, it is assumed to be related to the study drug for analysis purposes.

Multiple events will be counted once per subject in each summary level.

Any AE that has worsened in the severity will be recorded as a separate AE.

To evaluate the incidence of TEAEs, the number and percent of subjects who experienced a TEAE within each SOC or PT summary level will be summarized by treatment group. Subjects will only be counted once within each summary level. In addition, the total number of TEAEs within a summary level will be presented. A subject is counted at most once per SOC and PT at the maximum severity for TEAE summary by maximum severity. AEs with missing severity will be classified as “Severe.”

An overall summary table of TEAEs will include:

- Any TEAEs
- Serious TEAEs
- TEAEs related to study drug
- TEAEs leading to discontinuation of study drug
- Ophthalmic TEAEs

TEAEs will be summarized by treatment group (including overall), for:

- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- TEAE leading to discontinuation of study drug by SOC and PT
- Ophthalmic TEAEs by SOC and PT (study eye and fellow eye summarized separately)

AEs listings will be presented by treatment group, subject, start date, SOC and PT for:

- All AEs
- Serious AEs
- AEs leading to discontinuation of study drug

7.4.2 Ophthalmic Evaluations

Fellow (non-study) eye for all subjects will be pooled as an additional treatment group for summary analyses.

7.4.2.1 Best-Corrected Distance Visual Acuity (BCDVA)

Baseline, and post-baseline BCDVA values (“20/n” for Snellen, where n is the smallest line read correctly) will be summarized by treatment group and visit for both the Snellen and ETDRS (early treatment diabetic retinopathy study) charts.

A listing of BCDVA results and manifest refraction measurements will also be provided.

7.4.2.2 Intraocular Pressure (IOP)

Baseline, post-baseline, and change from baseline in IOP results will be summarized by treatment group and visit.

A listing of IOP results will also be provided. Results with clinical significance will be flagged.

7.4.2.3 Slit-lamp Biomicroscopy

Assessments of the eyelids, conjunctiva, cornea, anterior chamber, iris, and lens will be performed using slit-lamp biomicroscopy. The number and percentage of subjects with results in each ophthalmic structure assessment category will be summarized by treatment group and visit. The denominator will be the number of subjects with non-missing values for the given ophthalmic structure assessment and visit.

A listing of slit-lamp biomicroscopy results will also be provided. Results with clinical significance will be flagged.

7.4.2.4 Indirect Ophthalmoscopy (Dilated Fundus Exam)

Assessments of the vitreous, retina, macula, choroid, and optic nerve will be performed using indirect ophthalmoscopy, and the vertical cup-to-disc ratio will be calculated.

Baseline, post-baseline, and change from baseline vertical cup-to-disc ratio values will be summarized by treatment group and visit.

The number and percentage of subjects with results in each ophthalmic structure assessment category will be summarized by treatment group and visit. The denominator will be the number of subjects with non-missing values for the given ophthalmic structure assessment and visit.

A listing of assessment results and vertical cup-to-disc ratio will also be provided. Results with clinical significance will be flagged.

7.4.2.5 Ocular Comfort Index

Baseline, post-baseline, and change from baseline values for responses to the Ocular Comfort Index questionnaire will be summarized by treatment group, visit, and question.

A listings of questionnaire responses will also be provided.

7.4.3 Clinical Laboratory Values

All clinical laboratory tests (hematology, chemistry, urinalysis, and other) will be listed. Abnormal laboratory results and/or with clinical significance will be flagged.

7.4.4 Vital Signs and Body Measurements

Vital signs parameters will include temperature (Stage 1 only), systolic and diastolic blood pressure, and heart rate. Body measurements (Stage 1 only) will include height and weight. Baseline, post-baseline, and change from baseline values will be summarized by treatment group and visit. A vital signs and body measurements listing will also be presented. If a repeat pulse or blood pressure is collected, both values will be listed, and the second measurement will be used for analysis.

7.4.5 Physical Examinations

All physical examination data in Stage 1, including details of clinically significant findings will be listed.

8 CHANGE TO THE PLANNED ANALYSES FROM PROTOCOL

- Analyses of all efficacy endpoints will be performed using a model term for the actual baseline pterygium hyperemia grading as a continuous covariate, rather than the category used during stratification. Refer to Section 7.3 for details.

9 POWER AND SAMPLE SIZE

For Stage 1, up to 5 subjects will be treated in each dose cohort for a total of up to 20 subjects. No formal sample size calculation was performed.

In Stage 2, approximately 25 subjects will be treated in each treatment arm for a total of approximately 75 subjects. The sample size calculation was as follows.

For the primary efficacy endpoint of change from baseline in pterygium hyperemia grading at Day 28, a sample size of 25 completed subjects per arm provides approximately 90% power to detect a 0.66 statistically significant difference between an active dose arm and the placebo at the 0.05 significance level. This assumes that the treatment difference between an active dose arm and the placebo is at least 0.66 and that the within-treatment standard deviation is approximately 0.7 for all three treatment arms.

The within-treatment standard deviation comes from the published results of the study in patients with pterygium. The expected treatment difference is conservatively estimated as the observed difference from the study minus one standard error.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS® version 9.4 (or later).

the 1990s, the number of people in the UK who are aged 65 and over has increased from 10.5 million to 12.5 million, and the number of people aged 75 and over has increased from 4.5 million to 6.5 million (Office of National Statistics 2000). The number of people aged 85 and over has increased from 1.5 million to 2.5 million.

There is a growing awareness of the need to address the needs of older people in the UK. The Department of Health (2000) has published a strategy for older people, which sets out the government's commitment to improve the lives of older people and to ensure that they are able to live independently and actively for as long as possible.

The strategy identifies a number of key areas for action, including: improving the health and social care of older people; promoting independence and active living; and ensuring that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key challenges that the government faces in implementing its strategy, including: the need to improve the quality of care for older people; the need to ensure that older people have access to the services and support that they need; and the need to ensure that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key areas for research, including: the need to improve the understanding of the needs of older people; the need to develop new services and support for older people; and the need to evaluate the effectiveness of existing services and support.

The strategy also identifies a number of key areas for action, including: improving the health and social care of older people; promoting independence and active living; and ensuring that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key challenges that the government faces in implementing its strategy, including: the need to improve the quality of care for older people; the need to ensure that older people have access to the services and support that they need; and the need to ensure that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key areas for research, including: the need to improve the understanding of the needs of older people; the need to develop new services and support for older people; and the need to evaluate the effectiveness of existing services and support.

The strategy also identifies a number of key areas for action, including: improving the health and social care of older people; promoting independence and active living; and ensuring that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key challenges that the government faces in implementing its strategy, including: the need to improve the quality of care for older people; the need to ensure that older people have access to the services and support that they need; and the need to ensure that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key areas for research, including: the need to improve the understanding of the needs of older people; the need to develop new services and support for older people; and the need to evaluate the effectiveness of existing services and support.

The strategy also identifies a number of key areas for action, including: improving the health and social care of older people; promoting independence and active living; and ensuring that older people are able to live in their own homes and communities for as long as possible.

The strategy also identifies a number of key challenges that the government faces in implementing its strategy, including: the need to improve the quality of care for older people; the need to ensure that older people have access to the services and support that they need; and the need to ensure that older people are able to live in their own homes and communities for as long as possible.



[REDACTED]

[REDACTED]

