

**RMP-A03-001 Protocol**

**NCT05794204**

**29 March 2023**



## **Suzhou Raymon Pharmaceuticals**

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

**Protocol Number: RMP-A03-001**

**Protocol Version Number: V2.0**

**Protocol Date: 29 March 2023**



## HISTORY OF CHANGES

Protocol Amendment #1: 29 March 2023

Section/Original Content	Change
<b>General</b>	Editorial and typographical errors corrected Updated Sponsor Contact Information
<b>Synopsis, Sections 5.3, 9.8.2 (Stage 2)</b>	
<u>Inclusion criteria #2:</u> <b>Was:</b> Diagnosis of pterygium with a) pterygium vascularity [REDACTED] per Central Reading Center's assessment using anterior segment photography captured at Screening	<b>Is:</b> Diagnosis of pterygium with a) pterygium vascularity [REDACTED] per the Investigator's assessment using the slit-lamp and anterior segment photography confirmed by the Medical Monitor at Screening
<u>Secondary efficacy endpoints:</u> <b>Was:</b> Change from baseline in pterygium characteristics at Day 28 <ul style="list-style-type: none"> <li>○ length</li> <li>○ width</li> <li>○ area</li> </ul>	<b>Is:</b> Change from baseline in pterygium characteristics at Day 28 <ul style="list-style-type: none"> <li>○ length</li> <li>○ encroachment onto the cornea</li> <li>○ size at limbus</li> </ul>
[REDACTED]	[REDACTED]
<u>Assessments:</u> <b>Was:</b> <ul style="list-style-type: none"> <li>• Pterygium vascularity and size assessment using pterygium photography</li> </ul>	<b>Is:</b> <ul style="list-style-type: none"> <li>• Pterygium vascularity and size assessment</li> </ul>
<b>Table 1-1</b>	Added footnote #6 for clarification
<b>Table 1-2</b>	Modified footnote #5. Added footnote #7 for clarification
<b>Section 4.5 and Section 9.8.1</b>	
<b>Was:</b> Randomization schedule will be optimized to achieve a balanced distribution of treatment assignment by investigational site and baseline pterygium hyperemia grading [REDACTED]	<b>Is:</b> Randomization schedule will be optimized to achieve a balanced distribution of treatment assignment by baseline pterygium hyperemia grading [REDACTED]
<b>Section 5.5.4 / Clarification</b>	
<b>Was:</b> Subjects who discontinue before enrollment is complete may be replaced in the	<b>Is:</b> Subjects in Stage 1 who discontinue before enrollment is complete may be replaced in the



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study. Replacement subjects will be assigned unique subject numbers	study. Replacement subjects will be assigned unique subject numbers
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## 1. STUDY SYNOPSIS

<b>Sponsor</b>	Suzhou Raymon Pharmaceuticals
<b>Title</b>	A Phase 1/2a Study Evaluating the Safety and Efficacy of RMP-A03 Ocular Suspension in Healthy Volunteers and Patients with Pterygium
<b>Protocol No</b>	RMP-A03-001
<b>Study Drugs</b>	<p><b>Stage 1:</b></p> <p>RMP-A03 Ocular Suspension [REDACTED]</p> <p>RMP-A03 Ocular Suspension [REDACTED]</p> <p>RMP-A03 Ocular Suspension [REDACTED]</p> <p>RMP-A03 Ocular Suspension [REDACTED]</p> <p><b>Stage 2:</b></p> <p>Active: 2 doses of RMP-A03 Ocular Suspension (based on result from Stage 1)</p> <p>Placebo: RMP-A03 vehicle</p>
<b>Study Population</b>	<p>Healthy volunteers in Stage 1</p> <p>Patients with pterygium in Stage 2</p>
<b>Number of Subjects</b>	<p><b>Stage 1:</b> Approximately 20 participants, 5 in each dose cohort</p> <p><b>Stage 2:</b> Approximately 75 patients, 25 in each treatment arm, randomized in a 1:1:1 ratio</p>
<b>Dosage and Route of Administration</b>	RMP-A03 ocular suspension administered as an eye drop, one drop TID
<b>Phase of Development</b>	Phase 1/2a
<b>Objectives</b>	<p>Primary objective(s):</p> <ul style="list-style-type: none"> <li>Assess the safety and tolerability of RMP-A03</li> </ul> <p>Secondary objective(s):</p> <ul style="list-style-type: none"> <li>Evaluate the treatment response to RMP-A03 compared to vehicle as determined by change from baseline in pterygium characteristics in Stage 2</li> </ul>



<b>Study Design</b>	<p>This is a first-in-human study with a 2-stage design.</p> <p>Stage 1:</p> <p>Stage 1 is an open-label, 7-day dose escalation study to determine the maximum tolerated dose (MTD) among 4 evaluated doses of RMP-A03 in healthy volunteers. Four escalating doses will be evaluated in Stage 1 sequentially, with up to 5 subjects in each dose cohort. The first cohort will initiate with the lowest dose of study drug.</p> <p>Following informed consent, screening/baseline assessments will include a physical examination, vital signs, clinical labs, comprehensive ophthalmic assessments, and ocular comfort questionnaire. 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-dose evaluations on Day 1 will be performed at approximately 2+2 hours after the first dose.</p> <p>Upon confirmation of tolerability and no immediate safety concerns, study drug will be dispensed at the end of Day 1. 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 with the morning of Day 2 till 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.</p> <p>Escalation to the next dose cohort will only occur after the 7-day safety data for all subjects within the preceding cohort have been reviewed by the sponsor appointed safety committee (SC) and upon confirmation of no safety concerns. <b>Note, intrasubject escalation will not be permitted.</b></p> <p>Stopping Rules will be considered during the safety review if any of the following events are reported:</p> <ul style="list-style-type: none"> <li>• Worsening of BCDVA of <math>\geq 3</math> lines in the study eye, deemed as related to study drug in <math>&gt;2</math> subjects</li> <li>• IOP increase to <math>&gt; 27</math> mmHg that cannot be controlled by medication, deemed as related to study drug in <math>&gt;2</math> subjects</li> <li>• Ocular inflammation <math>&gt;</math> grade +2, deemed as related to the study drug in <math>&gt;2</math> subjects</li> <li>• Corneal edema worsening by <math>&gt; 2</math> grades, deemed as related to the study drug in <math>&gt;2</math> subjects</li> </ul>
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	<ul style="list-style-type: none"> <li>Any other serious ocular or systemic adverse event that, in the opinion of the Investigators, is related to the study drug in &gt; 2 subjects</li> </ul> <p>Stage 2:</p> <p>The doses of RMP-A03 to be evaluated in Stage 2 will be determined based upon the results from Stage 1.</p> <p>Stage 2 is a randomized, doubled-masked, placebo-controlled study, comparing the efficacy and safety of 2 doses of RMP-A03 with placebo (RMP-A03 vehicle). Approximately 75 patients with pterygium are planned to be enrolled in Stage 2.</p> <p>Screening (up to 60 days prior to the baseline visit) and baseline assessments will include heart rate and blood pressure, clinical labs, comprehensive ophthalmic assessments, and ocular symptomology questionnaire. At Day 1, after baseline assessment and confirming eligibility, participants will be randomized in a 1:1:1 ratio to either RMP-A03 or vehicle. 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. Study drug will be dispensed on Day 1 and participants will be instructed to instill a single drop in the study eye TID (at least 3 hours apart) for a total of 28 days. Four scheduled follow-up visits are planned on Day 7, Day 28, Day 56, and Day 84. A tele-visit to assess any change in medical/ocular health and compliance will be conducted on Day 14.</p>
<b>Inclusion Criteria of Stage 1</b>	<p>An IRB-/IEC-approved informed consent form (ICF) must be obtained prior to any study-specific procedures are performed.</p> <p>Participants must meet the following criteria for enrollment:</p> <ol style="list-style-type: none"> <li>Must be 18 years of age or older at time of consent</li> <li>Healthy as determined by a physician, based on a medical evaluation including medical history, physical examination, and laboratory tests</li> <li>Best-corrected visual acuity of 20/40 or better (Snellen equivalent) in both eyes</li> <li>Willingness to comply with the study procedures and study drug administration and to return for all study visits</li> </ol>



<b>Exclusion Criteria of Stage 1</b>	<p>Participants meeting any of the following criteria must be excluded:</p> <p>Ophthalmic:</p> <ol style="list-style-type: none"> <li>1. History or current eye disease other than refractive error, incipient cataract, strabismic amblyopia, or anisometropic amblyopia that might interfere with interpretation of the safety</li> <li>2. History of ocular surgery within the 3 months prior to screening</li> <li>3. Use of any ocular medication in either eye within 14 days of screening and throughout the study, with the exception of a) lid scrubs (which may be used prior to, but not after, screening), b) lubricating eye drops for dry eye (which may be used throughout the study no more than 2 times per day and at least 10 minutes between the study drug and the lubricating eye drop)</li> <li>4. Use of contact lenses in the study eye. Contact lenses wearers must discontinue wearing at least 3 days prior to Day 1 visit and throughout the study</li> <li>5. Known hypersensitivity to benzalkonium chloride or excipients of RMP-A03 ophthalmic solution</li> <li>6. Cannot demonstrate proper delivery of eye drops, or, in the investigator's opinion, unable to deliver eye drops consistently</li> </ol> <p>Systemic:</p> <ol style="list-style-type: none"> <li>7. Clinically significant abnormalities in laboratory tests at screening</li> <li>8. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic (including sensitive skin on the face), neurological, or psychiatric disease, or any other clinically significant disease not deemed acceptable by the Investigator</li> <li>9. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days prior to the first dose of study medication, unless in the opinion of the Investigator and Medical Monitor the medication will not interfere with the study procedures or compromise subject safety</li> <li>10. A positive pre-study drug/alcohol screen</li> <li>11. Participation in any investigational study within 30 days prior to screening</li> </ol>
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	<p>12. Female participants who are pregnant, or females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control (see section 5.6). Females of childbearing potential must have a negative pregnancy test at baseline</p>
<b>Inclusion Criteria of Stage 2</b>	<p>An IRB-/IEC-approved informed consent form (ICF) must be obtained prior to any study-specific procedures being performed.</p> <p>Participants must meet the following criteria for enrollment:</p> <ol style="list-style-type: none"> <li>1. Must be 18 years of age or older at time of consent</li> <li>2. Diagnosis of pterygium with a) pterygium vascularity [REDACTED] per the Investigator's assessment using the slit-lamp and anterior segment photography confirmed by the Medical Monitor at Screening, b) pterygium size at limbus [REDACTED] hour as determined by the Investigator under slit-lamp at Screening, c) encroachment onto the cornea [REDACTED] as determined by the Investigator under slit-lamp at Screening and d) T2 (intermediate) or T3 (opaque) as determined by the Investigator under slit-lamp following pterygium morphology grading scale at Screening</li> <li>3. Best-corrected visual acuity of 20/200 or better (Snellen equivalent) in both eyes</li> <li>4. Willingness to comply with the study procedures and study drug administration and to return for all study visits</li> </ol>
<b>Exclusion Criteria of Stage 2</b>	<p>Participants meeting any of the following criteria must be excluded:</p> <p>Ophthalmic:</p> <ol style="list-style-type: none"> <li>1. Presence of ocular disease in either eye (e.g., pinguecula, corneal abnormalities, active ocular infection or inflammation, glaucoma, retina diseases, history of herpes keratitis, or ocular neoplasia) which might interfere with interpretation of the study efficacy or safety assessments</li> <li>2. Double pterygium (i.e., nasal and temporal pterygium), pterygium that requires immediate surgery or pseudo-ptyerygium (e.g., chemical or thermal burn, trauma, marginal corneal disease)</li> <li>3. History of ocular surgery (e.g., corneal transplant, glaucoma surgery, retina surgery), or other surgeries within the 3 months prior to screening with the exception of pterygium surgery</li> </ol>



	<ol style="list-style-type: none"> <li>4. Ocular trauma within 6 months prior to screening or non-invasive laser treatment within the 3 months prior to screening</li> <li>5. Use of any ocular medication in either eye within 14 days of screening and throughout the study, with the exception of a) lid scrubs (which may be used prior to, but not after, screening), b) lubricating drops for dry eye (which may be used throughout the study no more than 2 times per day and at least 10 minutes between the study drug and the lubricating eye drop)</li> <li>6. Use of contact lenses in the study eye. Contact lenses wearers must discontinue wearing at least 3 days prior to Day 1 visit and throughout the study</li> <li>7. Known hypersensitivity to benzalkonium chloride or excipients of RMP-A03 ophthalmic solution</li> <li>8. Cannot demonstrate proper delivery of eye drops, or, in the investigator's opinion, unable to deliver eye drops consistently</li> </ol> <p>Systemic:</p> <ol style="list-style-type: none"> <li>9. Clinically significant abnormalities in laboratory tests at screening</li> <li>10. Clinically significant systemic disease which may place the participant at risk or confound study results</li> <li>11. Participation in any investigational study within 30 days prior to screening</li> <li>12. Female participants who are pregnant, or females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control (see Section 5.6). Females of childbearing potential must have a negative pregnancy test at baseline</li> </ol>
<b>Duration of Treatment</b>	7 days in stage 1; 28 days in stage 2
<b>Endpoints</b>	<p>Primary Efficacy Endpoint:</p> <ul style="list-style-type: none"> <li>• Change from baseline in pterygium hyperemia grading at Day 28</li> </ul> <p>Secondary Efficacy Endpoints:</p> <ul style="list-style-type: none"> <li>• Change from baseline in pterygium characteristics at Day 28 <ul style="list-style-type: none"> <li>○ length</li> <li>○ encroachment onto the cornea</li> <li>○ size at limbus</li> </ul> </li> </ul>



	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Incidence of AEs</li> </ul>
<b>Assessments</b>	<p>Efficacy:</p> <ul style="list-style-type: none"> <li>• Pterygium vascularity and size assessment</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events (AEs)</li> <li>• Bested corrected distance visual acuity (BCDVA)</li> <li>• Intraocular pressure (IOP)</li> <li>• Slit lamp biomicroscopy</li> <li>• Indirect Ophthalmoscopy</li> <li>• Ocular symptoms questionnaire</li> <li>• Laboratory assessments</li> <li>• Heart rate and blood pressure</li> <li>• Physical examinations</li> </ul>
<b>Sample Size</b>	<p>Stage 1 of this first-in-human study is to collect preliminary information in humans and therefore, no formal sample size calculations have been performed.</p> <p>In Stage 1, up to 5 subjects will be treated in each dose cohort for a total of 20 subjects.</p> <p>In Stage 2, approximately 25 subjects will be treated in each treatment arm for a total of 75 subjects.</p>
<b>Statistical Considerations</b>	Analysis Populations/Sets



For Stage 1 and Stage 2, the safety population/set will include all subjects who receive at least 1 dose of investigational product.

For Stage 2:

- Intent-to-Treat (ITT): The ITT set will include all randomized subjects.
- Modified Intent-to-Treat (mITT): The mITT set will include all randomized subjects who receive at least 1 dose of investigation product and have at least one post-dose primary efficacy assessment.
- Per Protocol (PP): The PP set will include subjects in the mITT who do not have significant protocol deviations that affect the primary endpoint analysis. Protocol deviations will be assessed prior to database lock and unmasking.

All efficacy and safety data will be summarized using descriptive statistics and graphically, by treatment group. In general, quantitative/continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum and maximum and qualitative/categorical variables will be summarized using frequencies (n) and percentages (%).

For Stage 2, the primary null hypothesis is that there is no difference among the three treatment arms in the change from baseline in pterygium hyperemia grading at Day 28. The alternative hypothesis is that there is a difference. The primary endpoint of change from baseline in pterygium hyperemia grading at Day 28 will be analyzed by a mixed-effects model with repeated measures (MMRM) using all the data collected post-baseline for the mITT Population. Each dose will be compared with the placebo arm at a 0.05 significance level. The least squares mean (LSM) for each treatment arm will be calculated together with its 95% confidence interval. In addition, the difference between each active treatment and the placebo will also be calculated together with its 95% confidence interval.

The secondary efficacy endpoints will be analyzed similarly as the primary endpoint.

#### Justification of the Sample Size

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



	<p>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 of approximately 0.7 for all the three treatment arms.</p> <p>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.</p>
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**Table 1-1: Schedule of Visits and procedures in Stage 1**

Procedures	Screening Day -60 to -1 (Visit 1)	Baseline Day 1 (Visit 2)	Post-dose Day 1 (Visit 3)	Follow-up/Exit <sup>1</sup> 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
Heart Rate and Blood pressure	X	X	X	X
Urine Pregnancy Test <sup>2</sup>	X	X		X
Clinical Labs	X			X
Adverse Events <sup>3</sup>		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
Eye Drop Instillation Evaluation <sup>6</sup>	X			
Study Drug Administration		X <sup>4</sup>		
Study Drug Dispensing			X	
Study Drug Accountability				X <sup>5</sup>

Abbreviations: SE= Study eye

<sup>1</sup> Every effort should be made to complete all Exit procedures at Early Termination<sup>2</sup> A negative result on a urine pregnancy test before administration of study drug for women of childbearing potential is required for eligibility<sup>3</sup> AEs should be assessed before and after administration of study drug<sup>4</sup> First dose to be administered by the study subject at Day 1. The study staff will observe the IP instillation<sup>5</sup> Collect dispensed kit at Exit visit<sup>6</sup> Study staff must confirm the subject can demonstrate proper delivery of eye drops prior to advancing to the Baseline/Day 1 visit. It should not be confused with the study staff observation of subjects' first dose of IP performed at the Baseline/Day 1, Visit 2

**Table 1-2: Schedule of Visits and procedures in 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 <sup>1</sup> (Visit 4)	Follow-up Day 28±3 days  (Visit 5)	Follow-up Day 56±4 days  (Visit 6)	Follow-up/ Exit <sup>2</sup> 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
Heart Rate and Blood Pressure	X	X	X		X	X	X
Urine Pregnancy Test <sup>3</sup>	X	X					X
Clinical Labs	X						X
Adverse Events <sup>4</sup>		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	SE	SE		SE	SE	SE
Pterygium Assessments	X	SE	SE		SE	SE	SE
Slit Lamp Biomicroscopy	X	X	X		X	X	X
Indirect Ophthalmoscopy	X	X	X		X	X	X
Eye Drop Instillation Evaluation <sup>7</sup>	X						
Study Drug Administration		X <sup>5</sup>					
Study Drug Dispensing		X					
Study Drug Accountability					X <sup>6</sup>		

Abbreviations: SE= Study eye

<sup>1</sup> 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

<sup>2</sup> Every effort should be made to complete all Exit procedures at Early Termination



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

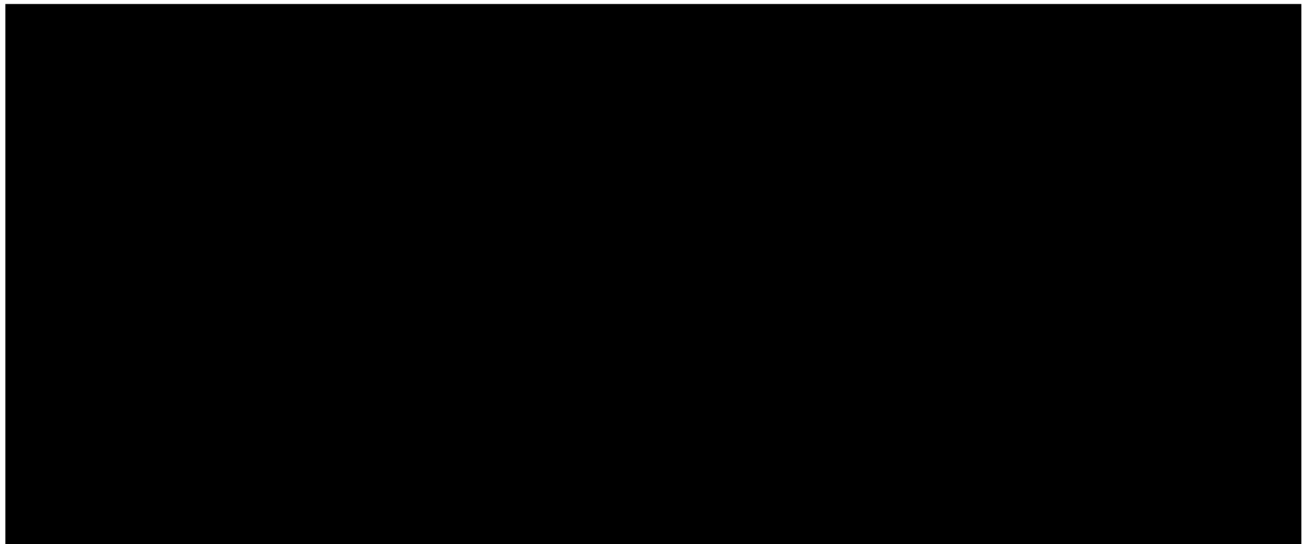
<sup>4</sup> AEs should be assessed before and after administration of study drug

<sup>5</sup> First dose to be administered by the study subject at Day 1. The study staff will observe the IP instillation

<sup>6</sup> Collect dispensed kit at Visit 5

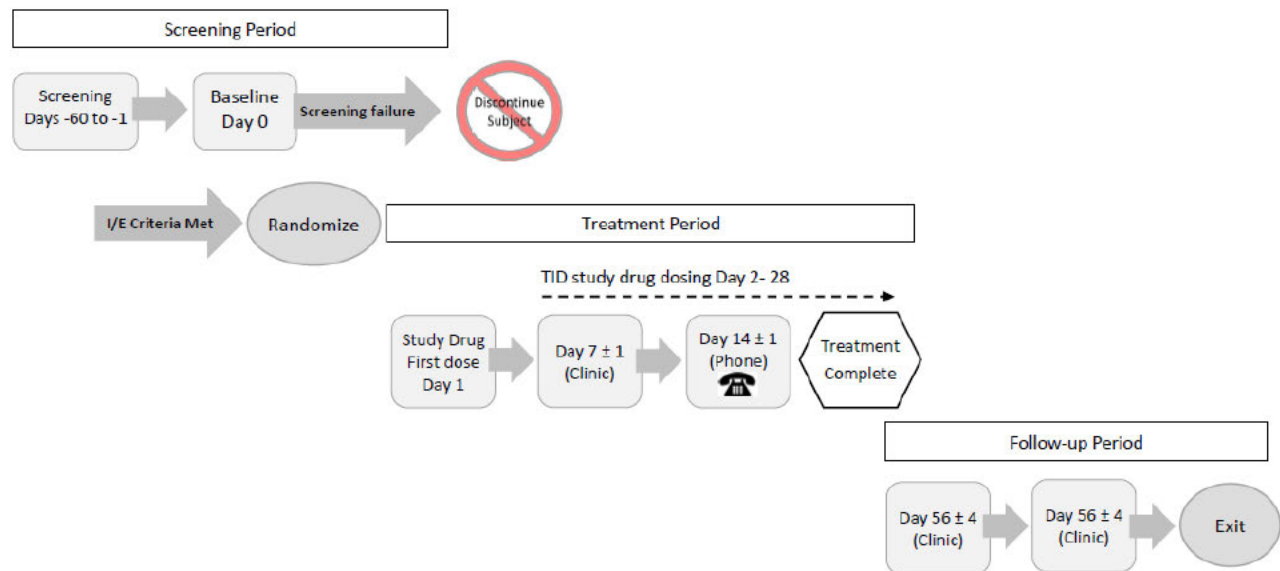
<sup>7</sup> Study staff must confirm the subject can demonstrate proper delivery of eye drops prior to advancing to the Baseline/Day 1 visit. It should not be confused with the study staff observation of subjects' first dose of IP performed at the Baseline/Day 1, Visit 2

**Figure 1: Study Flowchart**



Upon DMC Review of Stage 1 Safety Data and Determination Maximum Tolerated Dose:

## Stage 2





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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

**Table 0-1: Abbreviations and Specialist Terms**

Abbreviation	Definition
AE	adverse event
BCDVA	best corrected distance visual acuity
C <sub>max</sub>	maximum concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CYP Enzymes	cytochrome P450 oxidase
EPHA2	ephrin type-A receptor 2
ETDRS	early treatment diabetic retinopathy study
FGF	fibroblast growth factor
GCP	good clinical practice
GLP	good laboratory practice
hERG	human ether-à-go-go-related gene
HUVEC	human umbilical vein endothelial cell
ICF	informed consent form
IND	investigational new drug
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat
KDR	kinase insert domain receptor
MOP	manual of procedure
MedDRA	medical dictionary for regulatory activity
mg	milligram
mITT	modified intention-to-treat
mL	milliliter



Abbreviation	Definition
mmHg	millimeters mercury
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
OD	right eye
OS	left eye
PDGF	platelet derived growth factor
PK	pharmacokinetic(s)
QA	quality assurance
QC	quality control
TID	three times daily
SAE	serious adverse event
SOP	standard operating procedure
$t_{1/2}$	Half-life
TEAE	treatment emergent adverse event
TK	toxicokinetic
$T_{max}$	time to maximum concentration
TMF	trial master file
$\mu m$	micrometer
WHODD	world health organization drug dictionary
WOCBP	women of childbearing potential



## 2. BACKGROUND

### 2.1. BACKGROUND ON PTERYGIUM

Pterygium is a progressive ocular surface disease presenting as a wing-shape fold of fibrovascular tissue arising from the interpalpebral conjunctiva and extending onto the cornea. The estimated worldwide prevalence of pterygium is 12% ([Rezvan 2018](#)). In certain regions and ethnic groups, the prevalence was reported to be much higher, varying from 23.4% in Barbados study to 39% in Yunnan Minority Eye Study ([Luthra 2001, Zhong 2012](#)). Risk factors associated with the development and progression of pterygium include ultraviolet light exposure, age, gender, residence, level of education, and smoking ([Bradley 2010, Mackenzie 1992, Pyo 2016](#)).

Symptoms of pterygium in early stage include ocular irritation, redness and blurry vision. As the disease progresses, patients may experience visual disturbance or decreased vision due to pterygium induced astigmatism or encroachment onto the visual axis. Management of pterygium includes protecting the eyes from sun, dust, and wind, using artificial tears, prescribing anti-inflammation eye drops, or surgical removal if the lesion becomes cosmetically unpleasant or causes visual symptoms.

Currently, there are no FDA-approved medicinal treatments for pterygium. Therefore, there is a significant unmet medical need for the treatment of Pterygium.

### 2.2. INVESTIGATIONAL PRODUCT

While the etiology and pathogenesis of pterygium are not fully understood, studies have shown that the pathological changes in pterygium have involved fibroblastic proliferation, angiogenesis and inflammation. Elevation of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF) levels have been observed in pterygia tissue ([Aspiotis 2007, Bianchi 2012, Cox 2010, Lee 2001, Kria 1996, Kria 1998, van Setten 2003, Mai 2019, Lieu 2011, Wanzeler 2019](#)), which suggested that anti-VEGF or anti-fibrosis therapy may potentially be efficacious in the treatment of pterygium.

RMP-A03 [REDACTED] that is being developed by Suzhou Raymon Pharmaceuticals as a novel therapeutic agent in the treatment of pterygium.

[REDACTED]

[REDACTED]

## 2.3.SUMMARY OF RELEVANT DATA

A comprehensive panel of nonclinical studies have been conducted to evaluate the efficacy and safety of RMP-A03 to support the initiation of the first-in-human clinical trial. A brief summary of the information from nonclinical studies is presented below.

The pharmacology studies included the kinase inhibition of RMP-A03 at the molecular and cellular level, and the potential therapeutic effects of RMP-A03 on [REDACTED]

The nonclinical pharmacokinetic studies including absorption, distribution, metabolism and drug-drug interaction of RMP-A03 were evaluated in vitro and in preclinical species. [REDACTED]

[REDACTED] Following ocular instillation, the systemic exposure of RMP-A03 was negligible.

The toxicity of RMP-A03 was evaluated in single-dose (iv) and up to 28-day (ocular) repeat-dose GLP-compliant toxicity studies with the maximally formulatable concentration [REDACTED]. Measurable but extremely low systemic exposure was detected after ocular dosing. No test article-related untoward ocular effects or systemic toxicity were observed [REDACTED].

In summary, nonclinical studies performed to date have demonstrated an acceptable safety profile of RMP-A03 to initiate the IND opening clinical trial. Please refer to the Investigator's Brochure for detailed nonclinical study design and results.

## 2.4.RISKS AND BENEFITS TO HUMAN SUBJECTS

RMP-A03 is a new investigational drug and this study is the first-in-human clinical trial of RMP-A03. The risks associated with RPM-A03 are not well understood at this time.

Since there is no approved treatment for pterygium at this time point, if efficacious, RMP-A03 may slow down the progression of pterygium in clinical trial patients.

## 3. STUDY OBJECTIVES

Primary objective(s):

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

Secondary objective(s):

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

## 4. INVESTIGATIONAL PLAN

### 4.1. 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 designation of study eye in Section 4.1.1).

**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 by the SC and upon confirmation of no safety concerns.

**Note, intrasubject escalation will not be permitted.**

**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).

#### **4.1.1. 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.

#### **4.2.SAFETY COMMITTEE AND STOPPING RULES**

An SC will be assembled to provide assessment of safety data during the study. An essential component of risk management in early phase clinical trials is implementation of stopping rules to ensure the safety of study participants.

Stopping Rules will be considered during the safety review if any of the following events are reported:

- Worsening of BCDVA of  $\geq 3$  lines in the study eye, deemed as related to study drug in  $>2$  subjects
- IOP increase to  $> 27$  mmHg that cannot be controlled by medication, deemed as related to study drug in  $>2$  subjects
- Ocular inflammation  $>$  grade +2, deemed as related to the study drug in  $>2$  subjects
- Corneal edema worsening by  $> 2$  grades, deemed as related to the study drug in  $>2$  subjects
- Any other serious ocular or systemic adverse event that, in the opinion of the Investigators, is related to the study drug in  $> 2$  subjects

All available safety data for the cohort will be reviewed by the SC to evaluate feasibility of further dosing of the study drug, and/or the safety of dose escalation. Recommendations by the SC may result in amendment of the study design or discontinuation of a dose cohort, or the clinical trial.

#### **4.3.SCIENTIFIC RATIONAL FOR STUDY DESIGN**

The small sample size, single-arm, open-label, follow-up period is a common and acceptable study design for first-in-human studies. The sequential dose escalation allows for risk mitigation before exposing additional participants to subtherapeutic doses.

The randomized, doubled-masked, placebo-controlled methodology of the Stage 2 portion of the trial is optimal on clinical trials to reduce bias and provide reliable safety and efficacy information.

Stopping rules are implemented to minimize the risk to study participants.

#### 4.4.DOSING RATIONALE

The clinical doses, treatment period, and dosing regimen were selected based on preclinical data.

██████████ are selected as toxicological species for the GLP ocular toxicity studies of RMP-A03 based on comparable human eye size and anatomical structure. Toxicology studies indicated that no local and systemic toxicity of RMP-A03 were observed after 28-day ocular administrations in ██████████. Following RMP-A03 treatment at ██████████, for 28 continuous days, the NOAEL was defined as ██████████ in both studies. The corresponding systemic exposure of ██████████ ocular instillation was approximately ██████████, which was more than ██████████ lower than the  $C_{max}$  at NOAEL in 28 days iv repeated dosing.

Considering the totality of the nonclinical data, a first-in human (FIH) starting dose of ██████████ proposed. As RMP-A03 did not induce ocular toxicity in ██████████ in the 28-day ocular toxicity studies, nonclinical data support the maximum dose of ██████████.

#### 4.5.RANDOMIZATION

Randomization will be implemented in Stage 2. Consented subjects who meet all enrollment criteria will be randomly assigned to receive 1 of 3 treatments (RMP-A03 Dose 1, RMP-A03 Dose 2 or vehicle) in a 1:1:1 ratio. Randomization schedule will be optimized to achieve a balanced distribution of treatment assignment by baseline ██████████.

#### 4.6.MASKING

In Stage 2, 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.

If there is a need to unmask the study drug assignment for a subject, the Principal Investigator must notify the Sponsor's Medical Monitor prior to unmasking of the study drug. Refer to Section 10.7 for a description of emergency unmasking procedures.



The reason for unmasking must be documented in the source document for the subject. If a subject's study drug assignment is unmasked, the subject should remain in the study and continue the protocol-specified safety follow-up evaluations.

## **5. SELECTION AND WITHDRAWAL OF SUBJECTS**

### **5.1.INCLUSION CRITERIA OF STAGE 1**

Participants must meet all of the following criteria for enrollment in Stage 1:

1. Must be 18 years of age or older at time of consent
2. Healthy as determined by a physician, based on a medical evaluation including medical history, physical examination, and laboratory tests
3. Best-corrected visual acuity of 20/40 or better (Snellen equivalent) in both eyes
4. Willingness to comply with the study procedures and study drug administration and to return for all study visits

### **5.2.EXCLUSION CRITERIA OF STAGE 1**

Subjects meeting one or more of the following criteria must be excluded from the Stage 1:

Ophthalmic:

1. History or current eye disease other than refractive error, incipient cataract, strabismic amblyopia, or anisometropic amblyopia that might interfere with interpretation of the safety
2. History of ocular surgery within the 3 months prior to screening
3. Use of any ocular medication in either eye within 14 days of screening and throughout the study, with the exception of a) lid scrubs (which may be used prior to, but not after, screening), b) lubricating drops for dry eye (which may be used throughout the study no more than 2 times per day and at least 10 minutes between the study eye drop and the lubricating eye drop)
4. Use of contact lenses in the study eye. Contact lenses wearers must discontinue wearing at least 3 days prior to Day 1 visit and throughout the study
5. Known hypersensitivity to benzalkonium chloride or excipients of RMP-A03 ophthalmic solution
6. Cannot demonstrate proper delivery of the eye drop, or, in the investigator's opinion, unable to deliver the eye drop consistently

Systemic:

7. Clinically significant abnormalities in laboratory tests at screening
8. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic (including



sensitive skin on the face), neurological, or psychiatric disease, or any other clinically significant disease not deemed acceptable by the Investigator

9. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days prior to the first dose of study medication, unless in the opinion of the Investigator and Medical Monitor the medication will not interfere with the study procedures or compromise subject safety
10. A positive pre-study drug/alcohol screen
11. Participation in any investigational study within 30 days prior to screening
12. Female participants who are pregnant, or females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control (see Section 5.6). Females of childbearing potential must have a negative pregnancy test at baseline

### 5.3.INCLUSION CRITERIA OF STAGE 2

Participants must meet all of the following criteria for enrollment in Stage 2:

1. Must be 18 years of age or older at time of consent
2. Diagnosis of pterygium with a) pterygium vascularity [REDACTED] per the Investigator's assessment using the slit-lamp and the anterior segment photography confirmed by the Medical Monitor at Screening, b) pterygium size at limbus [REDACTED] as determined by the Investigator under slit-lamp at Screening, c) encroachment onto the cornea [REDACTED] as determined by the Investigator under slit-lamp at Screening and d) T2 (intermediate) or T3 (opaque) as determined by the Investigator under slit-lamp following pterygium morphology grading scale at Screening
3. Best-corrected visual acuity of 20/200 or better (Snellen equivalent) in both eyes
4. Willingness to comply with the study procedures and study drug administration and to return for all study visits

### 5.4.EXCLUSION CRITERIA OF STAGE 2

Subjects meeting one or more of the following criteria must be excluded from the Stage 2:

#### Ophthalmic:

1. Presence of ocular disease in either eye (e.g., pinguecula, corneal abnormalities, active ocular infection or inflammation, glaucoma, retina diseases, history of herpes keratitis, or ocular neoplasia) which might interfere with interpretation of the study efficacy or safety assessments
2. Double pterygium (i.e., nasal and temporal pterygium), pterygium that requires immediate surgery or pseudo-ptyerygium (e.g., chemical or thermal burn, trauma, marginal corneal disease)



3. History of ocular surgery (e.g., corneal transplant, glaucoma surgery, retina surgery) or other ocular surgeries within the 3 months prior to screening with the exception of pterygium surgery
4. Ocular trauma within 6 months prior to screening or non-invasive laser treatment within the 3 months prior to screening
5. Use of any ocular medication in either eye within 14 days of screening and throughout the study, with the exception of a) lid scrubs (which may be used prior to, but not after, screening), b) lubricating drops for dry eye (which may be used throughout the study no more than 2 times per day and at least 10 minutes between the study eye drop and the lubricating eye drop)
6. Use of contact lenses in the study eye. Contact lenses wearers must discontinue wearing at least 3 days prior to Day 1 visit and throughout the study
7. Known hypersensitivity to benzalkonium chloride or excipients of RMP-A03 ophthalmic solution
8. Cannot demonstrate proper delivery of the eye drop, or, in the investigator's opinion, unable to deliver the eye drop consistently

Systemic:

9. Clinically significant abnormalities in laboratory tests at screening
10. Clinically significant systemic disease which may place the participant at risk or confound study results
11. Participation in any investigational study within 30 days prior to screening
12. Female participants who are pregnant, or females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control (see Section 5.6). Females of childbearing potential must have a negative pregnancy test at baseline

## 5.5. WITHDRAWAL

### 5.5.1. WITHDRAWAL CRITERIA

Subjects may choose to withdraw from the study at any time for any reason. In addition, subjects may be withdrawn from the study by the Investigator for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol.
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor.



### 5.5.2. WITHDRAWAL PROCEDURES

- If it is necessary for a subject to discontinue the study drug/study earlier than planned, subjects should complete Early Termination procedures (see [Table 1-1](#) and [Table 1-2](#)) and return the study drug, as applicable. Date of last dose should be recorded.
- The Investigator must notify the Sponsor and the Medical Monitor within 24 hours when a subject has been withdrawn from the study. Any subject withdrawn because of a related AE (whether serious or non-serious), including clinically significant abnormal laboratory test values, will be evaluated by the Investigator or a designee and be treated and/or followed until the symptoms resolve or values return to normal or acceptable levels, as judged by the Investigator.
- If a subject does not return for a scheduled visit, every effort should be made to contact the subject. If a subject withdraws from the study, the Investigator or designee should inquire about the reason for withdrawal, and follow-up with the subject by phone as scheduled to collect AE information.
- If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent; these data will be included in the safety database.

### 5.5.3. DOCUMENTATION OF WITHDRAWAL

The reason(s) for withdrawal from the study drug/study must be recorded in the subject's medical record and case report forms (CRF).

### 5.5.4. REPLACEMENT OF SUBJECTS

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

### 5.5.5. TERMINATION OF STUDY BY SPONSOR

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical consideration, administrative reasons, or if required by the FDA or other regulatory authorities. Additionally, the study may be suspended as per the recommendations of the SC at any time for safety concerns.

## 5.6. PREGNANCY

Pregnant women are not eligible for inclusion in the study. Before enrolling WOCBP in this clinical trial, Investigators must advise WOCBP of the importance of avoiding pregnancy during



trial participation and the potential risk factors for an unintentional pregnancy. WOCBP must agree to use a medically acceptable and effective barrier method of contraception prior to study entry, for the duration of study, and for a period of at least 30 days after all study procedures are completed. Male subjects must also agree to use an accepted method of contraception for the duration of the study and for a period of at least 30 days after all study procedures are completed. This should be discussed with study participants during the informed consent process.

Acceptable forms of birth control include condoms plus intrauterine devices or condoms plus oral hormonal contraceptives, double barrier methods (e.g., condoms with spermicidal gel plus diaphragms). A post-pubescent female participant is considered to be of childbearing potential unless she is 1 year post-menopausal or 3 months post-surgical sterilization. All WOCBP must have a negative urine pregnancy test result at baseline prior to administration of study drug.

## 6. IDENTITY OF INVESTIGATIONAL PRODUCT

RMP-A03 ophthalmic suspension is a [REDACTED] suspension containing [REDACTED]

RMP-A03 ophthalmic suspension placebo is a [REDACTED] suspension containing [REDACTED]

### 6.1. PACKAGING AND LABELING OF CLINICAL SUPPLIES

RMP-A03 ophthalmic suspension and RMP-A03 ophthalmic suspension vehicle will be packaged [REDACTED] ophthalmic bottle. The bottles will be packaged in cartons in a format appropriate for the study. Each package will be labeled with an investigational label with the information required per regulatory requirement.

### 6.2. STORAGE OF CLINICAL SUPPLIES

The study drug will be stored as directed on the drug label in a secure area under the appropriate physical conditions for the product. Access to the study treatment will be limited to authorized site staff only. The temperature of the study treatment storage location at the site is to be monitored using a calibrated monitoring device and documented.

At time of dispensing, the subject will be instructed to store the bottle(s) as directed on the drug label.



### **6.3.STUDY DRUG DISPENSATION**

Study drug will be dispensed to the subject at the clinic, at the end of Day 1 during both Stage 1 and Stage 2 portions of the study.

### **6.4.DRUG ACCOUNTABILITY**

Subjects will be asked to return the used and unused study drug containers to the study site. It is the responsibility of the Investigator or his/her designee to maintain drug accountability at the clinical trial site and ensure that a current record of investigational product disposition is maintained. It is the responsibility of the Investigator or his/her designee to ensure that the investigational product is used only in accordance with the approved protocol. All records or logs must comply with applicable regulations and guidelines. The Sponsor will provide forms to facilitate accountability if the staff at the investigational site does not have an established system that meets these requirements.

## **7. STUDY DRUGS AND OTHER MEDICATIONS**

### **7.1.STUDY DRUG ADMINISTRATION**

The first dose of study drug will be administered at the clinic by study subjects during both Stage 1 and Stage 2 portions of the study. Study staff will observe the IP instillation. Subjects will self-administer the study drug 3 times a day (at least 3 hours apart) starting with Day 2 and until the last day of treatment for each stage of the study.

### **7.2.PRIOR AND CONCOMITANT MEDICATIONS**

The use of any ocular medication in either eye, are prohibited within 14 days of screening and throughout the study. In stage 1, use of prescription or non-prescription systemic drugs, including vitamins, herbal and dietary supplements are prohibited within 7 days prior to the first dose of study medication and throughout the study. In Stage 2, stable, ongoing systemic therapies will be permitted during the study given that the dose and regimen of the medication can remain consistent throughout the study. Any drug therapy initiated during the study should be discussed with the Medical Monitor prior to administration, if possible. Data on concomitant medications will be collected at each visit.

### **7.3.STUDY MEDICATION ADHERENCE**

Study sites will instruct subjects of the dosing requirements and proper dosing procedures prior to dispensing. In Stage 2, adherence will be assessed at each follow-up visit by asking the subject about any missed doses. Additionally, study staff will contact each subject on a scheduled telephone study visit on Day 14 to monitor the adherence. If the subject reports missing more



than 4 doses since the prior visit, the subject will be counseled on IP adherence. The subject will be given instructions on how to return any unused study drug/containers to the site.

## **8. EFFICACY ENDPOINTS, SAFETY, PHARMACOKINETIC, AND OTHER ASSESSMENTS**

### **8.1.EFFICACY ENDPOINTS**

Primary Efficacy in Stage 2:

- Change from baseline in pterygium hyperemia grading at Day 28

Secondary Efficacy in Stage 2:

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

[REDACTED]

■

[REDACTED]

■

[REDACTED]

■

[REDACTED]

■

[REDACTED]

### **8.2.OPHTHALMIC EXAMINATIONS**

#### **8.2.1. BEST-CORRECTED DISTANCE VISUAL ACUITY**

BCDVA will be measured on each eye starting at Screening and at all attended visits, using an early treatment diabetic retinopathy study (ETDRS) chart, with the use of standardized manifest refraction and testing protocol as described in the Manual of Procedures (MOP). BCDVA evaluation should precede a study procedure that requires contact with the eye or administration of eye drops.

#### **8.2.2. INTRAOCULAR PRESSURE**

IOP will be measured on each eye at Screening and at all other attended visits prior to pupil dilation. The same type of tonometer should be used throughout the study for the same subject.

### **8.2.3. SLIT-LAMP EXAMINATION**

Slit lamp examination will be performed on each eye starting at Screening and at all other attended visits. Assessment of the eyelids, conjunctiva, cornea, anterior chamber, iris, lens, and pterygium (Stage 2) will be documented.

### **8.2.4. DILATED FUNDUS EXAMINATION**

A dilated fundus examination will be performed on each eye at Screening at all other attended visits to assess change from baseline. Assessments of the vitreous, retina, macula, choroid, optic nerve, and cup/disc ratio will be documented.

## **8.3. OCULAR IMAGING AND OTHER EXAMINATIONS**

### **8.3.1. PTERYGIUM PHOTOGRAPHY**

Pterygium photography of the study eye will be obtained at Screening and all attended on-site visits until study exit.

## **8.4. SAFETY**

Safety assessments include AEs, physical and ophthalmic examinations, heart rate and blood pressure, and clinical laboratory tests. Safety signals must be promptly communicated to the Medical Monitor.

### **8.4.1. ADVERSE EVENTS**

Qualified study staff responsible for assessing adverse events (AEs) will be listed on the Delegation of Responsibilities Log. This includes assessment of AE severity and relationship to study medication. Adverse event information may be volunteered by the subject or solicited by study personnel through non-leading questions.

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF. Documentation of AEs/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome (See Section 10).

### **8.4.2. PHYSICAL EXAMINATION**

Complete physical examinations will be conducted in Stage 1 at Screening, and all attended visits until study exit. Physical examinations will include weight and height measurements, as well as HEENT, respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, neurological, blood/lymphatic, musculoskeletal, hepatic, allergies and psychological/psychiatric examinations.



### 8.4.3. VITAL SIGNS

Systolic and diastolic blood pressure and heart rate will be measured at Screening/Baseline and each attended visit. All measurements should be performed in the supine/semi-supine or seated position after the subject has rested in that position for at least 3 minutes. Blood pressure will be obtained with an automated or manual blood pressure apparatus in the same position. Blood pressure and pulse should be performed on the same extremity throughout the study and documented as such.

### 8.4.4. CLINICAL LABORATORY TESTS

The following clinical laboratory tests will be performed at Screening and Day 7 during Stage 1 and at Screening and Day 84 (Exit visit)/or Early Exit during Stage 2. Fasting is required prior to specimen collection during Stage 1.

- Complete blood count: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, mean platelet volume, platelet count, red blood cell count, and white blood cell count with differential (absolute).
- Clinical chemistry: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, amylase, lipase, calcium, magnesium, glucose, sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, and creatinine.
- Urinalysis: dipstick test and a microscopic examination if clinically indicated.

## 9. STATISTICAL METHODS AND DATA ANALYSES

### 9.1. GENERAL CONSIDERATION

A detailed SAP will be developed and finalized prior to the final database lock. Any deviations from the originally planned statistical analysis or SAP will be described and justified in the clinical study report. All statistical processing will be performed using the most current version of SAS® at the time of the analysis. Data listings will be provided for all baseline variables collected (subject disposition, all demographic and baseline characteristics, prior and concomitant medications, and study drug compliance), all efficacy outcomes, and all safety outcomes (deaths, AEs, clinical laboratory values, vital signs, physical examination). Individual data will be listed and sorted by treatment, subject ID, visit, and time point.

Summary statistics for continuous measurements will be reported using the number of study subjects with data values, mean, median, standard deviation (SD), minimum, and maximum. For continuous efficacy outcomes 95% confidence intervals will be provided.

Summary statistics for categorical variables will be reported using the number and percentage of study subjects within each level of the variable.



Medical history, concurrent therapies, and adverse events will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

Baseline is defined as the last non-missing measurement prior to the initiation of investigational product. Change from baseline will be calculated as Visit – Baseline. Baseline measures are defined as the last non-missing measure prior to the initiation of investigational product. Change from baseline will be calculated as Visit – Baseline. All primary and secondary analyses will be two-sided at a significance level of 0.10.

## **9.2.ANALYSIS POPULATIONS/SETS**

For Stage 1 and Stage 2, the safety population/set will include all subjects who receive at least 1 dose of investigational product.

For Stage 2:

- Intent-to-Treat (ITT): The ITT set will include all randomized subjects.
- Modified Intent-to-Treat (mITT): The mITT set will include all randomized subjects who receive at least 1 dose of investigation product and have at least one post-dose primary efficacy assessment.
- Per Protocol (PP): The PP set will include subjects in the mITT who do not have significant protocol deviations that affect the primary endpoint analysis. Protocol deviations will be assessed prior to database lock and unmasking.

## **9.3.UNIT OF ANALYSIS**

For efficacy endpoints measured at the eye level, the unit of analysis will be the “study eye” as defined in Section 4.1.1. Additional efficacy analyses may be presented for qualifying fellow eyes. Safety endpoints measured at the eye level will be presented by study eye and fellow eye. Ocular adverse events (AE) will be presented at the subject level if the AE occurred in either eye.

## **9.4.STATISTICAL HYPOTHESES**

For Stage 2, the primary null hypothesis is that there is no difference among the three treatment arms in the change from baseline in pterygium hyperemia grading at Day 28. The alternative hypothesis is that there is difference.

The secondary efficacy endpoints will be analyzed similarly as the primary endpoint.

## **9.5.JUSTIFICATION OF SAMPLE SIZE**

Stage 1 is a first-in-human study of the investigative product to collect preliminary information and there is no formal sample size calculation. In Stage 1, 5 subjects will be treated in each dose cohort for a total of 20 subjects.

In Stage 2, approximately 25 subjects will be treated in each treatment arm for a total of 75 subjects. 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 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 of approximately 0.7 for all the 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.

## **9.6.MISSING DATA HANDLING**

Missing data may be imputed. Details will be defined in the SAP.

## **9.7.INTERIM ANALYSES**

No interim analyses are planned in this study.

## **9.8.EFFICACY ANALYSIS**

### **9.8.1. PRIMARY EFFICACY ANALYSES**

The primary efficacy endpoint will evaluate change from baseline in pterygium hyperemia grading at Day 28. Summaries of pterygium hyperemia grading will be provided by visit and by treatment group. The primary endpoint of change from baseline in pterygium hyperemia grading at Day 28 will be analyzed by a mixed-effects model with repeated measures (MMRM) using all the data collected post-baseline for the mITT Population. The MMRM model will include model terms treatment, visit, treatment-by-visit interaction, baseline pterygium grading, and baseline pterygium hyperemia grading category used for stratification [REDACTED]. Each dose will be compared with the placebo arm at the 0.05 significance level at each visit. The least squares mean (LSM) for each treatment arm will be calculated together with its 95% confidence interval. In addition, the difference between each active treatment and the placebo will also be calculated together with its 95% confidence interval.

### **9.8.2. SECONDARY EFFICACY ANALYSES**

The secondary efficacy endpoint will evaluate change from baseline in pterygium characteristics on day 28 as defined by pterygium length, encroachment onto the cornea, and size at limbus.

Summaries of pterygium width, length, and area will be provided by visit and by treatment group. The secondary endpoint will be analyzed in the same manner as for the primary endpoint.



#### **9.8.4. SAFETY ANALYSES**

All untoward physical findings/laboratory results identified prior to initiation of study drug will be reported on the medical history and/or physical examination CRFs. After initiation of study drug, any clinically significant changes in physical findings/laboratory results or any new physical findings/laboratory results will be evaluated for AEs.

All safety endpoints including AEs, visual acuity, intraocular pressure, slit lamp biomicroscopy, dilated fundus exam, laboratory evaluations, and vital signs will be summarized by treatment group and visit using continuous and categorical summary statistics as appropriate. Changes or shifts from Baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. If necessary, the safety data will be summarized by study eye and fellow eye separately.

Full details of the safety analyses will be specified in the study SAP.

### **10. ADVERSE EVENTS**

#### **10.1. ADVERSE EVENT DEFINITIONS**

##### **10.1.1. ADVERSE EVENT**

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

AEs will be coded using the medical dictionary for regulatory activities (MedDRA). Frequencies and percentages of AEs will be summarized at the subject level by system organ class (SOC) and preferred term (PT). An AE is treatment emergent (TEAE) if it occurs or worsens after the first dose of study medication. Similar summaries will be presented for all TEAEs. Separate summaries will be performed for ocular and non-ocular AEs.

##### **10.1.2. LIFE-THREATENING ADVERSE EVENT OR LIFE-THREATENING SUSPECTED ADVERSE REACTION**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not

include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **10.1.3. SERIOUS ADVERSE EVENT OR SERIOUS SUSPECTED ADVERSE REACTION**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE - see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **10.1.4. UNEXPECTED ADVERSE EVENT OR UNEXPECTED SUSPECTED ADVERSE REACTION**

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure listed only cerebral vascular accidents. “Unexpected” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.



## 10.2. ADVERSE EVENT CLASSIFICATION

### 10.2.1. RELATIONSHIP TO INVESTIGATIONAL DRUG

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether or not there exists a reasonable possibility that the study drug caused or contributed to an AE, as described below:

- **Not Related:** The event is clearly related to other factors such as subject's clinical condition; therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.
- **Unlikely Related:** The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.
- **Possibly Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.
- **Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

### 10.2.2. SEVERITY

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

<b>Grade 1</b>	Mild	Present and noticeable, but not distressing, and no disruption of normal daily activities
<b>Grade 2</b>	Moderate	Bothersome, discomfort sufficient to possibly reduce or affect normal daily activity
<b>Grade 3</b>	Severe	Incapacitating, with inability to work or perform normal daily activity



A change in severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from severe to moderate. In either case, the start and stop dates should be recorded.

**Note:** a severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligation

### **10.3. EXPOSURE IN UTERO**

Subjects will be instructed to notify the Investigator if they or their partner becomes pregnant during the study. The Investigator must notify the Sponsor within 24 hours via telephone or e-mail and must complete the Pregnancy Notification Form and submit it to the Sponsor within 2 working days of being notified. The Investigator should obtain informed consent/assent from the subject or subject's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the subject or subject's partner provides informed consent/assent, the Investigator should follow the pregnancy until outcome. A final Pregnancy Notification Form should be completed when the outcome of the pregnancy is known.

### **10.4. MONITORING OF ADVERSE EVENT DATA**

The Investigator and the Sponsor or its representative will be responsible for the following:

- Reviewing AE data on an ongoing basis throughout the study. Should any AE report suggest that an unexpected Grade 3 or higher, and probably or definite study drug-related occur, the Investigator and Sponsor will take prompt and appropriate action to protect subject safety. These actions may range from no action (proceed with the study) to halting the study for safety reasons. The evaluation and action decided upon will be documented.
- Assessing the safety data and providing recommendations if the Sponsor should stop or modify the study.

### **10.5. DOCUMENTATION OF ADVERSE EVENTS BY INVESTIGATOR**

Subjects will be evaluated and questioned generally to identify AEs during the course of the study. Any events occurring prior to administration of the first dose will be recorded on the Adverse Event CRF as pre-treatment adverse event. Events occurring after administration of the first dose of study drug will be recorded on the Adverse Event CRF as TEAE.

Record all AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures on the Adverse Event Form for that visit. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on



the Adverse Event Form. In addition, an abnormal test finding must be classified as an AE if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE)
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an AE by the Investigator

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus rather than hyperglycemia).

For SAEs, a Serious Adverse Event Form must also be completed with as much information as possible and submitted within 24 hours of the investigator's knowledge of the SAE. When new significant information is obtained as well as when the outcome of an event become known, the Investigator should record the information on a new Serious Adverse Event Form, indicating that it is a follow-up report. If the subject was hospitalized, a copy of the discharge summary and any other relevant hospital records (e.g., admission report, laboratory test results) must be included as part of the subject medical file.

All AEs considered to be related (definitely, probably, or possibly related) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

## **10.6. NOTIFICATION ABOUT SERIOUS ADVERSE EVENTS AND SERIOUS AND UNEXPECTED SUSPECTED ADVERSE REACTIONS**

### **10.6.1. INVESTIGATOR REPORTING TO SPONSOR**

All SAEs that occur during the course of the study must be reported by the Investigator to the Sponsor and to the Medical Monitor within 24 hours by telephone or by text message.

Additionally, the SAE Form should be faxed/e-mailed within 1 working day from the point in time when the Investigator becomes aware of the SAE. In addition, all SAEs that occur up to and



including 30 days after administration of the last dose of study drug must be reported to the Sponsor within 1 working day from when the Investigator becomes aware of the SAE.

Investigators must report to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or Investigator Brochure. The report must include an assessment of causality.

For all SAEs, the Investigator is obligated to obtain and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the Adverse Event eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

The Sponsor's Medical Monitor will review the information submitted and seek further detail if deemed medically relevant and ideally concur on the severity and relatedness. However, the Medical Monitor may revise the severity and relatedness upward but may not reduce severity and/or relatedness. Such revisions will be documented in the Sponsor file and provided to the Investigator.

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### **10.6.2. REPORTING TO REGULATORY AGENCIES AND INSTITUTIONAL REVIEW BOARDS**

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency and all appropriate parties on an expedited basis. In addition, Sponsor must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigator Brochure.

It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB) of all serious and unexpected suspected adverse reactions involving risk to human subjects per IRB guidelines. Provide a copy of this communication to the Sponsor.



## 10.7. EMERGENCY IDENTIFICATION OF STUDY MEDICATION

In the event of a medical emergency, when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may obtain the treatment assignment of the subject experiencing the emergency through the unmasked statistician/designee. However, prior to unmasking, the Investigator should make every effort to contact the Medical Monitor.

If unmasking is necessary, the Investigator must document the reasons for unmasking in the subject's source documents but should not divulge the subject's treatment assignment to any individuals except the Medical Monitor (if required) and those individuals involved in the direct care of the subject. The date and the reasons for breaking the mask must be submitted to the Sponsor within 24 hours.

If a subject's treatment assignment is unblinded, the subject should remain in the study and continue the protocol-specified follow-up evaluations.

## 10.8. EMERGENCY SPONSOR CONTACT

In a medical emergency (such as an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor and the Sponsor Contact.

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## 11. ETHICS

### 11.1. INSTITUTIONAL REVIEW BOARD

The institutional review board (IRB) must comply with FDA requirements governing IRBs (21 CFR Part 56).



The Investigator will provide the Sponsor (or designee) with documentation of IRB approval of the following documents before the study begins at the study site(s): protocol, ICF, and any other relevant materials intended for or directed to subjects (e.g., subject diaries, advertisements). The Investigator will supply documentation to the Sponsor of IRB requirements regarding continuing review and approval of revisions to any of these documents.

## **11.2. ETHICAL CONDUCT OF THE STUDY**

This study will be conducted in accordance with the current IRB approved clinical protocol, International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and relevant policies and requirements of the national regulations and laws, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

## **11.3. SUBJECT INFORMATION AND INFORMED CONSENT**

Written informed consent/assent is required from each subject prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in 21 CFR Part 50.

The ICF will be used to explain the risks and benefits of study participation in simple terms before the subject will be entered into the study. The ICF will contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written informed consent must be given by the subject after the receipt of detailed information on the study and sufficient time to read it and have any questions answered. It is the responsibility of the Investigator to obtain consent/assent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor or its designee. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

## **12. STUDY ADMINISTRATION**

### **12.1. ADMINISTRATIVE STRUCTURE**

A list of individuals who will have key positions in this study will be saved in the Trial Master File (TMF). This list will include names, titles, and roles of selected individuals from the Sponsor and/or the contract research organization (CRO) that will contribute to this study.



## **12.2. QUALITY CONTROL AND QUALITY ASSURANCE**

### **12.2.1. OVERVIEW**

According to the GCP Guidelines, the Sponsor is responsible for implementing and maintaining quality assurance and control systems with written standard operating procedures (SOPs).

Quality Control (QC) will be applied to each stage of data handling. The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Site initiation visit
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data; and
- QC checks of the final clinical study report (CSR)

In addition, the Sponsor's (or designee) Clinical Quality Assurance (QA) Department may conduct periodic audits of the study processes, including, but not limited to study site, site visits, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized to Sponsor's representatives and regulatory authorities for all study-related documents, including medical history and concomitant medication documentation.

### **12.2.2. MONITORING**

Site Monitors will work in accordance with Sponsor or CRO SOPs. Monitors will establish and maintain regular contact between the Investigator or designee and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent/assent has been obtained from all subjects correctly and that data are recorded correctly and completely on the CRFs. Monitors are also required to compare entries in CRFs with corresponding source data and to inform the Investigator or designee of any errors or omissions. Monitors will also review adherence to the protocol and to regulatory requirements at the study site and discuss any deviations noted with the Investigator or designee. They will arrange for the study site to receive adequate supply of study drug and ensure appropriate storage conditions are maintained.



Monitoring visits will be conducted according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guideline for GCP. The monitor will make written reports to the Sponsor following each contact with the Investigator or designee, regardless of whether it is by phone or in person.

### **12.2.3. SAFETY OVERSIGHT**

The study site investigators assess each subject and record findings obtained during each visit. Subjects will be queried to report any observations, concerns or symptomatology, and a clinical assessment will also be made. This includes any evidence of disease exacerbation and/or progression. Safety reports made during the study will be promptly reviewed by the Sponsor's Medical Monitor and processed. This includes reporting to the FDA according to 21 CFR 312.32, "IND Safety Reporting," and taking any action necessary to protect subject safety.

### **12.2.4. DATA MANAGEMENT/CODING**

Study data will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor or CRO.

Adverse events will be coded using MedDRA and medications will be coded using World Health Organization Drug Dictionary (WHODD).

### **12.2.5. QUALITY ASSURANCE AUDIT**

Study sites, the study database, and study documentation may be subject to a Quality Assurance audit by the Sponsor or designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

## **12.3. DATA HANDLING AND RECORDKEEPING**

### **12.3.1. ELECTRONIC DATA**

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor will:

- Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)
- Maintain SOPs for using these systems
- Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)
- Maintain a security system that prevents unauthorized access to the data



- Maintain a list of the individuals who are authorized to make data changes
- Maintain adequate backup of the data
- Safeguard the masking, if any (e.g., maintain the masking during data entry and processing)

Documentation regarding electronic systems used in this protocol is available upon request from the CRO maintaining the electronic trial data system.

### **12.3.2. CASE REPORT FORM COMPLETION**

CRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

Electronic data capture will be used for the study. Data will be recorded on source documentation at each study location and entered electronically by the study center personnel. Data collected on each subject will be documented on the appropriate eCRF. Completed eCRFs are to be signed off by the Investigator or his/her designee.

### **12.3.3. DATA HANDLING**

If data are transformed during processing, records will be maintained so that it will be possible to compare the original data with the processed data.

An unambiguous subject identification code will be used that allows identification of all the data reported for each subject.

### **12.3.4. RETENTION OF STUDY RECORDS**

The Investigator must maintain essential study documents (protocol and protocol amendments, completed CRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor prior to disposing of any study records.

## **12.4. FINANCING AND INSURANCE**

Financing and insurance are addressed in a separate document.

## **12.5. CONFIDENTIALITY**

To maintain subject privacy, all CRFs, study drug accountability records, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subject will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of the investigational product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

## **12.6. PUBLICATION POLICY**

The data generated by this study are considered confidential information and the property of Sponsor and no publication will be allowed without the prior written consent of Sponsor. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Raymon Pharmaceuticals personnel and will be administrated by a steering committee.

## **12.7. DIRECT ACCESS TO SOURCE DATA**

The Investigators/institutions/clinical sites will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor designee, including direct access to source data/documents (e.g., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms) in addition to CRFs.

The Investigator or designee will prepare and maintain adequate and accurate source documents to support all observations and other pertinent data recorded on the CRFs for each subject randomized into the study.



The Investigator will allow the Sponsor (or designee), and authorized regulatory authorities to have direct access to all documents pertaining to the study.

## **12.8. CONTINGENCY MEASURES IN CASE OF A GLOBAL EMERGENCY**

In case of global or regional emergencies, such as the COVID-19 public health emergency, the investigational site may implement contingency plans to minimize the impact of the emergency on trial integrity and to reduce missing data, while ensuring the safety of study participants and the investigational site staff. In the event that study participants are unable or unwilling to attend in person study visits, telephone and virtual visits may be conducted for completion of assessments that can be conducted without requiring an in-person evaluation by the study investigator (e.g., subject reported symptomology and AEs). Virtual or telephone visits should be clearly documented as such in the case report forms to account for missing safety and efficacy assessment when summarized.

Deviations from the protocol may be unavoidable during the public health emergency. Delayed or missed visits due to COVID-19 illness and/or COVID-19 control measures should be documented as such in an effort to assess the potential impact of COVID-19 on study conduct and the collection of data.

## **12.9. PROTOCOL AMENDMENTS**

Changes to the conduct of the study should be prepared as a protocol amendment and implemented only upon approval of the Sponsor, or a representative of the Sponsor. Protocol amendments should also receive written IRB approval prior to implementation, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB, as appropriate.



### 13.REFERENCES

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